



Enteropathy with loss of enteroendocrine and Paneth cells in a patient with immune dysregulation: a case of adult autoimmune enteropathy

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Summary Autoimmune enteropathy (AIE) is a relatively rare condition found most frequently in children. It presents with persistent watery diarrhea and malabsorption and may require total parenteral nutrition for nutritional support. Rare cases have been reported in adults. On histology, the small intestinal villi are flattened but lack the intraepithelial lymphocytosis of celiac disease. In children and rarely in adults, some cases are linked to the IPEX syndrome (Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked inheritance). We report a 21-year-old man who presented with chronic persistent diarrhea for 4 years. The duodenal biopsies showed villous blunting, chronic inflammation, and decreased to absent goblet cells, Paneth cells, and endocrine cells by histology and electron microscopy. These changes are consistent with an AIE with involvement of non-enterocyte populations. Pathologists must be aware of the possibility of AIE in adults and consider it in the differential diagnosis of duodenitis, intraepithelial lymphocytosis, and small bowel villous flattening.

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1. Introduction

In children, autoimmune enteropathy (AIE) is an uncommon condition that presents with persistent diarrhea and malabsorption accompanied by small bowel damage on

histology. The terminology was first proposed by Unsworth and Walker-Smith [1], who suggested 4 criteria: presentation with diarrhea and enteropathy, no response to total parenteral nutrition (TPN) or exclusion diet, evidence of other autoimmune disease or a predisposition to this, and absence of severe immune deficiency. In a subgroup of children, the bowel changes are associated with the IPEX syndrome (Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked inheritance). Only 7 previous reports of AIE in adults have been identified [2,3], where patients

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present with villous atrophy and malabsorptive symptoms not responsive to a gluten-free diet.

We report a case of an adult male patient with chronic diarrhea requiring TPN, dysgammaglobulinemia, and autoimmune disorders with enteropathy. Marked loss of Paneth cells and endocrine cells was apparent on histology and electron microscopy.

2. Clinical history

A 21-year-old man was admitted for investigation for chronic persistent non-bloody diarrhea of 4 years' duration associated with an involuntary weight loss of more than 40 lb. His medical history included developmental delay, dysgammaglobulinemia, autoimmune hemolytic anemia, hypothyroidism, Raynaud phenomena, and exfoliative dermatitis. He had undergone upper gastrointestinal endoscopy after 1 year of symptoms and was subsequently put on a gluten-free diet after endoscopic duodenal mucosal biopsies showed mild villous atrophy and mildly increased intraepithelial lymphocytes, despite normal anti-endomysial and tissue transglutaminase results on serology. There was no response clinically or on follow-up endoscopy and histology, so the gluten-free diet was discontinued and he was then referred to St Michael's Hospital for further evaluation. On examination at admission, he appeared severely malnourished, with a hemoglobin of 108 g/L and a low total white cell count of $1.53 \times 10^9/L$ (normal $4-11 \times 10^9/L$) and lymphocytes at $0.26 \times 10^9/L$ (normal $1.0-3.2 \times 10^9/L$). Serum electrophoresis demonstrated abnormal immunoglobulin distribution (elevated IgG at 19.4 g/L, low to absent IgA at <0.07 g/L, and normal IgM). Anti-SSA(Ro), anti-SSB(La), anti-Smith, anti-RNP, and anti-parietal cell

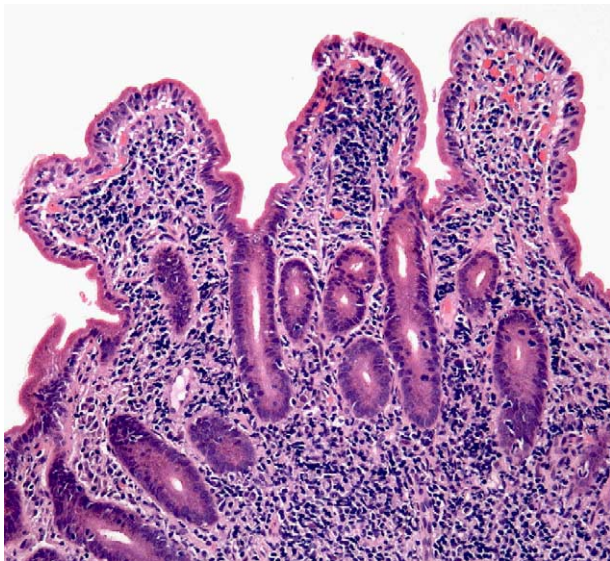


Fig. 1 Duodenal mucosa demonstrating mild villous atrophy and crypt hyperplasia. Intraepithelial lymphocytes are increased. Note the loss of goblet cells and Paneth cells (H&E, $\times 100$).

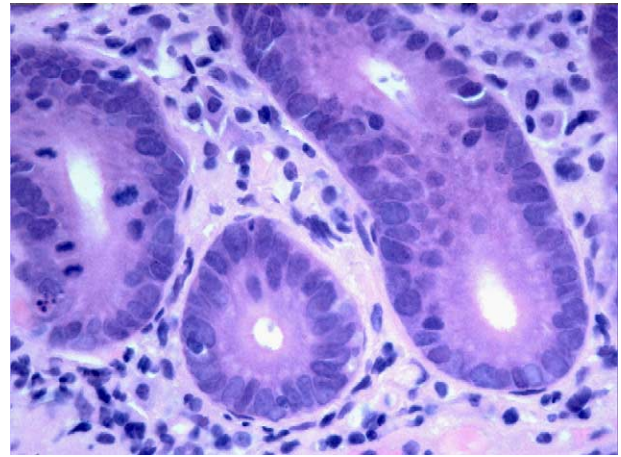


Fig. 2 High-power view of crypt bases in the duodenal mucosa; Paneth cells, endocrine cells, and goblet cells are not evident (H&E, $\times 400$).

antibodies were all negative. Rheumatoid factor and anti-nuclear antibody (ANA) were initially negative. Rheumatoid factor later became positive at 37 IU/mL, and ANA was later positive in a speckled pattern with a titer of 1:160. Upper and lower gastrointestinal endoscopy demonstrated no abnormalities, but biopsies were obtained. He was then given TPN and a 2-month course of prednisone, resulting in a weight gain of 20 pounds over 4 months and diminished diarrhea.

3. Pathological findings

Small bowel biopsies done at the time of his first two endoscopies had similar features of mild villous atrophy with associated crypt hyperplasia and mildly increased intraepithelial lymphocytes. Occasional neutrophils were present within the lamina propria. Goblet cells were evident but Paneth cells and endocrine cells were not identified on

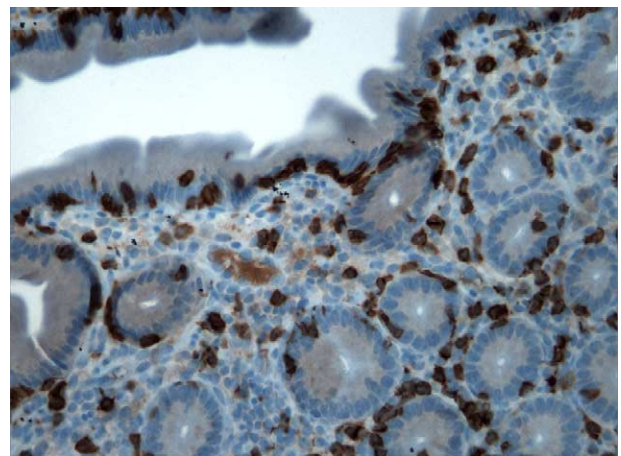


Fig. 3 Immunohistochemistry for CD8 demonstrates scattered CD8-positive T cells within the lamina propria, with a marked preponderance in the intraepithelial compartment.

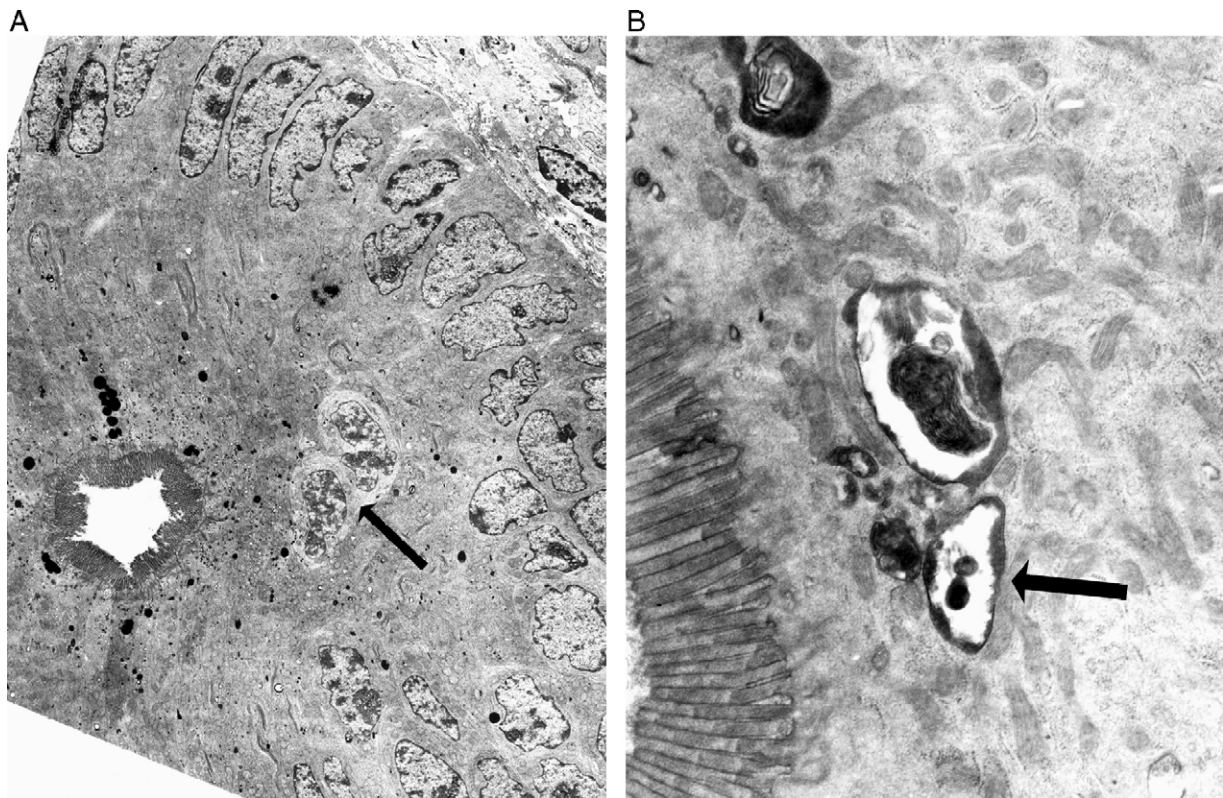


Fig. 4 Electron micrograph of the small bowel mucosa. A, Low-power view of a crypt base. Epithelial cells are noted with small lymphocytes with the epithelial compartment (arrow). The dense granules of endocrine cells and the larger, lumenally oriented granules of Paneth cells are not identified. B, High-power view of an epithelial cell. Note the normal microvilli. Vacuoles in the cytoplasm contain material consistent with intracellular bacteria (broad arrow).

the hematoxylin and eosin (H&E)-stained slides. Colonic biopsies contained mild chronic active colitis.

The biopsies taken during admission at our hospital demonstrated small bowel mucosa with villous blunting and crypt hyperplasia and focally increased intraepithelial lymphocytosis extending to the tips of the villi, up to 50 lymphocytes per 100 enterocytes. The enterocytes appeared reactive and goblet cells were depleted but not absent (Fig. 1). Paneth cells and endocrine cells could not be identified on routine H&E staining (Fig. 2). Immunohistochemistry for lysozyme, typically present in the Paneth cell granules, was negative. Chromogranin and synaptophysin immunohistochemical staining for endocrine cells were both negative. Most of the lymphocytes in the lamina propria were CD3⁺ and CD4⁺ lymphocytes. Occasional CD8⁺ lymphocytes were present within the lamina propria but these were the dominant lymphocytes in the epithelial compartment (Fig. 3). Rare CD20⁺ B cells were identified. Although plasma cells were identified in the lamina propria, no significant IgA production was detected by immunohistochemistry. Small numbers of cells positive for IgG and IgM were seen. Colonic biopsies at this time contained unremarkable large intestinal mucosa.

Small bowel mucosa submitted for electron microscopy identified the presence of intracellular bacteria within the enterocytes but no evidence of Paneth cells or endocrine

cells. The enterocytes had unremarkable microvilli with no evidence of vacuolization of the apical cytoplasm or loss of brush border (Fig. 4).

4. Discussion

We present the case of an adult male patient with enteropathy and diarrhea in the presence of various autoimmune disorders but without severe immune deficiency. We consider that he fulfills the Walker-Smith criteria for adult AIE because his improvement was associated with corticosteroid therapy, not just TPN. Clinically, he was considered to have the IPEX syndrome. Autoimmune enteropathies are uncommon in young children and are very rare in adults, with only 7 identifiable cases in the literature (discussed in Leon et al [2] and in Biagi and Corazza's commentary on Daum et al [3]) [3-6] and one presentation (S.C. Abrahams, Gastrointestinal Specialty Conference, United States and Canadian Academy of Pathology 2005 Annual Meeting).

Male patients with the IPEX syndrome are a subgroup of AIE. These patients have a germline loss of function mutation in a gene encoding a DNA-binding protein, *FOXP3*, which is important in the development and function of the CD4⁺ CD25⁺ group of regulatory T cells. Lacking this important group of regulatory T cells, these

patients develop large populations of activated T cells from which various autoimmune disorders develop. These patients present with various autoimmune disorders and enteropathy. In AIE and IPEX, enterocyte-directed autoantibodies are frequently detected, as well as more typical autoantibodies such as ASMA, ANA, and anti-LKM [1,7]. These antibodies are not considered specific to AIE as they can be found in other disorders such as ulcerative colitis [8]. These antibodies may be secondary to the intestinal inflammation as they can develop after the histological changes [8], suggesting that the damage is caused by the activated and uncontrolled T cells. Although these cases generally occur in the pediatric population and are fatal, a somewhat milder and later onset was reported in the original family described by Powell et al [9], in which two affected males survived into the second or third decade.

In AIE, the histopathologic appearance is variable. Most commonly, the patients have biopsies showing moderate to severe villous atrophy and variable crypt hyperplasia or hypoplasia; these patients often develop a circulating anti-enterocyte antibody. CD4⁺ lymphocytes predominate and intraepithelial lymphocytes can be significantly increased: similar changes may also affect the stomach and colon [2,10]. Alternatively, in a minority of cases, villous architecture is more often preserved and intraepithelial lymphocytes are within normal limits but the Paneth cells, goblet cells, and endocrine cells may be absent [11,12]. Our patient shows a combination of these two patterns as his IELs were increased and villous atrophy was marked, but he had lost Paneth cells, endocrine cells, and goblet cells. The loss of the Paneth cells is of particular interest: Paneth cells produce various defensins that protect against bacteria; the loss of these protective agents would be expected to lead to increased gut infections and may be the cause of the intracellular bacteria noted on electron microscopy.

Small bowel mucosal changes of villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytes are most frequently associated with celiac disease/gluten intolerance, where they are associated with anti-tissue transglutaminase and anti-endomysial IgA antibodies. However, this appearance is known to be nonspecific as a large number of conditions cause mucosal damage leading to crypt hyperplasia and villous blunting, including tropical sprue; increased intraepithelial lymphocytes may be seen postinfection. Therefore, discriminating AIE from these other disorders histologically is difficult even if loss of Paneth cells and endocrine cells is noted. However, pathologists should consider the possibility of this diagnosis in adults whose biopsies show changes most consistent with

celiac disease yet lack the characteristic antibodies and do not respond to dietary restriction. Many such cases, in the past, have been termed "refractory sprue" and it is probable that a small proportion of these cases are actually unrecognized AIE. Unfortunately, confirmation of the disease by anti-enterocyte or anti-goblet cell antibodies or genetic testing for IPEX is difficult as these tests are not widely available.

Treatment of AIE has been most commonly with steroids for immunosuppression, although there are reports of the effectiveness of tacrolimus [3] and intravenous immunoglobulin replacement [2].

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