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Adult Autoimmune Enteropathy: Mayo Clinic Rochester Experience

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Abstract

Purpose—Autoimmune enteropathy is a rare cause of intractable diarrhea associated with circulating gut autoantibodies and a predisposition to autoimmunity. It is rarely observed in adults with only eleven cases reported to date.

Methods—Fifteen adults with autoimmune enteropathy were identified at the Mayo Clinic, Rochester, from May 2001 to June 2006. The demographic, clinical and treatment data were abstracted from their records.

Results—The study population was 87% Caucasian, 47% females, with median age of 55 years (interquartile range: 42 to 67 years). All patients had diarrhea, weight loss and malnutrition. Celiac disease was excluded by lack of response to gluten free diet or absence of the celiac disease susceptibility HLA genotypes. Fourteen patients were tested for gut epithelial cell antibodies and 93% were positive for anti-enterocyte and/or anti-goblet cell antibodies. Predisposition to autoimmune diseases was noted in 80%, as indicated by a variety of circulating autoantibodies. Small intestinal histopathologic findings included subtotal villous atrophy and lymphoplasmacytic infiltration in the lamina propria with relatively few surface intraepithelial lymphocytes. T-cell receptor gene rearrangement studies were negative in all cases. Immunosuppressive therapy was required in 93% cases. Clinical improvement was noted in 60% after 1–8 weeks of steroid therapy.

Conclusion—Autoimmune enteropathy is a heterogeneous disease and should be considered in the differential diagnosis of malabsorption and small bowel villous atrophy. The presence of gut epithelial cell antibodies can help confirm the diagnosis. No single agent is unequivocally effective in inducing remission, and immunosuppressive therapy is required in most cases.

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Keywords

Autoimmune enteropathy; intractable diarrhea; anti-enterocyte antibodies; anti-goblet cell antibodies; malabsorption; refractory sprue; immunosuppressive agent

BACKGROUND

Autoimmune enteropathy (AIE) is a rare cause of intractable diarrhea associated with circulating gut autoantibodies and a predisposition to autoimmunity. The term AIE was first coined by Unsworth and Walker-Smith, two pediatric gastroenterologists from St. Bartholomew's Hospital in London, in 1982¹ after their experience with a 15 month old child who presented with protracted diarrhea, weight loss and vomiting. There was evidence of villous atrophy which did not respond to dietary exclusion of gluten, cow's milk, eggs or to 8 weeks of complete bowel rest with intravenous alimentation. The child was also positive for IgG anti-enterocyte antibodies which disappeared after treatment with cyclophosphamide, though the mucosal abnormalities persisted to some degree¹. The diagnostic criteria for AIE, proposed by Unsworth and Walker-Smith, include: (1) severe villous atrophy not responding to any dietary restriction; (2) circulating gut autoantibodies and/or associated autoimmune conditions, and (3) lack of severe immunodeficiency². Although it is primarily considered to be a disease of children, adult-onset AIE has recently been described, with a total of eleven cases reported to date. The pathophysiology of AIE is not completely understood but the available evidence suggests a hyperactive immune state due to a defect in regulatory T-cell homeostasis³. Autoimmune enteropathy must be distinguished from refractory sprue, which is a form of celiac disease no longer responsive to a gluten free diet⁴. Due to the rarity of the disease, there is scarce data regarding the epidemiology, natural course and therapeutic options for AIE. Thus, treatment decisions are primarily guided by anecdotal experience. Many treatments, including corticosteroids, immunosuppressive drugs like azathioprine, cyclophosphamide, tacrolimus, cyclosporine and infliximab, have been used with varying success^{5–9}. In the present study, we sought to describe the clinical features, treatment and outcome of adult patients with AIE seen at our institution over the past five years.

METHODS

All patients seen at Mayo Clinic, Rochester from May, 2001 to June, 2006 with a diagnosis of adult-onset AIE were identified either retrospectively through the diagnostic index and Department of Pathology database, or prospectively through our outpatient clinics. AIE was defined as adult onset protracted diarrhea not responsive to any dietary exclusion and associated with intestinal villous atrophy, circulating gut autoantibodies and/or predisposition to autoimmunity. All pathology slides, except one, were reviewed by a single Mayo GI pathologist (SCA). Serological testing and indirect immunofluorescence staining for the gut epithelial cell antibodies (GECA), namely anti-enterocyte (AE) and anti-goblet (AG) were performed at The Children's Hospital of Philadelphia. Demographic, clinical and treatment data were abstracted from the medical records and outcome data was supplemented by follow-up telephone interviews. The study was approved by Mayo Internal Review Board.

RESULTS

Clinical Features

We identified 15 cases of AIE (Tables 1 and 2) during the study period, with a median age of 55 years (interquartile range: 42 – 67 years) at diagnosis. The majority of patients, 87%, were Caucasians with eight males and seven females. All patients had protracted chronic diarrhea, weight loss and malnutrition. The median duration of symptoms prior to the diagnosis was 1.5

years (interquartile range: 1 – 4.5 years). Seven patients (47%) required parenteral nutritional support because of significant weight loss. Celiac disease (CD) was excluded in 13 patients (87%) by lack of any response to a gluten free diet (GFD) and absence of the CD susceptibility HLA genotypes. The other 2 patients (13%) fulfilled criteria for refractory sprue. Both the patients had CD associated HLA genotype, positive IgA tissue transglutaminase antibodies (tTG), and histologic picture compatible with sprue in one case and features of both AIE and sprue in the other case. Both these patients were unresponsive to strict GFD and tested positive for anti-enterocyte antibodies. T-cell receptor gene rearrangement studies, by PCR amplification ruled out any clonal proliferation in both the cases. Fourteen patients were tested for gut epithelial cell autoantibodies (GECA) (Table 3); 13 (93%) were positive for anti-enterocyte (Figure 1) and/or anti-goblet cell antibodies (Figure 2), including two who fulfilled criteria for refractory sprue. Abdominal CT was unremarkable in all cases except prominent mesenteric lymph nodes in 6 cases (40%). The average stool output, estimated at the time of diagnosis in 9 cases (60%), was 4256 g/day, with an average fecal fat content of 60 g/day on a high fat diet (≥ 100 g/d). Additional laboratory abnormalities included elevated hepatic transaminases (2 to 5 times upper limit of normal) in 10 (67%), fat-soluble vitamin deficiencies in 9 (60%), elevated IgA tTG antibodies in 5 (33%), and mild immunoglobulin deficiencies either IgG subtype, IgM or IgA in 5 patients (33%). Another 2 patients (18%) had concurrent common variable immunodeficiency (CVID). A predisposition to autoimmunity was noted in 12 patients (80%), as indicated by a variety of circulating autoantibodies and associated autoimmune disorders (Table 3).

Initial esophagogastroduodenoscopy (EGD) was grossly abnormal in 8 patients (53%) showing duodenal scalloping, fissuring, mosaic pattern and villous atrophy. Capsule enteroscopy (CE) was performed in 7 patients (47%). Capsule failed to leave the stomach in one case and in all others CE showed abnormal small bowel (SB). In five cases (71%) CE changes of fissuring, scalloping and mosaic pattern were restricted to the proximal SB. One case had aphthous ulceration in the mid-SB and edema of the distal SB.

Histopathology

Small bowel biopsies were available for review (by SCA) in 14 of 15 cases. In 8 patients (57%) (all but one with anti-enterocyte and/or anti-goblet cell antibodies), the biopsies demonstrated classic histopathologic features of AIE as previously described in children including increased mononuclear inflammation in the lamina propria, lymphocytic infiltration into deep crypt epithelium with a relative paucity of surface lymphocytosis (< 40 lymphocytes per 100 epithelial cells), and increased numbers of crypt apoptotic bodies (Figure 3). In all patients except one, the lamina propria mononuclear infiltrates were composed of both plasma cells and lymphocytes; one patient with CVID lacked mucosal plasma cells but had prominent lymphocytic lamina propria infiltrates. Villous blunting was evident in all biopsies, ranging from mild (villous: crypt ratio 1:1; $n = 2$), to moderate ($n = 4$), to severe (total or near-total villous atrophy; $n = 2$). In 5 of these cases, there was neutrophilic cryptitis and villitis. Goblet cells were absent from the epithelium in 6 cases and Paneth cells in 3 cases. Many patients had evidence for an autoimmune process involving the entire gastrointestinal tract (Figure 4). Concomitant colonic biopsies were taken in 5 of 8 patients; only one was normal, whereas the others all demonstrated histologic abnormalities identical to those seen in the small bowel. Gastric biopsies were taken in 3 patients and revealed autoimmune atrophic gastritis in two cases and normal histology in one.

In 3 patients (21%), small bowel biopsies demonstrated histopathologic features of both AIE and celiac disease (Figure 5). All showed near-total villous atrophy with surface intra-epithelial lymphocytosis (IEL) ranging from 50 lymphocytes per 100 epithelial cells to ≥ 100 lymphocytes per 100 epithelial cells. All had neutrophilic cryptitis, increased numbers of deep

crypt apoptoses, and deep cryptal lymphocytosis. In one patient, there was absence of goblet cells. This group of patients included 2 with positive anti-enterocyte antibodies (GECA were not tested in the other), 2 with positive gluten-sensitivity antibodies, and one with celiac disease-associated HLA type (DQ2). Concomitant colon biopsies were obtained in 2 patients; one was normal, and the other demonstrated mild lymphocytic colitis (20 lymphocytes/100 epithelial cells). Gastric fundal biopsy obtained in one patient revealed autoimmune atrophic gastritis.

In 3 patients (21%) with positive GECA (anti-enterocyte antibodies in 2 cases and anti-goblet cell antibody in the other), small bowel biopsies lacked classic features of AIE and instead revealed sprue-like changes. There was surface intra-epithelial lymphocytosis ranging from 50 lymphocytes/100 epithelial cells to ≥ 100 lymphocytes/100 epithelial cells. Villous blunting was mild in one patient and near-total in the other two. One patient had CVID and showed an absence of plasma cells in the lamina propria. None of the biopsies had neutrophilic inflammation or absence of goblet cells. Gluten-sensitivity antibodies were demonstrated in 2 of these 3 patients, and one also had the celiac-associated HLA type DQ2.

The remaining patient, whose small bowel biopsy had previously been reviewed by another Mayo GI pathologist and was not available for review by SCA, showed total villous atrophy, crypt hyperplasia, increased IEL (60–80 lymphocytes per 100 epithelial cells) and chronic inflammation suggestive of celiac sprue. This patient had both positive anti-enterocyte antibodies (IgG) and positive gluten-sensitivity antibodies (tTG IgA, anti-gliadin IgG and IgA). Celiac-associated HLA type, however, was negative.

Treatment and Outcomes

Fourteen patients (93%), including two with CVID that failed prior treatment with IV immunoglobulins, received immunosuppressive therapy (Table 4); prednisone alone was used in 4, prednisone followed by budesonide in 2, prednisone followed by azathioprine or 6-mercaptopurine in 3, prednisone followed by budesonide and azathioprine in one, budesonide followed by prednisone in one, budesonide followed by azathioprine in one, and prednisone followed by either 6-mercaptopurine (6-MP) or azathioprine with infliximab in 2 patients. The remaining one patient received metronidazole 500 mg orally three times a day for 4 weeks and diphenoxylate without benefit.

Overall, 9 patients (60%) responded clinically with near/complete resolution of diarrhea, 3 patients (20%) had a partial response with less than 50% reduction in bowel frequency, and 3 patients (20%) failed to respond. Follow-up small bowel endoscopic biopsies were available in six of the nine responders and showed normal appearing small bowel mucosa with preserved villous architecture and without significant inflammatory infiltrate. Persistent villous atrophy was noted in follow-up endoscopic biopsies from those with partial clinical response. Rapid clinical response to high dose steroids (defined as steroids ≥ 40 mg/day) was noted in two cases. However, 3 to 11 months later both these patients required additional immunomodulatory therapy to maintain clinical remission. One patient responded quickly to prednisone 10 mg/day and remained in remission on prednisone 5 mg/day during 14 months of follow-up. One patient, refractory to intravenous high dose methylprednisolone and 6-MP for six months, had a dramatic response to infliximab (5 mg/kg) within one week of the second dose. Infliximab was given as an induction dose at 0, 2, 6 weeks followed by a maintenance dose every 8 weeks. The patient first experienced resolution of abdominal pain, followed by steady weight gain, then improvement of diarrhea, and finally discontinuation of parenteral nutritional support within six weeks of first dose. The other five responders achieved remission on 20–60 mg/day prednisone in 4–8 weeks. Two of these were later switched to budesonide 6–12 mg/day for maintenance. Azathioprine 2mg/kg/day was added in one of these two cases. Three partial responders had a waxing and waning course despite immunomodulator therapy.

Follow-up

Follow-up of more than one year was available in 13 patients (87%). The median length of follow-up from the onset of symptoms to the date of last clinical contact was 2 years (interquartile range: 1–4.8 years). One patient died six months after the onset of symptoms from overwhelming septicemia complicating unremitting underlying disease. There were two thromboembolic events, without any known risk factors, including sagittal venous sinus thrombosis and deep venous thrombosis with pulmonary embolism 6–8 months after the onset of symptoms.

DISCUSSION

AIE is defined as a condition with adult-onset chronic diarrhea, malabsorption, complete lack of response to GFD or other dietary exclusions with specific small intestinal histologic features and is usually characterized by the presence of circulating GECA. Based on our experience a proposed diagnostic criteria for AIE is listed in Table 6.

The current study represents the largest series of adult patients reported to date with the diagnosis of AIE. All these cases share a constellation of clinical features which are similar to what has previously been reported in children ^{1, 10–13} and more recently in adults ^{6, 14–20} (Table 5).

AIE appears to represent a spectrum of generalized immune dysregulation. One third of the patients in our series showed evidence of autoimmune gastroenterocolitis. Similar findings have been reported in children ¹³ and two adults with AIE ^{14, 18}. In addition, a high number of patients (80%) in the current study had an associated autoimmune disorder or circulating autoantibodies. A predisposition to other autoimmune diseases has been reported in other cases of AIE ^{13, 17, 21}. Extensive intestinal and extra-intestinal clinical involvement with a variety of associated antibodies supports the hypothesis that AIE represents one feature of a generalized hyperactive immune state, with an apparent loss of proper controls ²².

Pathophysiology of AIE is not known but deficiency or dysfunction of CD25⁺CD4⁺ regulatory T cells can have a contributing role. ²³ Naturally occurring CD25⁺CD4⁺ regulatory T cells engage in the maintenance of immunological self-tolerance and down-regulation of various immune responses ²⁴. These regulatory T cells specifically express FOXP3, a member of the forkhead/winged-helix family of transcriptional regulators, which encodes a transcription-repressor protein called scurfin ²⁵. Experimental data suggests that scurfin is implicated in regulation and suppression of T-cell activation ²⁶. Mutations in the FOXP3 gene have been identified in patients with a rare X-linked recessive disorder of early childhood involving immune dysregulation, polyendocrinopathy, and enteropathy (IPEX syndrome) ²⁷. There is increasing evidence of similarities between AIE and IPEX syndrome ^{3, 28, 29}. IPEX syndrome tends to be lethal in male infants but now milder phenotypic variants have been described that may affect young adults ^{21, 28}.

The pathogenic significance of GECA, including anti-enterocyte and anti-goblet cell antibodies is not entirely clear ²². The detection of these autoantibodies remains observer-dependent and subjective, however, and no standardized test currently exists. Anti-enterocyte antibodies have not been reported in celiac disease, Crohn's disease or ulcerative colitis ^{12, 30, 31}, though they have been described in adult AIDS patients without digestive symptoms ³². However, anti-goblet cell antibodies have been reported in patients with chronic inflammatory bowel disease ³³, as well as in their asymptomatic first-degree relatives ³⁴. Intestinal biopsies have shown marked depletion of goblet cells in cases with positive anti-goblet cell antibodies ^{35, 36}. In the current study, we did not observe any association between the clinical course, intestinal histology and the type of gut epithelial cell antibodies. The causative role of these antibodies

have been questioned as they have been reported to appear after the onset of intestinal mucosal injury and disappear before the return to a normal mucosa³⁷. Follow-up gut epithelial cell antibody testing was not done in our patients to corroborate these findings. Nevertheless, GECA offer a useful diagnostic tool in cases with protracted diarrhea and malabsorption.

Histologically both CVID and celiac disease are characterized by crypt hyperplastic villous atrophy^{38, 39} that grossly resembles AIE. However, CVID is characterized by absence of plasma cells in the intestinal biopsy specimens and on the other hand AIE may show an increase in the lamina propria plasma cells^{38, 40}. Similarly, in most cases AIE can be distinguished from celiac sprue by the lack of any significant IELs (defined as > 40 IEL per 100 epithelial cells)^{41, 42}. However, in the current study, only about half of the cases (n = 8) had histologic features characteristic of AIE, including minimal IELs, dense lamina propria inflammation, and increased crypt apoptotic bodies. The remaining seven cases either showed mixed AIE and sprue-like histology or classic sprue-like histology with none of the features of AIE. It is possible that these CD like mucosal changes represent wide spectrum of histological abnormalities that could also be observed in AIE. However, results from our series suggest that these two conditions can coexist. Five out of the seven patients with either sprue-like or mixed histologic picture also had elevated IgA tTG antibodies compared to normal celiac serology in all those with classic AIE-like histology. Two of these five patients fulfilled all the criteria for CD including, celiac associated serology, histology and HLA type, with the exception of a lack of response to the strict GFD. Both these patients could be categorized as having refractory sprue^{43, 44}, defined by the lack of response to GFD, with concurrent AIE as evident by the presence of gut epithelial antibodies. In both cases immunohistochemical studies showed normal IEL phenotype, primarily CD3+ CD4+ lymphocytes, most of which were also positive for β F1. None of the two patients had aberrant clonal T-cell receptor gene re-arrangement studies which can be seen in majority of cases with refractory sprue^{45, 46}. This highlights the fact that superimposed AIE should be considered, while excluding CD associated malignant complications^{47, 48}, in cases that otherwise fulfill criteria for gluten-refractory enteropathy⁴. Testing for GECA can help confirm the diagnosis of AIE. Early initiation of immunosuppressive therapy in all such cases can reduce AIE associated morbidity and malabsorptive complications.

Diarrhea associated with AIE tends to be unremitting without aggressive immunosuppression. Large doses of steroids are often necessary to control active disease and some patients do not respond to this conventional treatment. In the current study, over half (60%) of the patients responded to steroid therapy. However, two thirds of these patients either became steroid-dependent or refractory and required additional immunomodulators for maintenance of remission. Only one patient remained in long term clinical remission (> 1 year) on low dose prednisone (5mg/day) without any additional immunosuppression. Infliximab was used in two cases with a rapid and complete resolution of symptoms. A similar experience has been reported by others⁴⁹. However, the uncontrolled nature of this study and relatively small sample size makes it difficult to compare different treatment regimens, and strong immunosuppressants like infliximab should only be used after thorough consideration of the risks versus benefits. Immunosuppressive medication can also induce cell mediated immune deficiency, which, when combined with humoral immune deficiency, can render patients highly susceptible to serious infections. Therefore, while instituting immunosuppressive treatment, we recommend a cautious approach and close monitoring especially in those with concomitant CVID.

Conclusions

Autoimmune enteropathy is a rare heterogeneous disease that should be considered in the differential diagnosis of malabsorption with small bowel villous atrophy. The presence of gut epithelial cell antibodies can help confirm the diagnosis of AIE. In most cases,

immunosuppression is needed for the induction and maintenance of remission. Others are encouraged to report their findings to promote a better understanding of this rare entity.

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Abbreviations used in this paper

AIE	autoimmune enteropathy
GECA	gut epithelial cell antibodies
CD	Celiac disease
AE	anti-enterocyte
AG	anti-goblet
tTG	tissue transglutaminase

Figure 1. Anti-enterocyte antibodies

Indirect immunofluorescence using the patient's serum on frozen section of normal human small bowel shows a linear fluorescence pattern along the brush border of the enterocytes ($\times 300$).

Figure 2. Anti-goblet cell antibodies
Immunofluorescence staining in the goblet cells mucus, sparing the enterocytes ($\times 100$)

Figure 3.

Histopathologic findings in a patient with autoimmune enteritis associated with anti-goblet cell antibodies. **(A)** Low-power view of the jejunum shows near-total villous atrophy and dense lymphoplasmacellular inflammation in the lamina propria. **(B)** At higher power, there is surface epithelial injury with disruption of the brush border (arrow) and intense neutrophilic inflammation including crypt abscesses (asterisk). There is no abnormal lymphocytosis in the surface epithelium.

Figure 4.

Histopathologic findings in a patient with anti-goblet cell antibodies and pan-gastrointestinal autoimmune disease. **(A)** Duodenal biopsy demonstrates moderate villous blunting and absence of goblet cells; there is no abnormal surface lymphocytosis. **(B)** Colonic biopsy with absent goblet cells, mild lymphocytosis in the deep crypt epithelium (arrow), and crypt apoptosis (arrowhead). **(C)** Gastric biopsy taken from the fundus demonstrates features of autoimmune atrophic gastritis, with complete absence of oxyntic glands and partial replacement by pseudo-pyloric metaplasia (arrow).

Figure 5.

Histopathologic features in overlap between autoimmune enteropathy and celiac disease. **(A)** The duodenal biopsy shows near-total villous blunting with crypt architectural distortion including crypt branching (arrow) and crypt destruction (arrowhead), both unusual features of “pure” celiac disease. **(B)** At high power, there is intense surface intraepithelial lymphocytosis typical for celiac disease, but there is also neutrophilic cryptitis (arrow) and scattered neutrophils in the surface epithelium. This patient had positive anti-enterocyte antibodies, HLA type DQ2, and a weakly positive IgA tissue-transglutaminase antibody.

Table 1
Summary of Clinical Characteristics of Study Population

Patient Characteristics	Data (N = 15)
Median age at diagnosis in yrs. (IQR)	55 (42 – 67)
Median duration of symptom in yrs. prior to AIE diagnosis (IQR)	1.5 (1 – 4.5)
Male (%)	8 (53)
Median follow-up in yrs. (IQR)	2 (1 – 4.8)
GECA (%) (Table 3)	13 (87)
Other autoantibodies (Table 2)	10 (67)
tTG positive (%)	5 (33)
Associated autoimmune disorders (%) (Table 2)	13 (87)

IQR: Interquartile range (25th – 75th percentile), AIE: Autoimmune enteropathy

GECA: gut epithelial cell antibodies (anti-enterocyte antibodies and/or anti-goblet cell antibodies).

tTG: Tissue transglutaminase antibodies

Table 2

Clinical Characteristics of 15 Adult Patients with Autoimmune Enteropathy

No.	Age at Dx. (yrs)	Sex	Gut epithelial Antibodies	Other Auto-Antibodies	Gluten sensitivity Antibodies		Associated Disorders	Celiac associated HLA	Duration of Sx. Prior to Dx (months)	Histologic Features
					tTG	Anti-gliadin				
1	37	M	AE IgG +	ANA	—	—	PI	—	13	AIE-like
2	75	M	AE IgG + and AG IgG +	AchR Ab, Striated muscle Ab, anti-GAD65 Ab	—	—	MG, thymoma, AIM, AGE	—	8	AIE-like
3	46	F	AG IgG +		—	—	Psoriatic arthritis	—	15	AIE-like
4	42	F	AG IgG +		—	+	Atopic dermatitis, AGE	—	204	AIE-like
5	38	F	AG IgG +	Parietal cell Ab	—	+	PI, AGE	—	180	AIE-like
6	76	F	AE IgG +	ANA	—	—		+	5	AIE-like
7	55	M	Negative		—	—	HG, ↓ IgG, ↓ IgM	—	4	AIE-like
8	40	M	AE IgM +	ANA	—	—	CVID, AC	—	32	AIE-like
9	54	M	AG IgG +		—	—	PHGG	—	120	Sprue-like
10	67	M	AE IgA +		+	+	SS, RA, RP, RS, LC	—	36	Sprue-like
11	45	F	AE IgG +, AG IgG +	Anti-SSA, anti-phospholipid antibody	+	+		+	10	Sprue-like

No.	Age at Dx. (yrs)	Sex	Gut epithelial Abs	Other Auto-Abs	Gluten sensitivity Antibodies		Associated Disorders	Celiac associated HLA	Duration of Sx. Prior to Dx (months)	Histologic Features
					tTG	Anti-gliadin				
12	59	M	AE IgG +	ANA	—	—	AGE	—	18	Mixed (AIE + Sprue)
13	75	M	Not checked	ASCA	+	+	PHGG, AGE	—	13	Mixed (AIE + Sprue)
14	61	F	AE IgG +	p-ANCA, ANA	+	—	Hypothyroidism, RS	+	12	Mixed (AIE + Sprue)
15	59	F	AE IgG +	ANA	+	+	LC, hypothyroid	—	360	Sprue-like *

AchR: acetylcholine receptor; Ab: Antibodies; AC: Autoimmune colopathy; AE: Antienterocyte antibodies; AG: Antigoblet cell antibodies; AGE: Autoimmune gastroenterocolitis; AIE: Autoimmune enteropathy; AIM: Autoimmune inflammatory myopathy; ASCA: Anti-saccharomyces cerevisiae antibodies; ANA: antinuclear antibody; CVID: Common Variable Immune Deficiency; Dx: Diagnosis; GAD: Glutamic acid dehydrogenase; HG: Hypogammaglobulinemia; IFX: Infliximab; LC: Lymphocytic colitis; MG: Myasthenia gravis; 6-MP: 6-Mercaptopurine; PHGG: Polyclonal hypergammaglobulinemia; PI: Pancreatic insufficiency (documented by pancreatic function testing); p-ANCA: Perinuclear neutrophil cytoplasmic antibody; RA: Rheumatoid arthritis; RP: Raynaud's phenomenon; RS: Refractory sprue; SS: Sjogren's syndrome; Sx: symptoms; tTG: Tissue transglutaminase antibodies

* Pathology not reviewed by SCA, previously reviewed pathology report consistent with celiac sprue.

Table 3**Gut Epithelial Cell Autoantibodies (GECA)**

GECA	No. (%)
Anti-enterocyte IgG antibodies	5 (33)
Anti-enterocyte IgM antibodies	1 (7)
Anti-enterocyte IgA antibodies	1 (7)
Anti-goblet cell IgG antibodies	4 (27)
Anti-enterocyte IgG plus anti-goblet cell IgG antibodies	2 (13)
Total	13 (87)

Table 4
Treatment Regimens and Outcome in 15 Patients with Autoimmune Enteropathy

No	Gender	Age at Dx.	Drug in mg/day (mo received)	Response to Immunosuppressants	F/U in yrs*
1	M	37	P 30 (5), IV P 50 (2), IV P 25 (14), B 9 (2), AZA (2), 6-MP 75 (13), IFX (4)	Responsive to IFX	2
2	M	75	P 40 taper (4), P 20 (11), AZA (2)	Responsive to high dose P, AZA	1.6
3	F	46	P 40 taper (2), P10 (4)	Responsive to high dose P	2
4	F	42	B 9 (3) followed by P 20 (4)	Responsive to P	17
5	F	38	P 40 taper (12), B 9 (6), AZA (2)	Responsive to P, B, AZA	13.7
6	F	76	IV P 40 (0.5)	Unresponsive	0.5
7	M	55	P 40 taper (1.3)	Responsive to P	0.5
8	M	40	P 30 taper (2), P 5 (10), AZA (3), IVIG (12)	Partial response to P, AZA	3.8
9	M	54	P 40 taper (12), 6-MP (48)	Partial response to P, 6-MP	4.8
10	M	67	P 10 (4), P 5 (10)	Responsive to P	3.5
11	F	45	P 30 (13), B 9 (3)	Responsive to high dose P, B	1
12	M	59	P 40 taper (3), P 30 (2), CsA (0.5), T (2), AZA (1), IFX (1)	Responsive to high dose P, AZA and IFX	1
13	M	75	M (1)	Immunosuppressants not used	1.2
14	F	61	B 3 (24), AZA (1)	Partial response to B	35
15	F	59	P 60 taper (6), B 9 (0.5)	Unresponsive	2

AZA= Azathioprine 2- 2.5 mg/kg, B= Budesonide, CsA= Cyclosporine 100 mg BID, IVIG= IV Immunoglobulin, IFX= Infliximab 5 mg/kg (0, 2, 6 wk and then every 8 wk) P=Prednisone, IV P= Methylprednisolone sodium succinate, M= Metronidazole 500 mg TID, 6-MP= 6- Mercaptopurine 1- 1.5 mg/kg daily, T= Tacrolimus 4mg BID, Dx= diagnosis

* Length of follow-up from onset of symptoms to date of last clinical contact.

Table 5
Summary of 11 Adult Autoimmune Enteropathy Cases Reported in the Literature

Age/ Sex [Ref.]	Anti- enterocyte antibodies	Other Autoantibodies	Associated autoimmunity	HLA typing	Treatment	Outcome
38/F ¹⁵ 47/F ¹⁵	+	-- Antimicrosomal Ab, AP Ab	-- --	DQ2+ DQ2+	P 50 mg/d P 40mg/d	Steroid responsive Steroid responsive
59/M ²⁰ 52/M ¹⁹ 48/F ¹⁹ 58/F ¹⁷	Not checked + - -	Anti-intrinsic factor Ab -- -- ANA, antimicrosomal Ab, AT Ab, antigliadin IgG Ab, AP Ab ANA, p-ANCA	Atrophic gastritis, colitis Concurrent Thymoma Post-thymoma resection Thyroiditis, Sicca syndrome, polyneuropathy, Lymphocytic gastritis --	ND ND ND ND	P 40mg/d Thymectomy IVIG, TPN P 60 mg/d, cyclophosphamide 50 mg/d P 50 mg/d, cyclosporine 250 mg IV, tacrolimus 4mg bid (5µg/l) P 0.5mg/kg, budesonide 3mg/d	Steroid responsive Improved after thymectomy No response to IVIG and TPN No response to steroids and cyclophosphamide Responsive to high dose IV steroids, IV cyclosporine and oral tacrolimus Responsive to steroids
54/M ⁶ 50/F ¹⁸	+	Antigliadin IgG Ab	Food intolerance, colitis, HCV	DQ2-		
Age/Sex [Ref.]	Anti-enterocyte antibodies	Other Autoantibodies	Associated autoimmunity	HLA typing	Treatment	Outcome
39/F ¹⁴ 58/M ⁵⁴ 21/M ²¹	+	Antimicrosomal Ab, AT Ab AP Ab, AT Ab, thyroid peroxidase Ab ANA, RF	ITP, PSC, immune deficiency, atrophic gastritis, colitis AIH, hypothyroidism, ED	ND DQ2+ ND	IVIG, P 50 mg/d Cyclosporine TPN, P	Responsive to IVIG and steroids Responsive to cyclosporine Responsive to prednisone

Ab: antibodies, AIH: Autoimmune hemolytic anemia, ANA: antinuclear antibody, AT: antithyroglobulin AP: Antiparietal cell, ED: Exfoliative dermatitis, IVIG: IV immunoglobulins, ITP: Idiopathic thrombocytopenic purpura, HCV: hepatitis C virus, ND: Not done, p-ANCA: Perinuclear neutrophil cytoplasmic antibody, P: Prednisone, PSC: Primary sclerosing cholangitis, RF: Rheumatoid factor, RP: Raynaud's phenomenon, TPN: Total parenteral nutrition

Table 6
Proposed Diagnostic Criteria for Adult Autoimmune Enteropathy

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Major Criteria:

- 1 Adult-onset chronic diarrhea (> 6 weeks duration)
  - 2 Malabsorption
  - 3 Specific small bowel histology;
    - a. Partial/complete villous blunting
    - b. Deep crypt lymphocytosis
    - c. Increased crypt apoptotic bodies
    - d. Minimal intra-epithelial lymphocytosis
  - 4 Exclusion of other causes of villous atrophy including celiac disease, refractory sprue and intestinal lymphoma.
  - 5 Anti-enterocyte and/or anti-goblet cell antibodies
-

Criteria 1–4 are required for a definite diagnosis of AIE. Presence of anti-enterocyte and/or anti-goblet cell antibodies is an important diagnostic support but their absence does not exclude the diagnosis of AIE.