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CASE REPORT | SMALL BOWEL

Seronegative Adult Autoimmune Enteropathy in a Male Traveler

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ABSTRACT

Autoimmune enteropathy (AIE) is rare but damaging. The lack of consistent objective findings makes diagnosis a challenge. A 45-year-old male developed noninfectious diarrhea with significant weight loss and electrolyte abnormalities. Computed tomography delineated enteritis. Colonoscopy and esophagogastroduodenoscopy showed villous atrophy, chronic inflammation, and ulceration of the terminal ileum and cecum. Pathology showed cryptitis with apoptosis and abscesses throughout the small and large bowel and absent goblet cells. Steroids rapidly improved symptoms. Anti-enterocyte antibody serologies were negative. Management can be challenging, and, in this case, the patient initially improved with budesonide and infliximab but required alternative anti-tumor necrosis factor therapy after relapsing. This is an unusual presentation of seronegative AIE, which should be considered in cases of persistent severe diarrhea.

INTRODUCTION

Autoimmune enteropathy (AIE) is a rare disease usually diagnosed in children, but its prevalence is increasing in the adult population. Its symptoms, often intractable malabsorptive diarrhea refractory to gluten-free or lactose-free diets, can mimic inflammatory bowel disease. Further, autoimmune enteropathy lacks clear, consistent markers for confident diagnosis, although the presence of anti-goblet cell antibodies and anti-enterocyte antibodies can help. Histologically, it can resemble more focal diseases such as celiac disease, but can more diffusely involve the small and large bowel. Treatment remains equally elusive, usually consisting of steroids and the addition of calcineurin inhibitors and anti-tumor necrosis factor (TNF) therapy, sometimes with diminishing effects.

CASE REPORT

A healthy 45-year-old male without significant previous past medical history or family history was hospitalized for severe hypokalemia due to protracted large-volume diarrhea and 18-kg unintentional weight loss, which began 5 weeks before presentation after recently returning to the United States from Mexico. Infectious workup was negative, including human immunodeficiency virus screening. Abdominal computed tomography (CT) with intravenous contrast showed enteritis. Endoscopic biopsies revealed nearly complete duodenal and terminal ileum villous atrophy with increased chronic inflammatory cells throughout the lamina propria and numerous small crypts in the colon. No parasites were found. The patient was discharged on antibiotics because the patient's history and symptoms supported an infectious etiology albeit undiagnosed. Two days later, he was re-admitted for persistent symptoms. Celiac serologies were negative, and during this span a gluten-free diet was not attempted. Repeat CT illustrated ileal loops with wall thickening (Figure 1). Failure to thrive led to initiation of total parenteral nutrition and transfer to our institution.

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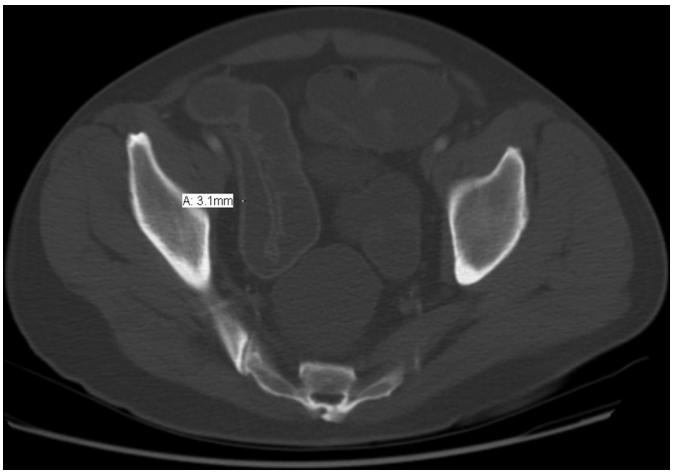

Figure 1. Abdominal/pelvic computed tomography with contrast showing diffuse dilatation and edema of the small bowel consistent with but not specific for AIE.

Endoscopy revealed mild scalloping of the duodenal mucosa, a clean-based cecal ulcer, and multiple deep terminal ileum ulcerations (Figure 2). Duodenal and terminal ileum biopsies showed acute cryptitis, scattered crypt apoptosis, and severe villous blunting and atrophy. The latter displayed rare cytomegalovirus inclusions on immunohistochemistry. No goblet cells were seen throughout the small bowel biopsy specimens. Gastric biopsy showed chronic inactive gastritis without organisms. Random colon biopsy demonstrated prominent crypt apoptosis, scattered acute cryptitis and crypt abscesses, and chronic inflammation.

The severe inflammation but rare inclusions suggested that cytomegalovirus was a superinfection. Intravenous ganciclovir produced no improvement. Multiple findings, including the severity of diarrhea with electrolyte imbalances, biopsies showing diffuse inflammation and increased apoptosis without granulomas in the colon and small bowel and most severely in the duodenum, and negative serologies, argued against diagnosis of inflammatory bowel disease. Intravenous steroids were empirically started for AIE, which reduced stool output within 48 hours, leading to eventual discharge on prednisone taper. On histology, the inflammation pervaded the entire breadth of the colonic specimens, including a random one apart from the sample of the ulcer, suggesting that the process was diffuse throughout the lower gastrointestinal tract.

The patient relapsed 2 weeks later, having up to 16 bowel movements and 10 L of stool daily. He weighed 55 kg compared to his baseline of 81 kg. Higher doses of prednisone rapidly improved symptoms. His anti-enterocyte antibody assays returned negative. P-ANCA and anti-GAD 65 antibodies were not tested. After starting infliximab and transitioning to budesonide, the patient had 3 formed bowel movements a day but relapsed months later, requiring hospitalization and replacing budesonide with prednisone.

One year after initial endoscopy, the patient underwent repeat endoscopy to assess the degree of inflammation and evaluate repeated failures due to recurrences of profuse diarrhea in weaning completely from prednisone, which he had been taking for over a year. The upper GI tract showed diffuse duodenal scalloping and villous flattening grossly, while histological analysis showed inflamed mucosa with marked villous blunting, cryptitis, crypt abscesses, and apoptotic bodies. Poor prep marred evaluation of the lower tract, which revealed abnormal, ulcerated glandular tissue in the distal rectum and anal canal grossly, and on histology revealed normal mucosa with rare foci of apoptotic crypt cells. Furthermore, serum infliximab levels were found to be zero despite infusions every 6 weeks. Infliximab was then stopped, and the patient started on adalimumab while continuing his prednisone with the intent to taper.

DISCUSSION

While more common in pediatric patients, AIE does afflict adults. Some cases are diagnosed after workup is completed in adulthood for symptoms beginning in childhood or

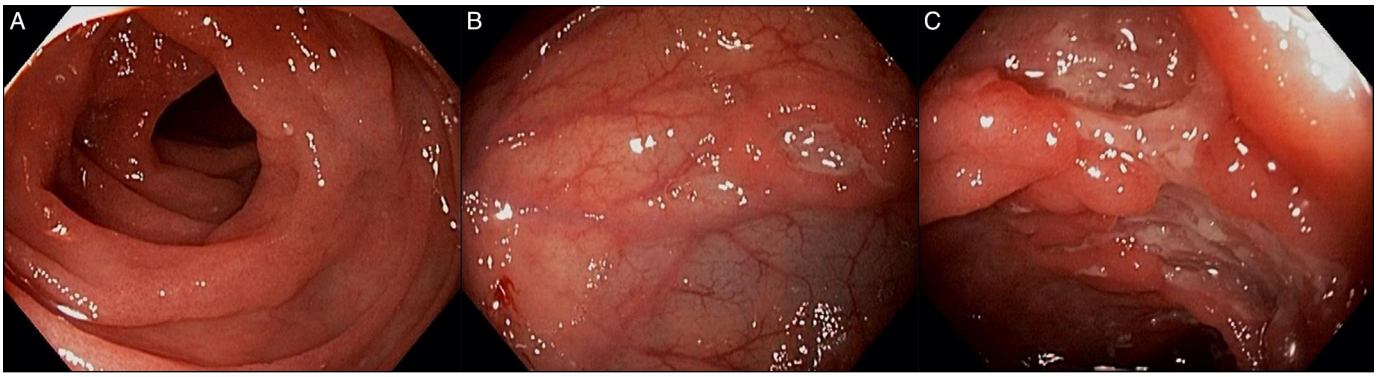

Figure 2. Endoscopy showing (A) scalloping of duodenal mucosa, (B) a cecal ulcer indicating that inflammation extended beyond the small bowel, and (C) terminal ileum ulceration.

adolescence.[1-3] AIE remains a diagnosis of exclusion. Current criteria define AIE as chronic, malabsorptive diarrhea lasting more than 6 weeks, blunted small bowel villi, deep crypt lymphocytosis, increased crypt apoptotic bodies, and minimal intraepithelial lymphocytosis after other causes of villous atrophy have been ruled out.[4-6] Symptoms are nonspecific, and AIE can coexist with other autoimmune diseases.[7,8] The type of chronic diarrhea has rarely been reported, appears to vary, and is often described as profound, up to 9 L over 24 hours, and with weight loss as great as 20 kg.[1-3,6] Lack of improvement on a gluten-free diet and negative celiac disease studies often help rule out celiac disease.[9] On endoscopy, the small bowel often features mucosal scalloping, fissuring, and mosaic patterns.[4] Capsule endoscopy has been used to help diagnose cases of AIE, primarily by ascertaining inflammation diffusely involving the small bowel, whereas esophagogastroduodenoscopy and colonoscopy alone may have suggested more focal processes.[10] Anti-enterocyte and anti-goblet cell antibodies correlate with diagnosis of AIE but are not required for it. Having unclear sensitivity and specificity, they are present in 50% to more than 90% of cases.[4,5,9] Elevated titers have been seen in patients with inflammatory bowel disease, celiac disease, protein-losing enteropathy, and asymptomatic HIV.[11,12] Few laboratories run the assays, which are observer-dependent, marring consistent reproducibility.[4,11,12] Studies have been unable to discern if the antibodies cause the disease or are a byproduct of the disease.[13] The antibodies are noted to appear after mucosal destruction and disappear during treatment, and they do not seem to correspond to severity.[11,14] No association among clinical course, histology, and the type of gut epithelial cell antibodies has been found.[4,12] The anti-75 KDa antibody has been thought to compromise tight junctions between intestinal cells, thereby producing inflammation.[14]

Pathognomonic histologic findings for AIE are elusive. In 13 of 25 pediatric and adult cases, the small intestinal villi were blunted, and mixed inflammation predominated by mononuclear inflammation and neutrophilic cryptitis expanded the lamina propria, creating an active chronic duodenitis picture.[12] In several cases, histologic changes suggested celiac disease and acute graft-versus-host disease (GvHD). Unlike in celiac disease, the changes extend beyond the small bowel, most frequently into the stomach, then the colon, and finally the esophagus, and the presence of crypt microabscesses favors a diagnosis of AIE although in many cases they are absent.[12] Increased intraepithelial lymphocytosis, villous blunting, and increased crypt epithelial apoptosis evoke acute GvHD. However, AIE often has neutrophilic cryptitis and lacks the crypt dropout more commonly found in GvHD.[12] Further, AIE has a relative lack of surface lymphocytosis, which is usually defined as fewer than 40 lymphocytes per 100 epithelial cells and often decreased or absent goblet cells, Paneth cells, and endocrine cells.[1,4,12] Many cases, however, do not show these traits histologically, including lower levels of intraepithelial lymphocytosis.[4,9,15] Celiac disease often has higher levels. Some bowel biopsies regardless of serologies have shown characteristics of both diseases, suggesting that celiac disease and AIE can coexist.[4,15] Colonic biopsies have shown active chronic inflammation with injury patterns similar to that seen in the duodenum, as well as patterns that do not correlate with duodenal findings within the same patient.[12,14]

Treatment of AIE consists of immunosuppression, often with steroids.[4,5,15] In one review, 60% of subjects had nearly full resolution after 1-8 weeks of therapy, but dependence or tachyphylaxis often developed.[4] Other agents include infliximab, 6-mercaptopurine, azathioprine, cyclosporine, and tacrolimus.[3,13] Histologic changes may lag behind symptomatic improvement, sometimes by up to 6 months.[3,6] Sometimes multiple therapies prove ineffective, even resulting in death.[3] AIE has also developed postpartum and been treated successfully with the TNF-α antagonist adalimumab. [16] This case along with 4 others, one of which was pediatric, demonstrated that anti-TNF-α therapy produced significant symptomatic improvement.[3,4,13] However, there are too few cases to confidently report an adequate response or remission rate. In a separate case, a 49-year-old female had remission after taking a course of abatacept, necessitated by complications from taking azathioprine, infliximab, and methotrexate.[6] The few side effects and lack of need for monitoring of therapeutic levels also made abatacept an appealing option, which might be applied effectively to other refractory cases.

DISCLOSURES

Author contributions: P. McCabe collected and analyzed data and wrote the manuscript. L. Alli-Akintade collected and analyzed data. J. Stondell analyzed data, edited the manuscript, and is the article guarantor.

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