Adult-Onset Autoimmune Enteropathy in an European Tertiary Referral Center

Roy L.J. van Wanrooij, MD, PhD[1], E. Andra Neefjes-Borst, MD[2], Hetty J. Bontkes, PhD[3], Marco W.J. Schreurs, PhD[4], Anton W. Langerak, PhD[4], Chris J.J. Mulder, MD, PhD[1] and Gerd Bouma, MD, PhD[1]

INTRODUCTION: **Adult-onset autoimmune enteropathy (AIE) is a rare cause of severe chronic diarrhea because of small intestinal villous atrophy. We report on patients with adult-onset AIE in an European referral center.**

METHODS: **Retrospective study including patients diagnosed with AIE in the Amsterdam UMC, location VUmc, between January 2003 and December 2019. Clinical, serological, and histological features and response to treatment were reported. The specificity of antienterocyte antibodies (AEA) was evaluated by examining the prevalence of AEA in (i) controls (n = 30) and in patients with (ii) AIE (n = 13), (iii) celiac disease (CD, n = 52), (iv) refractory celiac disease type 2 (n = 18), and (v) enteropathy-associated T-cell lymphoma (EATL, n = 10).**

RESULTS: **Thirteen AIE patients were included, 8 women (62%), median age of 52 years (range 23–73), and 6 (46%) with an autoimmune disease. AEA were observed in 11 cases (85%), but were also found in CD (7.7%), refractory celiac disease type 2 (16.7%), and EATL (20%). Ten patients (77%) were human leukocyte antigen DQ2.5 heterozygous. Total parenteral nutrition was required in 8 cases (62%). Steroids induced clinical remission in 8 cases (62%). Step-up therapy with rituximab, cyclosporine, infliximab, and cladribine in steroid-refractory patients was only moderately effective. Four patients died (31%), but 4 (31%) others are in long-term drug-free remission after receiving immunosuppressive treatment, including 1 patient who underwent autologous stem cell transplantation.**

DISCUSSION: **Adult-onset AIE is a rare but severe enteropathy that occurs in patients susceptible for autoimmune disease. Four patients (31%) died secondary to therapy-refractory malabsorption, while immunosuppressive therapy leads to a long-lasting drug-free remission in one-third of patients.**

Clinical and Translational Gastroenterology 2021;12:e00387. https://doi.org/10.14309/ctg.0000000000000387

INTRODUCTION

Autoimmune enteropathy (AIE) is a rare cause of chronic diarrhea because of small intestinal villous atrophy. AIE was first identified in infants as hallmark of the Immunodysregulation Polyendocrinopathy Enteropathy X-linked (IPEX) syndrome that manifests at an early age and carries a poor prognosis (1). Unsworth and Walker-Smith postulated the following criteria for AIE in children: (i) severe malabsorption not responding to dietary restrictions, (ii) anti-enterocyte antibodies (AEA) and/or associated autoimmune conditions, and (iii) absence of immunodeficiency (2). In 1997, it was recognized that AIE can also occur in adults (3). Since then, it has been recognized that immunodeficiency syndromes (hypogammaglobulinemia and common variable immunodeficiency disorder [CVID]) and certain medications (sartans, nonsteroidal anti-inflammatory drugs, and mycophenolate) can mimic clinical, serological, and histological features of adult-onset AIE (4). Reports on classical adult-onset AIE, without any known triggers, only entail case reports or small case series with 1 larger case series by the Mayo Clinic that included 30 patients (5). This group postulated refined criteria for adult AIE, implying that characteristic histological findings and absence of other causes for villous atrophy are additional major criteria for the diagnosis of AIE, while presence of gut-specific antibodies is no longer required for the diagnosis (6). Nevertheless, reported histological findings in AIE remained heterogenic, and recently, a subdivision has been proposed based on 4 histologic patterns (7). The most common histologic pattern is that of an active chronic enteritis which is characterized by villous blunting with a mixed inflammatory infiltrate in the lamina propria, often with cryptitis and crypt abscesses but rarely with

[1]Department of Gastroenterology and Hepatology, Amsterdam UMC, Vrije Universiteit Amsterdam, AGEM Institute, Amsterdam, the Netherlands; [2]Department of Pathology, Amsterdam UMC, Amsterdam, the Netherlands; [3]Laboratory Medical Immunology, Department of Clinical Chemistry, Amsterdam UMC, AGEM Research Institute, AI & I Institute, Amsterdam, the Netherlands; [4]Laboratory Medical Immunology, Department of Immunology, Erasmus MC, University Medical Center, Rotterdam, the Netherlands. **Correspondence:** Roy L.J. van Wanrooij, MD, PhD. E-mail: rl.vanwanrooij@amsterdamumc.nl.

Received February 2, 2021; accepted June 28, 2021; published online August 1, 2021

prominent epithelial apoptosis or intraepithelial lymphocytosis (7). The celiac disease (CD)-like pattern was observed in 20% of AIE patients while the remainder of patients displayed a graft-vs-host disease (GvHD)-like pattern or a mixed-type pattern (8). In clinical practice, the diagnosis of AIE, therefore, remains a challenge, given the considerable overlap with other immune-mediated enteropathies such as CD, olmesartan-associated enteropathy, CVID, and refractory CD (RCD) (9).

Here, we report on 13 patients diagnosed with adult-onset AIE in an European referral center and evaluate the value of AEA in the diagnosis of AIE.

METHODS

Patient selection and diagnostic workup

All patients diagnosed with AIE at the Amsterdam UMC, location VUmc, between January 2006 and December 2019 were included in this study. AIE was defined according to the previously described Akram criteria (6). All patients presenting at our clinic underwent standardized diagnostic workup, as described in detail previously (10). In short, medical history, symptoms, and medication history were retrieved from the medical records. Recent use of angiotensin II inhibitors (e.g., olmesartan) and mycophenolate was an exclusion criterion. HLA genotype and serum autoantibodies were determined (see below). Serum immunoglobulin levels IgA, IgM, and IgG were measured. Duodenal biopsies were collected during upper endoscopy, and histological features were evaluated by an experienced pathologist (EANB), and in addition, phenotypical analysis of intraepithelial lymphocytes and T-cell receptor (TCR)-gamma rearrangement studies were performed. Colonoscopy, capsule endoscopy, and abdominal imaging were performed on indication.

As control cohorts, 30 controls and patients with CD (n = 52), RCD type 2 (n = 18), or enteropathy-associated T-cell lymphoma (EATL) (n = 10) were included. Controls were adult patients presenting with abdominal symptoms and who were diagnosed with either dyspepsia or irritable bowel syndrome. All patients tested negative for anti-tissue transglutaminase antibody (TGA), and duodenal biopsies taken during upper gastrointestinal endoscopy were without abnormalities. Controls were not matched to the study group. AEA were determined at time of diagnosis of RCD or EATL. CD diagnosis was based on presence of TGA, Marsh >2, and an HLA-DQ2.2, -DQ2.5, or -DQ8 genotype. RCD type 2 was defined as a lack of response to a strict gluten-free diet (GFD) in CD patients with duodenal histologic abnormalities (Marsh III) and an increased percentage of intraepithelial lymphocytes (IELs) with an aberrant surface$CD3^-$cytoplasmatic$CD3^+CD7^+$ phenotype (>20% of total IELs) (11). Patients with EATL all presented with EATL and concomitant CD that was previously unrecognized.

Histological analysis

An expert pathologist evaluated all slides according to a standardized protocol. Biopsies were scored for the presence of inflammation (active and chronic), IEL count, villous atrophy, goblet cells, Paneth cells, apoptotic bodies, and plasma cells (to evaluate CVID). Furthermore, histological patterns were classified as one of the 4 currently recognized histological phenotypes of AIE which include active chronic enteritis (type 1), CD-like (type 2), GvHD-like (type 3), and mixed-type (type 4) (7).

Autoantibody testing and human leukocyte antibody genotyping

For human leukocyte antibody (HLA) genotyping, whole blood was obtained for typing of HLA-DQA1* and DQB1* alleles, performed with a combined single-stranded conformation polymorphism/heteroduplex method by a semiautomated electrophoresis and gel staining method on the Phastsystem (Amersham Pharmacia-Biotech, Sweden). For IgA and IgG AEA testing, both a direct and indirect immunofluorescence analysis using patient's serum on cryostat sections of normal human small bowel was performed. Slides were assessed by 2 independent technicians. IgG against the AIE-associated antigen AIE-75 was tested by the radioimmunoprecipitation in the Volkmann laboratory, in Karlsruhe, Germany. Furthermore, antibodies against TGA, thyroid peroxidase, and thyroglobulin were analyzed using enzyme-linked immunosorbent assay assays (Thermo Fisher Scientific, Uppsala, Sweden) on a Phadia 250 analyser (Thermo Fisher Scientific) according to the manufacturer's protocol. Other autoantibodies such as endomysium, goblet cell (AGCA), smooth muscle tissue, parietal cell (PCA), neutrophil cytoplasmic antigen, and nuclear antigen were analyzed by the indirect immunofluorescence test using in house-prepared substrate slides, with the exception of nuclear antigen antibodies for which a kit was used.

Intestinal fatty acid–binding protein

Intestinal fatty acid–binding protein (I-FABP) serum levels of AIE patients were compared with levels reported in controls and patients with RCD type 2 who we previously reported (12). I-FABP levels were measured using a commercial enzyme-linked immunosorbent assay kit (Hycult Biotech, Wayne, PA) according to the manufacturer's specifications.

Phenotypical and TCR-gamma clonality analysis of intraepithelial lymphocytes

IELs were isolated and analyzed as previously described (13). The epithelial layer was separated using dithiothreitol (DTT) (Fluka BioChemika, Buchs, Switzerland) and ethylenediaminetetraacetic acid (Merck, Darmstadt, Germany). Surface marker expression was evaluated using monoclonal antibodies directed against CD3, CD4, CD7, CD8, CD16 + 56, CD19, CD30, CD45 (all from BD Biosciences, San Jose, CA), and CD52 (Serotec, Düsseldorf, Germany). Cytoplasmic staining of CD3 was performed after cell permeabilization by Cytofix/CytoPerm Plus (BD Biosciences). Stained cells were analyzed on a standard 4-color flow cytometer (FACSCalibur, BD Biosciences). TCR-gamma (TCRG) chain gene rearrangements were analyzed in duplo on whole cryopreserved biopsy specimens. DNA was extracted using proteinase-K digestion and ethanol precipitation and subsequently analyzed by multiplex polymerase chain reaction amplification, using primers described by the BIOMED-2 consortium.

Treatment and follow-up

Per patient, the treatment regime was noted, and the patient was followed until December 2019 or death.

Statistical analyses

For comparing serum levels of I-FABP between patients with AIE, RCD type 2, EATL, and controls, Kruskal–Wallis 1-way analysis of variance was performed, and a P value < 0.05 was considered statistically significant.

Table 1. Patient characteristics

Case	Sex	Age	Time onset of symptoms to diagnosis	Presentation	Medical history	HLA genotype	Gut-associated antibodies	AIE-75kd	Other autoimmune antibodies
1	F	23	<1 mo	Profuse diarrhea and weight loss	Juvenile rheumathoid arthritis	DQ2.5 heterozygous	IgA, IgG (BB) AEA	+	—
2	F	63	<1 mo	Profuse diarrhea and weight loss	—	DQ2-8 negative	IgA (Cyt) AEA	—	SMA and PCA
3	F	36	7 mo	Profuse diarrhea and weight loss	COPD and deep venous thrombosis	DQ2.5 heterozygous	IgA (BB, Cyt) AEA	—	ANA
4	F	40	4 mo	Profuse diarrhea and weight loss	Type 2 diabetes mellitus	DQ2.5 heterozygous	—	n.p.	TPO
5	M	67	6 mo	Profuse diarrhea and weight loss	Hypothyroidism	DQ2.5 heterozygous	IgA (BB) AEA	—	PCA and TGab
6	M	52	2.5 yr	Profuse diarrhea and weight loss	—	DQ2.5 heterozygous	IgA, IgG (BB) AEA	—	SMA
7	M	57	3 mo	Profuse diarrhea and weight loss	—	DQ2-8 negative	IgG (BB) AEA	+	ANA and pANCA
8	M	73	2 yr	Weight loss	Appendectomy	DQ8 heterozygous	IgG (BB, Cyt) AEA	—	ANA and pANCA
9	M	59	2 mo	Profuse diarrhea and weight loss	Celiac disease	DQ2.5/8 heterozygous	IgA (Cyt) AEA	—	PCA
10	F	30	3 mo	Profuse diarrhea and weight loss	Celiac disease	DQ2.5 heterozygous	IgA, IgG (BB, Cyt) AEA	+	ANA and SMA
11	F	52	2 yr	Profuse diarrhea and weight loss	Larsen syndrome and appendectomy	DQ8 heterozygous	IgA AGA	n.p.	—
12	F	36	20 yr	Profuse diarrhea	Type 1 diabetes mellitus, cholecystectomy, and atrophic gastritis	DQ2.5 heterozygous	IgA AGA	n.p.	PCA
13	F	39	<1 mo	Profuse diarrhea and weight loss	Hypothyroidism, asthma, and chronic myelocytic leukemia	DQ2.5 heterozygous	IgA, IgG (BB) AEA	+	PCA

AEA, anti-enterocyte antibodies; AGA, anti-goblet cell antibodies; AIE, autoimmune enteropathy; AIE-75, autoimmune enteropathy–related 75-kilodalton antigen; ANA, antinuclear antibody; BB, brush border; Cyt, cytoplasmic; F, female; HLA, human leukocyte antigen; M, male; pANCA, perinuclear anti-neutrophil cytoplasmic antibodies; PCA, anti-parietal cell antibodies; SMA, anti-smooth muscle antibodies; TPO, anti-thyroid peroxidase antibodies; TGab, anti-thyroglobulin antibodies.

Ethical approval

The study protocol was approved by the Medical Ethics Committees from the Amsterdam UMC, location VUmc, Amsterdam, the Netherlands.

RESULTS

Patient characteristics at presentation

Thirteen patients fulfilled the criteria for the diagnosis AIE. All were whites, 8 were women (62%), and the median age at diagnosis was 52 years, with a wide range from 23 to 73 years (Table 1). All patients presented with profuse diarrhea (5–20 times per day) with a median time interval of 3 months (range 1 month–20 years) between onset of symptoms and time of diagnosis. Median stool production was 850 g per 24 hours (range: 130–4,000 g) with significant loss of fat (median: 47 g/24 hours; range 36–130 g/24 hours). Diarrhea resulted in hypokalemia requiring intravenous suppletion in 9 patients (69%). The median self-reported weight loss at time of AIE diagnosis was 15 kg (range: 3–25 kg). Hypoalbuminemia was present in all patients with a median serum albumin concentration of 26 g/L (range: 13–31 g/L). Abdominal discomfort was commonly reported (77%), but was consistently rated as mild.

AEA

In 10 of 13 patients (77%), AEA were found: 4 were positive for both IgA and IgG antibodies, 4 were positive only for IgA antibodies, and 2 were positive only for IgG antibodies (Table 1). Previously, a 75-kDA protein (referred to as AIE-75) has been identified as an antigen for AEA found in AIE patients (14). AIE-75 participates in tight-junction integrity, and anti-AIE-75 antibodies are believed to hamper the intestinal permeability, which may precipitate inflammatory enteropathy (15,16). On indirect immunofluorescence AEA were found in the intestinal brush border (n = 5), in the enterocyte's cytoplasm (n = 2), or in both (n = 3), see Figure 1. In our cohort, anti-AIE-75 antibodies were found in 4 of 10 (40%) patients tested, and in these patients, AEA

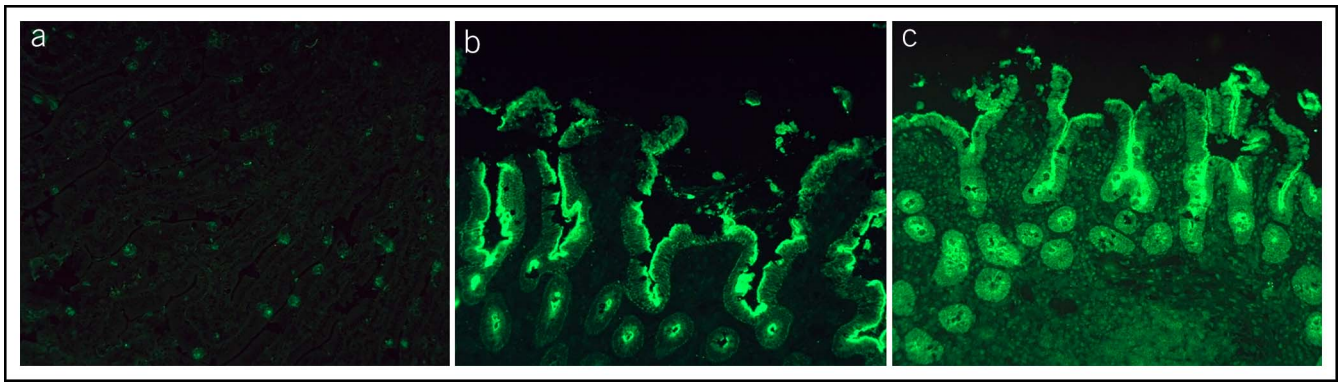

Figure 1. Indirect immunofluorescence for IgA and IgG AEA. Immunofluorescence analysis of IgG AEA on normal human small intestine. No expression is present in a control (**a**), while in (**b**), the intestinal brush border abundantly expresses IgG AEA, and in (**c**), IgA AEA is expressed in both the intestinal brush border as well as intracellular. AEA, antienterocyte antibodies.

were located in the brush border. In the other 60%, the specific autoantigen was unidentified. There was no correlation between the AEA titer nor the location of the AEA (brush border vs cytoplasm) and the severity of histological inflammation or villous atrophy, but numbers are likely too small to detect such a correlation. After onset of treatment, AEA titers often decreased or became negative; yet, this appears independent of clinical or histologic responses. Two patients with histological abnormalities corresponding with AIE lacked AEA but instead AGCA were found. None of the patients with AEA additionally displayed anti-goblet cell antibodies. In 1 case (case 5) with duodenal histologic abnormalities concomitant with AIE, neither AEA nor AGCA were found at all.

With the goal to evaluate the clinical specificity of AEA, we performed additional tests in controls and patients with uncomplicated and complicated (RCD type 2, EATL) celiac disease. AEA were absent in 30 controls (0%), but could be detected in patients with CD4/52 (7.7%), type 2 RCD 3/18 (16.7%), and EATL 2/10 (20%).

I-FABP

I-FABP is a protein present in the cytosol of enterocytes and is released into the serum after intestinal damage. Indeed, I-FABP serum levels correlated with the severity of intestinal damage in CD patients (17). With the aim to compare the extent of intestinal damage, serum I-FBAP levels in the group of AIE patients were measured and compared with the levels that we have previously reported in controls and RCD type 2 (Table 2) (12). I-FABP levels in the serum of AIE patients were significantly higher (1,150 [45–2,650] pg/mL: $P < 0.05$) than the levels in controls (229 [85–1,338] pg/mL), but similar to those in RCD type 2 patients (870 [106–2,234] pg/mL) (12).

Duodenal histology

Total villous atrophy was seen in 11/13 cases (Table 3). Six of those 11 cases showed clear intraepithelial lymphocytosis (>40 IELs/100 enterocytes), whereas in 4 cases, a mild increase of IELs (>30 < 40 IELs per 100 enterocytes) was found. In only 1 of 11 cases (case 8), no intraepithelial lymphocytosis was seen. In this group with total villous atrophy, 8 cases showed active and chronic inflammation, whereas in 3, only chronic inflammation was observed. In 6 cases, goblet cells were reduced or absent, and of those, 4 Paneth cells were affected as well. On the contrary, Paneth cell depletion always co-occurred with goblet cell depletion. Furthermore, apoptotic bodies were found in 8 cases, including 3 cases with normal goblet cells and Paneth cells. Vice versa, 2 cases presented with impaired numbers of goblet cells but without apoptotic bodies.

Remarkably, in 2 cases (case 5 and 12) presenting with severe steatorrhea, weight loss, and AEA or AGCA, no villous atrophy could be observed in the duodenal biopsies. Nonetheless, other histologic features of AIE were present in these patients: In case 12, apoptotic bodies were found in absence of goblet and Paneth cells, while case 5 showed active and chronic enteritis. Also, I-FABP levels in these patients were elevated implying pathological enterocyte damage. Both patients responded to immunosuppressive treatment which further supports the notion that the enteropathy was indeed immune mediated.

Table 2. Intraepithelial lymphocyte populations in AIE

	Intraepithelial lymphocyte phenotype								
Case	% CD3	% CD8	% CD4	% NK cell	% B cell	% γδ T cell	% Ab	TCR-gamma clonality	iFABP pg/mL
1	83	64	24	6	1	6	3	Polyclonal	45
2	92	31	56	5	1	10	4	Polyclonal	95
3	95	89	8	3	0	1	3	Monoclonal	1,720
4	98	85	14	1	1	7	1	Polyclonal	2,200
5	67	56	9	11	0	3	12	Monoclonal	1,150
6	95	87	8	0	4	0	0	Polyclonal	1,250
7	95	83	11	2	2	1	1	Polyclonal	947
8	97	60	40	1	2	1	1	Polyclonal	1,030
9	69	31	38	26	2	1	5	Monoclonal	1,760
10	93	83	6	5	2	9	5	Monoclonal	126
11	98	85	15	1	0	1	2	Polyclonal	563
12	94	82	12	1	0	0	0	Polyclonal	2,650
13	98	85	14	1	1	7	1	Monoclonal	2,490

AIE, autoimmune enteropathy; Ab, aberrant phenotype; iFABP, intestinal fatty acid-binding protein; TCR, T-cell receptor.

Table 3. Histological findings in patients with AIE

Case	Villous atrophy	IEL count/100 enterocytes	Goblet cells	Paneth cells	Apoptotic bodies	Inflammation	Histological classification	Stomach	Colon
1	Complete	>40	-	0	0	Active and chronic	Type 1	0	0
2	Complete	>40	0	0	++	Chronic	Type 2	0	0
3	Complete	>40	–	–	0	Active and chronic	Type 1	0	Chronic active colitis
4	Complete	>40/	–	-	++	Active and chronic	Type 1	0	np
5	None	<30	0	0	0	Active and chronic	Type 1	0	0
6	Complete	>30 < 40	-	0	++	Active and chronic	Type 1	0	0
7	Complete	>30 < 40	–	-	++	Active and chronic	Type 1	0	0
8	Complete	<30	0	0	+	Chronic	Type 3	0	np
9	Complete	>40	0	0	++	Active and chronic	Type 1	0	np
10	Complete	>40	0	0	++	Active and chronic	Type 1	0	0
11	Complete	>30 < 40	–	-	+	Chronic	Type 2	AIG	Chronic active colitis
12	None	<30	–	–	+	None	Type 3	AIG	0
13	Complete	>30 < 40	0	0	0	Chronic	Type 2	FLG	0

++: severe increase, +: modest increase, 0: normal, –: modest decrease, and –: absent.
AIE, autoimmune enteropathy; AIG, autoimmune gastritis; FLG, focal lymphocytic gastritis; np, not performed.
Histological classification of AIE according to Umetsu et al. (7) type 1: active chronic enteritis, type 2: celiac disease–like, type 3: graft-vs-host disease–like, and type 4: mixed/no predominant pattern.

Using the histology-based classification, the majority of patients (8/13 62%) was classified as active chronic enteritis (type 1), 3 (23%) as CD-like (type 2), and 2 (15%) as GvHD-like (type 3) (7).

Phenotype of intraepithelial lymphocytes

The epithelial T-cell infiltrate was dominated by $CD8^+$ IELs over $CD4^+$ IELs in 11 of 13 patients, which is also seen in normal duodenum and in CD. In the 2 other patients, the $CD4^+$ T-cell population was slightly larger than the $CD8^+$ T-cell population (CD4/CD8 ratio 1.1–2.8). The γδ-IEL population is commonly increased in CD, with the γδ-IELs making up over 14% of total IELs in most CD patients. However, none of the AIE patients, including the 2 patients who were diagnosed previously with CD, was such an upregulation noted (18). Another relevant IEL subset are those IELs with an aberrant phenotype ($surfaceCD3^+cytoplasmaticCD3^-$ $CD7^-$ $CD45^+$) considered a premalignant cell population and characteristic for RCD type 2, but again, no significant expansion was observed in any of the AIE patients (19).

TCRG clonality analysis

TCRG rearrangement studies were performed in all 13 patients. In 5 (38%) patients, a monoclonal rearrangement pattern was found, while the pattern was polyclonal in the other 8 (62%) patients.

Involvement of the gastrointestinal tract

Extent of involvement of the gastrointestinal tract was evaluated in all patients by gastroduodenoscopy and colonoscopy, while 7 patients also underwent capsule endoscopy of the small intestine. No macroscopic abnormalities were observed in the stomach in 10 patients, yet histologically, a nonspecific chronic inflammation was present in all cases. In addition, in 2 patients, histological signs of autoimmune gastritis with congruent PCA were found and in 1 patient focal lymphocytic gastritis. All patients had involvement of the proximal intestine, whereas the distal part was involved in 6 of 13 patients (based on endoscopic and histologic evaluation of the terminal ileum). Histological findings included villous atrophy, intraepithelial lymphocytosis, and goblet cell deficiency, which were identical to the duodenal pattern including the severity of the abnormalities. Finally, the colon was affected in 2 patients (case 3 and 11) in whom a mild-to-moderate colitis was observed.

Other autoimmune disease, autoimmune antibodies, and association with HLA-DQ2.5

Six patients (46%) were previously diagnosed with an autoimmune disease: 2 with CD, 2 with autoimmune thyroid disease, 1 with juvenile rheumatoid arthritis, and 1 with type 1 diabetes (Table 1). Further underlining the susceptibility to autoimmune

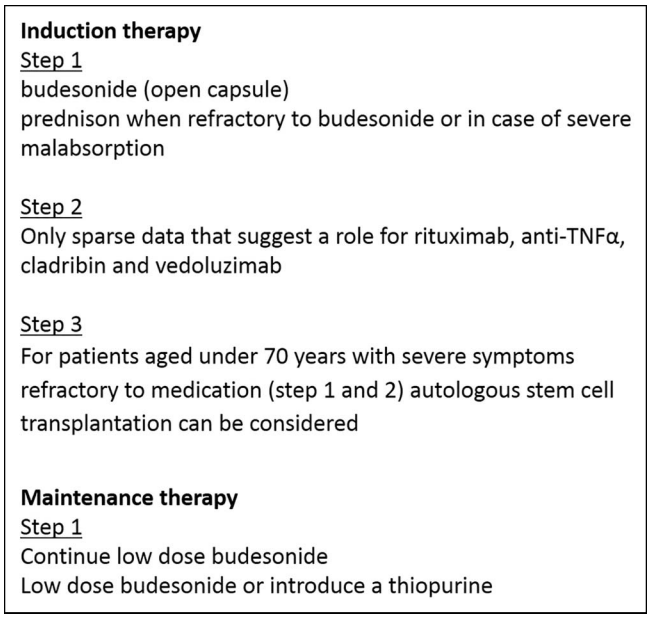

Figure 2. Proposed treatment algorithm adult-onset autoimmune enteropathy.

disease in these patients is the presence of 1 or more circulating autoantibodies, other than AEA, as found in 11 patients (85%). Most frequently found were PCA (5/13) including the 2 patients with autoimmune gastritis, antinuclear antibodies (4/13), and smooth muscle antibodies (3/13).

Two patients (cases 9 and 10) had been diagnosed with CD 2 and 20 years before the onset of AIE diagnosis. Both patients had high titers of TGA (>100 U/mL) at the time of diagnosis. One patient was HLA-DQ2.5 heterozygous, and the other carried both the HLA-DQ2.5 and -DQ8 haplotypes. They initially responded to a GFD, and at the time of reoccurrence of symptoms, transglutaminase antibodies were undetectable. Histology showed villous atrophy with active chronic enteritis as well as apoptotic bodies in both. No findings in support of RCD type 1 or type 2 were found, i.e., no increased counts of γδ-IELs nor IELs with an aberrant phenotype.

Remarkably, 9 of the 11 patients (82%) without a history of CD carried 1 of the CD-associated HLA genotypes: 7 were HLA-DQ2.5 heterozygous, and 2 were HLA-DQ8 heterozygous. TGA and anti-endomysium antibodies tested negative in all these patients at time of AIE diagnosis. Nevertheless, to exclude seronegative CD, all 11 patients underwent a trial with a GFD but without clinical effect.

Treatment and response

Median follow-up of patients since AIE diagnosis was 56 months (range: 13–148 months). Four patients have died since AIE diagnosis. Three patients died because of severe malnutrition and cachexia because they failed to respond to various treatment strategies, whereas 1 patient died because of the complications of chronic myelomonocytic leukemia unrelated to AIE.

Total parenteral nutrition was required in 8 cases (62%) to maintain adequate nutritional status, while enteral tube feeding was sufficient in 5 other cases. For induction of remission, all patients were initially treated with budesonide (n = 5) or prednisolone (n = 8). Ambulant patients were treated with 3 budesonide capsules 3 mg once a day. One capsule was taken normally, while 2 capsules were opened followed by grinding the content briefly with the teeth before swallowing, with the goal of delivering active drug metabolites in the proximal small intestine. Open capsule budesonide alleviated diarrhea in 60% of patients. Patients with more severe disease who required hospitalization received prednisolone therapy instead of budesonide with a clinical effect in 62%. Patients who failed on steroid therapy or were dependent on steroids because of recurrent disease received various second-line treatments including cyclosporine (n = 2), infliximab (n = 1), rituximab (n = 4), and cladribine (n = 3), and 1 therapy-refractory patient was eventually treated with autologous stem cell transplantation (autSCT) after high-dose chemotherapy. Rituximab, an anti-CD20 monoclonal antibody which directs against B cells, was administered in 4 patients (4 doses of 250 mg once a week) and was clinically effective in 2 patients (20,21). Three other patients were treated with intravenous cladribine (0.1 mg/kg in 2 hours for 5 days), a purine analog, which has proven to be effective in another severe enteropathy, namely RCD type 2 (22). Two patients failed to show a clinical response to this treatment, but 1 patient (case 6) who was steroid-dependent (30-mg prednisolone per day) for 4 years as treatment with infliximab, rituximab, and thiopurines failed went into steroid-free clinical remission lasting for over 3 years after 1 cycle of cladribine treatment. Cyclosporine (intravenous 2 mg/kg/d for 7 days, including therapeutic drug monitoring) and infliximab (intravenous 5 mg/kg on week 0, 2, and 6, hereafter every 8 weeks, including therapeutic drug monitoring) have shown promise in AIE, but in 3 patients in our series failed to induce a clinical effect (6,23–25). One patient (case 1) who failed on prednisolone, cladribine, cyclosporine, and tioguanin therapy and still suffered from severe malabsorption requiring total parenteral nutrition underwent autSCT with a cyclofosfamide and anti-thymocyte globulin regimen, analogous with the treatment of RCD type 2 (26). This patient recovered clinically with normalization of stool frequency and weight gain, in addition to complete recovery of the duodenal histology. Currently, the patient is in remission for 140 months.

For maintenance therapy in patients in clinical remission, thiopurines were the mainstay of treatment. Patients were treated with tioguanin (n = 6), mercaptopurin (n = 2), or azathioprine (n = 1). In 6 patients (67%), persistent remission, including normalization of stool frequency and consistency, >10% weight gain, and improvement of duodenal histology (according to the Mash criteria), was achieved with thiopurines. Two patients had to discontinue therapy at an early stage because of intolerance and acute pancreatitis, respectively. In 1 additional patient, tioguanin had to be discontinued after 13 months because of increased serum liver enzymes. In 3 of the 9 patients, the drug failed to maintain a clinical and histologic effect. The 2 patients who did not tolerate thiopurines therefore received budesonide maintenance treatment which proved clinically effective.

Noteworthy, 4 patients (31%) are in long-lasting drug-free remission. Case 1 is still in clinical remission 140 months after autSCT. Three others are in clinical remission without treatment for 28, 48, and 76 months, respectively, after receiving immunosuppressive treatment for 48, 50, and 90 months.

DISCUSSION

Here, we report on the experience of an European tertiary referral center where 13 patients were diagnosed with AIE over a 13-year

period. Diagnosis of AIE remains challenging as we show in this report because of the rarity and complexity of this disease.

Our case series is the second largest after the series reported by the Mayo Clinic that initially described 15 adult-onset AIE patients and more recently reported on a total of 30 patients (5,6). The authors report that AIE patients present with more severe diarrhea and malabsorption-related symptoms than patients with RCD type 1 (5). Our series underscores the severity of AIE because almost two-thirds of patients required total parenteral nutrition and 3 of the 13 (23%) died because of severe therapy-refractory malabsorption.

One of the challenges in the differential diagnosis of AIE is the resemblance with CD. In our group of AIE patients, the CD-related HLA-genotype HLA-DQ2.5 was strongly over-represented (79%). This is in contrast with the observation from the Mayo Clinic where the prevalence was similar to the general population (34% vs 35%) (5,6). Although considering the relatively small number of patients included in this study, the recently observed association of HLA-DQ2 with olmesartan-associated enteropathy draws attention to the role of HLA-DQ2 in immune-mediated enteropathies other than CD (27). Not only are AEA found in 30% of patients with olmesartan-associated enteropathy, but the histologic abnormalities observed in olmesartan-associated enteropathy can also mimic those in AIE (28,29).

In line with previous reports, AIE often occurred in patients with other autoimmune diseases, and circulating autoimmune antibodies were observed in most patients (6,30–32). These data support the suggestion that AIE is in fact a feature of a generalized hyperactive immune state (33). Reports of adult-onset AIE developing in patients with ulcerative colitis, autoimmune hepatitis, and rheumatoid arthritis further strengthen this hypothesis (34–36). The association with other immune-mediated enteropathies such as (refractory) CD is considered a clinical conundrum because differentiation among them is challenging (6). Our experience strongly suggests that both enteropathies can indeed coexist because 2 patients previously diagnosed with CD later became nonresponsive to a strict GFD and developed AEA and histologic abnormalities corresponding with AIE but not to RCD. Furthermore, differentiating AIE from CVID can be challenging, but in our series, CVID was excluded based on clinical presentation, serum immunoglobulin levels, and absence of plasma cells on duodenal histology (6).

Histologic analysis of the duodenum showed classical features of AIE such as absence of goblet and Paneth cells and or presence of increased numbers of apoptotic bodies in 11 of 13 cases (86%). According to the histological classification of AIE, the majority of patients (62%) were classified as "active chronic enteritis" pattern (type 1), indeed the most common histologic pattern seen in AIE (7). Underlining the heterogeneity in AIE is that the other cases corresponded with a CD-like (23%) or GVDH-like (15%). The majority (59%) of adults with immunodeficiency syndromes who develop an enteropathy display CD-like histological abnormalities, while active chronic enteritis seen in classical AIE is extremely rare in immunodeficiency syndromes which further underlines differences between these disease entities (37). Notably, in 2 patients, no villous atrophy was observed in the biopsies taken. Considering the severe malabsorption observed in these patients combined with other histologic features of AIE, high I-FABP serum levels and their response to immunosuppressive treatment strongly suggest an immune-mediated enteropathy as the cause of the malabsorption. The most likely reason that villous atrophy was not seen in their biopsies is sampling error because of patchy disease, or that deeper intubation into the small intestine is required.

The role of AEA in the pathogenesis of AIE is still unclear. In this study, AEA titers did not correlate with severity of villous atrophy, confirming previous observations (38). Yet, after initiation of treatment, AEA did disappear in most patients, although a clear correlation with clinical or histologic response could not be established. Others have suggested that AEA are a secondary phenomenon that arise after initiation of T-cell–mediated tissue damage of the intestine because this may lead to the release of (auto)antigens which subsequently induce production of (auto) antibodies (21). To address this, we evaluated AEA in patients with other enteropathies, including CD, RCD type 2, and EATL. Although absent in controls, AEA were found in a low percentage of CD patients, and in up to 20% in EATL patients, thereby suggesting to be indeed secondary to (severe) enteropathy. These data are in contrast with a previous report that AEA are very specific in a population involving 2,200 patients who underwent duodenal biopsy (39), yet others have also found AEA in patients with olmesartan-associated enteropathy, inflammatory bowel disease, and human immunodeficiency virus infection (16,40,41). In 3 patients, the diagnosis of AIE was based on clinical and histologic features in absence of AEA as the latter are not absolutely required for the diagnosis (6). One patient lacked both AEA and AGCA, while in 2 others, AGCA were observed, findings in line with previous reports (6,42,43). The relevance of this finding is, however, unclear because AGCA can be found in up to 28% of patients with CD (44), and some experts suggest that AGCA should not be used for the diagnosis of AIE (39).

Steroid therapy induced clinical remission in 62% of the patients in our study, which is similar to previous reports (6). Depending on disease severity, steroid treatment can vary from budesonide for mild symptoms to intravenous prednisolone for severe cases. When induction treatment with prednisone is successful, maintenance treatment with open capsule budesonide or thiopurines both seem reasonable options. In our series, thiopurines were effective in 63% of patients when tolerated, and other series have shown promising effects for open capsule budesonide (5). For patients refractory to steroid therapy, it is currently unclear what the best step-up therapy is. This is illustrated in our study because these patients were treated with a variety of step-up therapy such as rituximab, ciclosporin, cladribine, and infliximab. Because of small sample size, no conclusions can be drawn from our and other series, especially since patients often received multiple treatments within a short timeframe making it impossible to identify the effective therapy. No single treatment was noted to be consistently effective in AIE patients. Therapies that have shown to be effective in our series are rituximab (2/4 patients) and cladribine (1/3 patients). Infliximab has been reported to induce clinical remission in 4 cases, although in our study, it was ineffective in the 1 case it was tried (6,23,25). Another promising therapy is vedoluzimab that regulates inflammation by blocking lymphocyte trafficking in the intestine and has been reported to be effective in adult-onset AIE (45). Based on the currently available data, we propose that patients refractory to prednisone should receive treatment with infliximab, rituximab, or vedoluzimab (Figure 2). When severe malabsorption persists, despite these various treatment strategies in patients younger than 70 years, ASCT could be considered.

We here describe the first patient with adult-onset AIE who has been successfully treated with ASCT currently being in a

drug-free remission for over 10 years. In children with IPEX, allogeneic stem cell transplantation is the only curative treatment available (46). Immunopathogenesis in IPEX differs from AIE and is characterized by a mutated *FoxP3* gene resulting in dysfunctional regulatory $CD4^+CD25^+FOXP3^+$ T cells and lack of control of autoreactive T and B cells in the affected patient (47). A comparable gene mutation disturbing immunological regulation has not been found in AIE; however, dysfunctional or reduced numbers of regulatory cells may yet be involved in its pathogenesis. In general, allogeneic stem cell transplantation is accompanied by a substantial higher (15%–30%) transplant–related morbidity and mortality than ASCT (<5%), which has directed treatment in severely ill patients with autoinflammatory disease toward the latter (48). The rationale behind ASCT is that the conditioning regime followed by infusion of hematopoietic stem cells eradicates autoreactive immune cells allowing the generation of a de novo self-tolerant immune system (49). ASCT has proven safe and effective in another severe enteropathy, RCD type 2, and was therefore attempted in therapy-refractory AIE with severe diarrhea and wasting (26,50).

Maintenance therapy with thiopurines proved reasonable effective in our group when disease activity was under control. When thiopurines are not tolerated, long-term use of budesonide appears a good alternative (5). Remarkably, in addition to the patient who was successfully treated with ASCT, 3 other patients are in a long-lasting drug-free clinical remission after being treated for 3–7 years with immunosuppressive therapy. Although it is unclear what the natural course of the disease would have been, these data do suggest that immunosuppressive treatment can restore the equilibrium between proinflammatory and anti-inflammatory responses in some AIE patients.

Development of EATL in patients with AIE has been sporadically reported, but this has not occurred in our case series including 70 patients after 4 years of follow-up (51,52). In contrast to RCD type 2 where phenotypical analysis can accurately identify a premalignant IEL population, in AIE, no such population is present and patients are therefore screened with the less specific TCRG clonality analysis (19). Caution is required when interpreting the relatively high number (38%) of monoclonal TCRG rearrangement patterns found in AIE patients because clonal patterns were regularly found in patients with uncomplicated CD, possibly reflecting a dominant inflammatory T-cell clone rather than a malignant T-cell clone (53,54).

Altogether, it is clear that adult-onset AIE occurs in genetic susceptible patients who are prone for autoimmunity, yet the group is remarkably heterogenic considering age at diagnosis, histological findings, and the clinical course of disease. The considerable overlap of AIE with several other enteropathies regarding histological findings, HLA genotype, and presence of AEA suggests, at least to some extent, a shared pathogenesis among those enteropathies. Furthermore, our data strongly suggest that there are multiple AIE-associated autoantigens, but it remains unclear whether they play a role in disease pathogenesis, and if so, whether different autoantigens result in a different course of disease. Likewise, it is unknown what triggers the inflammatory response in AIE, and whether this trigger (e.g., virus or medications other than olmesartan, nonsteroidal anti-inflammatory drugs, and mycophenolate) is the same among patients. The long-lasting drug-free remission seen in a subgroup of AIE patients after long-term immunosuppressive medication shows that the equilibrium in the immune response can be restored. Whether the fortuitous elimination of the so far unidentified trigger responsible for instigating this inappropriate immune response has contributed to the restored balance in these patients remains speculation at this point.

AIE is a rare but severe enteropathy that requires parenteral feeding in more than half of the patients and can lead to death because of severe therapy-refractory malabsorption. Although patients with AIE are prone to autoimmunity in general, serum AEA might be secondary to the intestinal inflammation because they were found in patients with other enteropathies as well. This study further shows a high prevalence of HLA-DQ2.5 in AIE patients. Remission induction treatment with steroids is effective in most AIE patients, and maintenance treatment consists of budesonide or thiopurines. In steroid-refractory patients, there is a variety of therapies that can be considered, but none have been shown to be superior. In therapy refractory, patients with severe symptoms younger than 70 years autologous stem cell treatment can be considered. After long-term immunosuppressive treatment, one-third of patients are in long-lasting drug-free clinical remission, which shows that adult-onset AIE is curable in a subset of patients.

CONFLICTS OF INTEREST

Guarantor of the article: Roy L.J. van Wanrooij, MD, PhD.
Specific author contributions: R.L.J.W. and G.B.: designed the study, analyzed data, and wrote the article. E.A.N.B.: performed histological analyses and critically reviewed the manuscript. H.J.B.: performed tests, analyzed data, and wrote the article. M.J.W.S. and A.W.L.: performed tests, analyzed data, and critically reviewed the manuscript. C.J.M.: critically reviewed the manuscript.
Financial support: None to report.
Potential competing interests: None to report.

Study Highlights

WHAT IS KNOWN

- ✓ Adult-onset autoimmune enteropathy is a rare disease that occurs in patients susceptible for autoimmune disease.

WHAT IS NEW HERE

- ✓ One-third of patients died because of therapy-refractory malabsorption.
- ✓ Immunosuppressive therapy lead to a long-lasting drug-free remission in one-third of patients, including one patient who underwent autologous stem cell transplantation.

REFERENCES

1. Walker-Smith JA, Unsworth DJ, Hutchins P, et al. Autoantibodies against gut epithelium in child with small-intestinal enteropathy. Lancet 1982;1:566–7.
2. Unsworth DJ, Walker-Smith JA. Autoimmunity in diarrhoeal disease. J Pediatr Gastroenterol Nutr 1985;4:375–80.
3. Corazza GR, Biagi F, Volta U, et al. Autoimmune enteropathy and villous atrophy in adults. Lancet 1997;350:106–9.
4. van Wanrooij RLJ, Bontkes HJ, Neefjes-Borst EA, et al. Immune-mediated enteropathies: From bench to bedside. J Autoimmun 2021;118:102609.
5. Sharma A, Choung RS, Wang XJ, et al. Features of adult autoimmune enteropathy compared with refractory celiac disease. Clin Gastroenterol Hepatol 2018;16:877–83.e1.
6. Akram S, Murray JA, Pardi DS, et al. Adult autoimmune enteropathy: Mayo Clinic Rochester experience. Clin Gastroenterol Hepatol 2007;5:1282–45. quiz 1245.

7. Umetsu SE, Brown I, Langner C, et al. Autoimmune enteropathies. Virchows Arch 2017;472:55–66.
8. Masia R, Peyton S, Lauwers GY, et al. Gastrointestinal biopsy findings of autoimmune enteropathy: A review of 25 cases. Am J Surg Pathol 2014;38: 1319–29.
9. Malamut G, Cerf-Bensussan N, Cellier C. Identification of new cases of severe enteropathy has recently increased the spectrum of intestinal non-coeliac villous atrophy. Expert Rev Gastroenterol Hepatol 2015;9:719–21.
10. van Wanrooij RL, Bouma G, Bontkes HJ, et al. Outcome of referrals for non-responsive celiac disease in a tertiary center: Low incidence of refractory celiac disease in The Netherlands. Clin Transl Gastroenterol 2017;8:e218.
11. van Gils T, Nijeboer P, van Wanrooij RL, et al. Mechanisms and management of refractory coeliac disease. Nat Rev Gastroenterol Hepatol 2015;12:572–9.
12. Gross S, Adriaanse MP, Nijeboer P, et al. Serum intestinal-fatty acid binding protein as a biomarker for refractory coeliac disease. J Gastrointestin Liver Dis 2015;24:258–9.
13. Tack GJ, van Wanrooij RL, Langerak AW, et al. Origin and immunophenotype of aberrant IEL in RCDII patients. Mol Immunol 2012;50:262–70.
14. Kobayashi I, Imamura K, Kubota M, et al. Identification of an autoimmune enteropathy-related 75-kilodalton antigen. Gastroenterology 1999;117:823–30.
15. Bitner-Glindzicz M, Lindley KJ, Rutland P, et al. A recessive contiguous gene deletion causing infantile hyperinsulinism, enteropathy and deafness identifies the Usher type 1C gene. Nat Genet 2000;26:56–60.
16. Montalto M, D'Onofrio F, Santoro L, et al. Autoimmune enteropathy in children and adults. Scand J Gastroenterol 2009;44:1029–36.
17. Adriaanse MP, Tack GJ, Passos VL, et al. Serum I-FABP as marker for enterocyte damage in coeliac disease and its relation to villous atrophy and circulating autoantibodies. Aliment Pharmacol Ther 2013;37: 482–90.
18. Nijeboer P, van Gils T, Reijm M, et al. Gamma-delta T lymphocytes in the diagnostic approach of coeliac disease. J Clin Gastroenterol 2019;53: e208–13.
19. Verbeek WH, Goerres MS, von Blomberg BM, et al. Flow cytometric determination of aberrant intra-epithelial lymphocytes predicts T-cell lymphoma development more accurately than T-cell clonality analysis in Refractory Celiac Disease. Clin Immunol 2008;126:48–56.
20. Bishu S, Arsenescu V, Lee EY, et al. Autoimmune enteropathy with a CD8+ CD7- T-cell small bowel intraepithelial lymphocytosis: Case report and literature review. BMC Gastroenterol 2011;11:131.
21. Gentile NM, Murray JA, Pardi DS. Autoimmune enteropathy: A review and update of clinical management. Curr Gastroenterol Rep 2012;14: 380–5.
22. Tack GJ, Verbeek WH, Al-Toma A, et al. Evaluation of Cladribine treatment in refractory coeliac disease type II. World J Gastroenterol 2011;17:506–13.
23. Elwing JE, Clouse RE. Adult-onset autoimmune enteropathy in the setting of thymoma successfully treated with infliximab. Dig Dis Sci 2005; 50:928–32.
24. Sanderson IR, Phillips AD, Spencer J, et al. Response to autoimmune enteropathy to cyclosporin A therapy. Gut 1991;32:1421–5.
25. Sondhi AR, Nayak LJ, Rice MD. A case of unremitting diarrhea. Gastroenterology 2020;158:62–4.
26. Al-toma A, Visser OJ, van Roessel HM, et al. Autologous hematopoietic stem cell transplantation in refractory coeliac disease with aberrant T cells. Blood 2007;109:2243–9.
27. Ianiro G, Bibbò S, Montalto M, et al. Systematic review: Sprue-like enteropathy associated with olmesartan. Aliment Pharmacol Ther 2014; 40:16–23.
28. Burbure N, Lebwohl B, Arguelles-Grande C, et al. Olmesartan-associated sprue-like enteropathy: A systematic review with emphasis on histopathology. Hum Pathol 2016;50:127–34.
29. Scialom S, Malamut G, Meresse B, et al. Gastrointestinal disorder associated with olmesartan mimics autoimmune enteropathy. PLoS One 2015;10:e0125024.
30. Al Khalidi H, Kandel G, Streutker CJ. Enteropathy with loss of enteroendocrine and paneth cells in a patient with immune dysregulation: A case of adult autoimmune enteropathy. Hum Pathol 2006;37:373–6.
31. Casis B, Fernández-Vázquez I, Barnardos E, et al. Autoimmune enteropathy in an adult with autoimmune multisystemic involvement. Scand J Gastroenterol 2002;37:1012–6.
32. Hill SM, Milla PJ, Bottazzo GF, et al. Autoimmune enteropathy and colitis: Is there a generalised autoimmune gut disorder? Gut 1991;32: 36–42.
33. Russo PA, Brochu P, Seidman EG, et al. Autoimmune enteropathy. Pediatr Dev Pathol 1999;2:65–71.
34. Iaquinto G, Panico L, Luongo G, et al. Adult autoimmune enteropathy in autoimmune hepatitis patient. Case report and literature review. Clin Res Hepatol Gastroenterol 2021;45:101673.
35. Rodriguez NJ, Gupta N, Gibson J. Autoimmune enteropathy in an ulcerative colitis patient. ACG Case Rep J 2018;5:e78.
36. Volta U, De Angelis GL, Granito A, et al. Autoimmune enteropathy and rheumatoid arthritis: A new association in the field of autoimmunity. Dig Liver Dis 2006;38:926–9.
37. Villanacci V, Lougaris V, Ravelli A, et al. Clinical manifestations and gastrointestinal pathology in 40 patients with autoimmune enteropathy. Clin Immunol 2019;207:10–7.
38. Unsworth J, Hutchins P, Mitchell J, et al. Flat small intestinal mucosa and autoantibodies against the gut epithelium. J Pediatr Gastroenterol Nutr 1982;1:503–13.
39. Di Sabatino A, Biagi F, Lenzi M, et al. Clinical usefulness of serum antibodies as biomarkers of gastrointestinal and liver diseases. Dig Liver Dis 2017;49:947–56.
40. Martin-Villa JM, Camblor S, Costa R, et al. Gut epithelial cell autoantibodies in AIDS pathogenesis. Lancet 1993;342:380.
41. Skogh T, Bodemar G, Kihlström E, et al. Anti-brush border antibodies (ABBA) in sera from patients with ulcerative proctocolitis and in sera with antibodies against Yersinia enterocolitica 0:3. J Clin Lab Immunol 1986; 19:117–8.
42. Hori K, Fukuda Y, Tomita T, et al. Intestinal goblet cell autoantibody associated enteropathy. J Clin Pathol 2003;56:629–30.
43. McCabe P, Alli-Akintade L, Stondell J. Seronegative adult autoimmune enteropathy in a male traveler. ACG Case Rep J 2017;4:e19.
44. Biagi F, Bianchi PI, Trotta L, et al. Anti-goblet cell antibodies for the diagnosis of autoimmune enteropathy? Am J Gastroenterol 2009;104: 3112.
45. Robbins G, Tracht J, Davis D, et al. New treatment option for autoimmune enteropathy: A rare case of intractable diarrhea treated with vedolizumab. ACG Case Rep J 2018;5:e92.
46. Barzaghi F, Amaya Hernandez LC, Neven B, et al. Long-term follow-up of IPEX syndrome patients after different therapeutic strategies: An international multicenter retrospective study. J Allergy Clin Immunol 2018;141:1036–49.e1305.
47. Ahmed Z, Imdad A, Connelly JA, et al. Autoimmune enteropathy: An updated review with special focus on stem cell transplant therapy. Dig Dis Sci 2019;64:643–54.
48. Al-Toma A, Mulder CJ. Review article: Stem cell transplantation for the treatment of gastrointestinal diseases: Current applications and future perspectives. Aliment Pharmacol Ther 2007;26(Suppl 2):77–89.
49. Arruda LC, Clave E, Moins-Teisserenc H, et al. Resetting the immune response after autologous hematopoietic stem cell transplantation for autoimmune diseases. Curr Res Transl Med 2016;64:107–13.
50. Tack GJ, Wondergem MJ, Al-Toma A, et al. Auto-SCT in refractory coeliac disease type II patients unresponsive to cladribine therapy. Bone Marrow Transpl 2011;46:840–6.
51. Ciccocioppo R, Croci GA, Biagi F, et al. Intestinal T-cell lymphoma with enteropathy-associated T-cell lymphoma-like features arising in the setting of adult autoimmune enteropathy. Hematol Oncol 2018;36:481–8.
52. Malamut G, Verkarre V, Callens C, et al. Enteropathy-associated T-cell lymphoma complicating an autoimmune enteropathy. Gastroenterology 2012;142:726–4. quiz e713–724.
53. Celli R, Hui P, Triscott H, et al. Clinical insignficance of monoclonal T-cell populations and duodenal intraepithelial T-cell phenotypes in celiac and nonceliac patients. Am J Surg Pathol 2019;43:151–60.
54. Hussein S, Gindin T, Lagana SM, et al. Clonal T cell receptor gene rearrangements in coeliac disease: Implications for diagnosing refractory coeliac disease. J Clin Pathol 2018;71:825–31.