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Clinical manifestations and gastrointestinal pathology in 40 patients with autoimmune enteropathy

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ABSTRACT

Autoimmune enteropathy (AIE) is a rare condition that may affect pediatric and adult patients, frequently associated with primary immunodeficiencies. We performed a retrospective study on clinical and histological findings from 40 AIE patients. Histological presentation showed a prevalent celiac disease pattern (50%), followed by the mixed pattern (35%), independently of age, chronic active duodenitis (10%), and GVHD-like pattern (5%). Patients with primary immunodeficiencies (24/40) presented mainly with the celiac disease pattern (72.2% versus 22.2%; $p < .0001$), while patients without primary immunodeficiencies presented with a mixed histological pattern (61.1% versus 13.6%; $p < .0001$). Our study shows that the prevalent histological presentation is the celiac disease-like pattern, independently of age, and, for the first time, that the histological presentation of AIE differs significantly between patients with and without primary immunodeficiencies. These findings may be helpful for more precise and timely diagnosis and management of this rare disorder.

1. Introduction

Autoimmune enteropathy (AIE) is a rare pathological condition characterized by severe and protracted diarrhea [1–3]. Diagnosis of AIE is based on the following criteria [1]: a) protracted diarrhea; b) failure to respond to an exclusion diet; c) evidence of autoimmunity (i.e., circulating autoantibodies against antigens of the intestinal epithelium and/or presence of concomitant autoimmune diseases); d) absence of severe immunodeficiency.

AIE is currently divided in 5 subcategories [1]: 1) primary AIE (pediatric); 2) syndromic AIE (pediatric); 3) primary (sporadic) AIE of adults; 4) secondary (iatrogenic driven) AIE of adults; and 5) paraneoplastic AIE. The endoscopic aspects vary from mucosal hyperemia, to "scalloping", presence of ulcerations, and "mosaic" appearance [1,2]: However, none of these endoscopic characteristics has proved yet to be specific and pathognomonic of the condition.

Abbreviations: AIE, Autoimmune enteropathy; GHVD, graft versus host disease; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; APECED, Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; H&E, hematoxylin and eosin; PID, Primary immunodeficiency; CVID, common variable immunodeficiency; CMV, cytomegalovirus; g-i, gastrointestinal; ANA, anti-nuclear antibodies; ASMA, anti-smooth muscle antibodies; p ANCA, anti-neutrophil cytoplasmic antibodies of the perinuclear type; CD, celiac disease

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Table 1
Demographic and clinical features of the 40 index AIE patients.

No	Age	Sex	Associated immunodeficiency (ID)	Other associated pathological conditions	Onset symptoms	Laboratory abnormalities	AE or AGC Abs
1	7	F	Hypogammaglobulinemia	Herpetic mucositis	Diarrhea	No	No
2	28	F	Autosomic recessive agammaglobulinemia	COPD, bronchectasis, thalassemic trait	Diarrhea, fever	↑fecal calprotectin	No
3	16	M	X-linked agammaglobulinemia	No	Diarrhea	No	No
4	2	M	B lymphocyte maturative defect	Alopecia, CMV infection	diarrhea	↑fecal calprotectin	No
5	57	F	CVID	No	Diarrhea	No	No
6	15	F	CVID	No	Diarrhea	No	No
7	28	M	X-linked agammaglobulinemia	No	Diarrhea	No	No
8	12	F	Hyper-IgM syndrome	Sclerosing cholangitis	Diarrhea	No	No
9	23	M	X-linked agammaglobulinemia	HCV-related cirrhosis	Diarrhea	No	No
10	45	F	No	Type I diabetes, hepatic steatosis, chronic thyroiditis, thalassemic trait	Diarrhea, abdominal pain	↑CRP	No
11	30	M	X-linked agammaglobulinemia	Multiple superficial lymphoadenopathies	Diarrhea	No	No
12	28	M	CVID	Celiac disease	Diarrhea, abdominal pain	No	No
13	73	M	No	No	Diarrhea, vomiting	↑CRP	
14	55	F	CVID	No	Diarrhea, vomiting	↑fecal calprotectin and CRP	No
15	65	F	No	HCV-related cirrhosis, chronic pancreatitis	Diarrhea, vomiting, weight loss	No	AE+
16	46	F	CVID	No	Diarrhea, vomiting, bloating, fever	No	No
17	54	F	No	Adrenal insufficiency	Diarrhea, abdominal pain	No	No
18	1	F	Hypogammaglobulinemia	Silver-Russell syndrome	Diarrhea	No	ND
19	6	M	Hypogammaglobulinemia	Trico-hepato-enteric syndrome, splenomegaly	Diarrhea	No	No
20	11	M	Hypogammaglobulinemia	Trico-hepato-enteric syndrome, splenomegaly	Diarrhea	No	ND
21	3	F	No	No	Diarrhea	No	AE+
22	2	M	No	No	Diarrhea, bloating	No	ND
23	7	F	No	Autoimmune uveitis	Diarrhea	↑fecal calprotectin and CRP, ANA+	No
24	6	F	No	No	Diarrhea	No	AHA+
25	45	F	No	No	Diarrhea, abdominal pain	ANA and ASMA+	No
26	8	F	No	Giant cell hepatitis, splenomegaly, glomerulopathy	Diarrhea, abdominal pain	ANA and pANCA+	No
27	18	M	CVID	Granulomatous hepatitis, atypic mycobacteriosis	Diarrhea	No	ND
28	1	F	No	Chronic mucocutaneous candidiasis, bronchoectasis with recurrent pulmonary infections	Diarrhea, bloating	No	No
29	11	F	CVID	Chronic cholestatic hepatitis, hepatic adenomatosis	Diarrhea	No	No
30	48	M	CVID	CMV infection	Diarrhea	No	No
31	2	M	No	No	Diarrhea	No	ND
32	2	F	No	No	Diarrhea	No	ND
33	18	M	CVID	Sclerosing cholangitis, splenomegaly, large-cell B non-Hodgkin oral lymphoma	Diarrhea	No	ND
34	5	M	No	Multiple superficial lymphoadenopathies	Diarrhea, vomiting	No	AE+
35	4	M	No	CMV infection	Diarrhea	↑CRP	ND
36	3	M	Hypogammaglobulinemia	No	Diarrhea, vomiting	No	ND
37	6	M	No	No	Diarrhea, fever	No	No
38	3	M	No	CMV infection	Diarrhea, vomiting	No	No
39	63	F	CVID	No	Diarrhea	No	ND
40	2	F	No	No	Diarrhea	No	ND

Abbbreviations: Ab = antibodies; AE = anti-enterocytes; AGC = anti-goblet cells; AHA = anti-harmonin antibodies; ANA = anti-nuclear antibodies; ASMA = anti-smooth muscle antibodies; CMV = cytomegalovirus; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; CVID = common variable immunodeficiency; ID = immunodeficiency; IPEX = immunodysregulation polyendocrinopathy enteropathy X-linked; ND = not done; pANCA = perinuclear anti-neutrophil cytoplasmic antibodies.

Available data in the literature refer mostly to case reports [4–11], while only a few cohort studies have been published [12–16], with the largest one including 30 adult patients [16]. These authors proposed a morphological classification related to the duodenal mucosa, based on the identification of four main histological patterns, i.e., A) active duodenitis, B) celiac disease-like pattern (characterized by villous atrophy, glandular crypt hyperplasia, and marked increase in the number of T lymphocytes in the surface epithelium (> 25 lymphocytes/100 epithelial cells, confirmed by monoclonal anti-CD3 antibody), C) acute graft versus host (GVH)-like disease, and D) mixed pattern.

In the present study, we describe the clinical presentation and morphological alterations according to the patterns proposed by Masia et al. [16] of the largest cohort of patients with AIE reported ($n = 40$). We also aimed to describe, in cases with biopsies from other segments of the gastro-intestinal tract (esophagus, small bowel, colon), the endoscopic and morphological aspects of these districts and correlate them with the duodenal findings. The overall aim of our study is to better define the morphological features in the different gastrointestinal segments in patients with AIE and correlate them with clinical symptoms and prognosis.

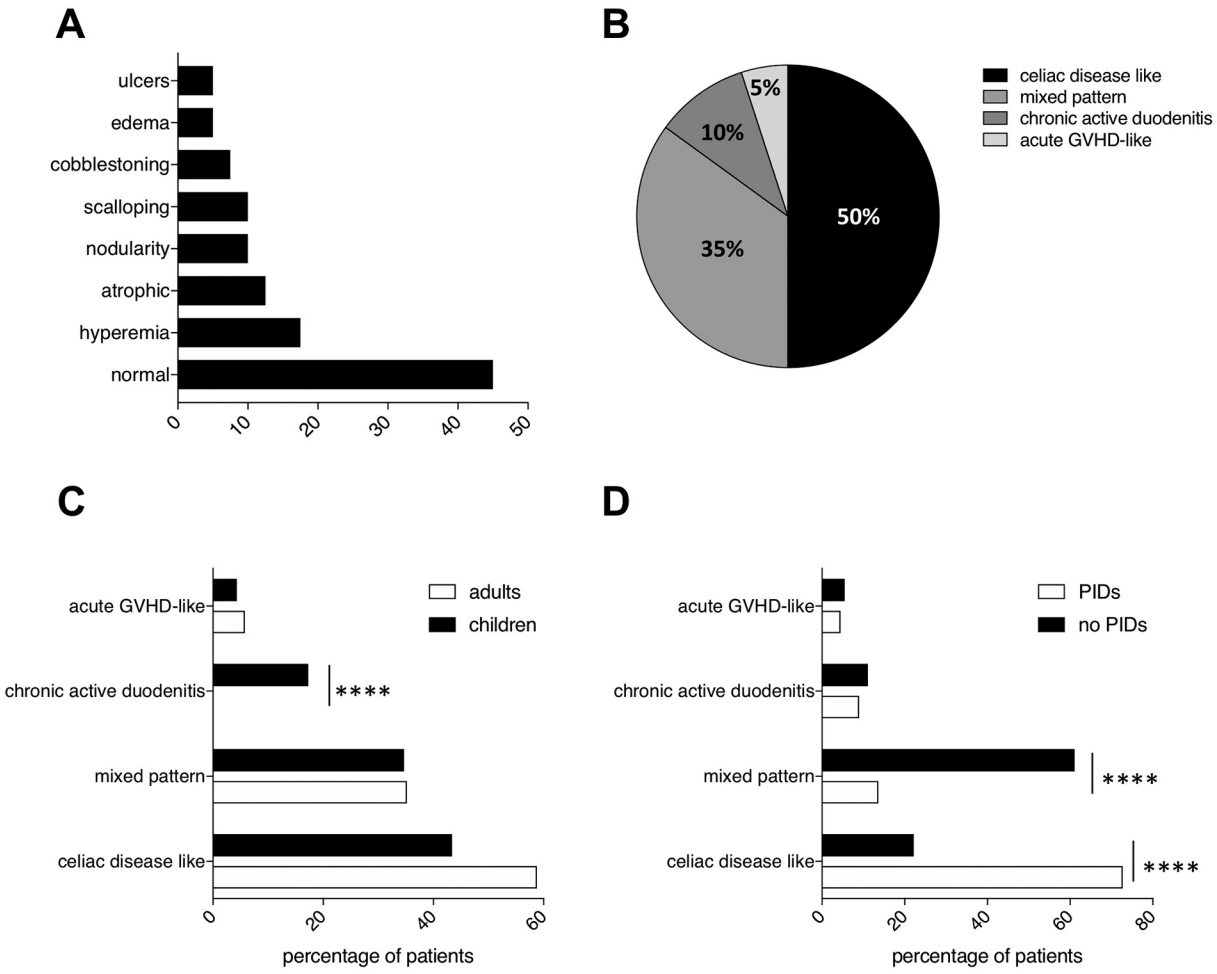

Fig. 1. Endoscopic and histologic findings in the duodenum of 40 patients with AIE. **A.** Endoscopic presentation of the index cases; **B.** Pattern of histological presentation; **C.** Comparison of histological findings between pediatric and adult AIE patients; **D.** Comparison of histological findings between AIE patients with and without primary immunodeficiency. Statistical analysis was performed with the Fischer's exact test.

2. Methods

Data from patients diagnosed with AIE, in the period January 2000–December 2015, based on the criteria proposed by Akram et al. [13] were retrospectively retrieved and analyzed.

The study has been approved by the local ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

For each case, the following variables were obtained: a) demographic and clinical data. These included the presence/absence of syndromic forms (e.g., immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) and Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome) [17–21], of associated immunodeficiencies, of other concomitant pathologies; b) laboratory data, including the presence/absence of anti-enterocytes antibodies; c) endoscopic evaluation of different gut segments, where available; d) pathological evaluation, by reviewing the biopsies (hematoxylin and eosin (H&E) and CD3 stainings) obtained at the time of the diagnosis; these were classified according to Masia et al. [16].

3. Results

3.1. Clinical presentation

Data from 40 cases of AIE, 20 of which evaluated in our pediatrics and gastroenterology departments, the remaining evaluated as consultancy from other hospitals. The male: female ratio was 47:53 (19 male patients versus 21 female ones). Age at diagnosis ranged from 2 months to 73 years. Of note, 23 (57%) patients (12 females and 11 males, average age at diagnosis 3.4 years, range 2 months-16 years) were pediatric (< 18 years) and 13 of them had < 9 years at the time of diagnosis. The adult group consisted of 17 (43%) patients, 9 females and 8 males (average age at diagnosis 42.5 years, range 18–73 years).

The onset of disease was characterized by secretory-type diarrhea in all patients, resulting in delayed growth in the pediatric population and weight loss in adult patients (Table 1). Diarrhea was associated with fever in three cases, and with vomiting in seven cases. Subjective feeling of abdominal tension and/or abdominal pain were also present in five cases.

Primary immunodeficiency (PID) was diagnosed in 60% (24/40 patients) of patients with AIE (Table 1). The most prevalent form of PID was humoral immunodeficiency present in 21 out of 40 patients (52.5%). More in detail, ten patients were affected with common variable immunodeficiency (CVID), five with agammaglobulinemia (4 with X-linked form and 1 with autosomal recessive one), five patients with hypogammaglobulinemia and one with B cell maturational defect. Finally, five patients presented the syndromic form of AIE: two diagnosed as IPEX (one with genetically confirmed IPEX and another one with an IPEX-like phenotype without genetic diagnosis), two patients were affected with trico-epato-enteric syndrome and one patient was affected with Silver Russell syndrome (Table 1).

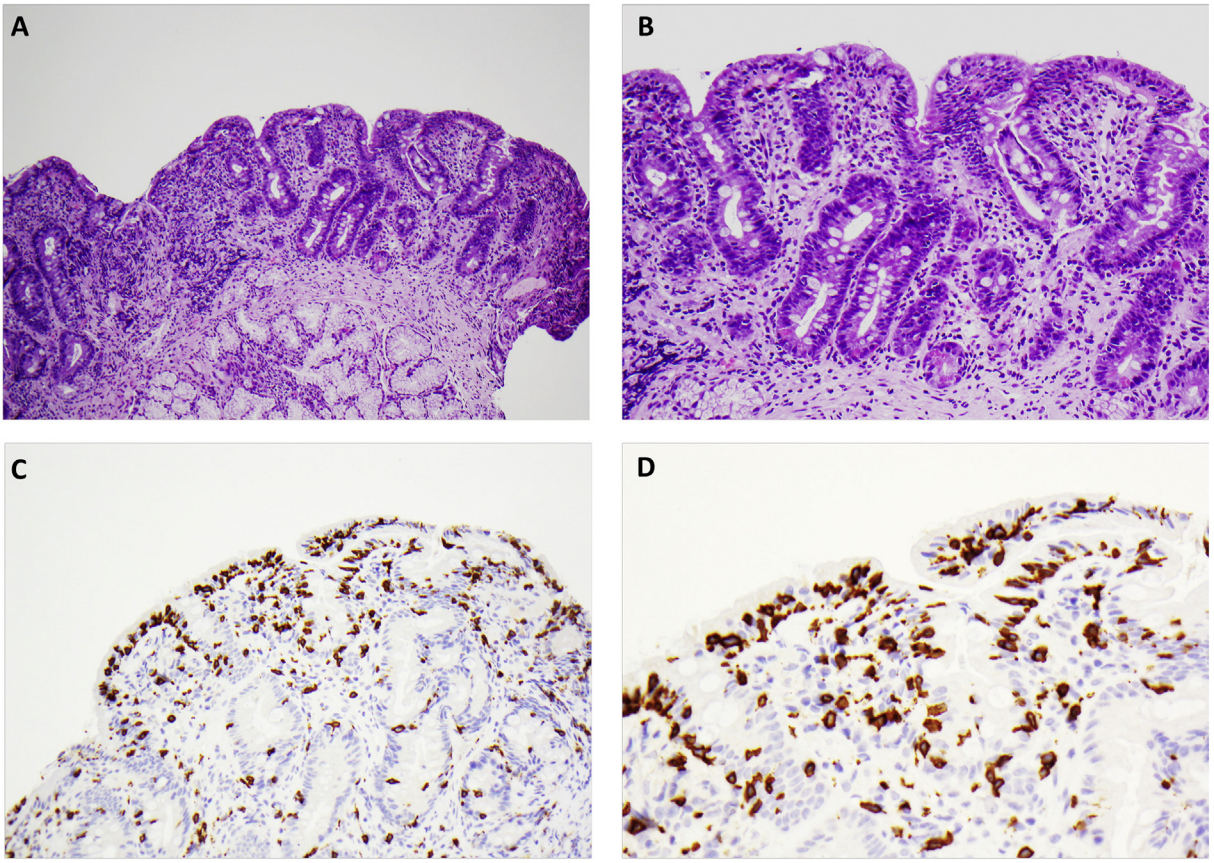

Fig. 2. "Celiac disease-like" pattern: histologically atrophy of villi, hyperplasia of ondular crypts **(A-B)** and marked increase in the number of CD3 + T lymphocytes in the surface coating epithelium (> 40 lymphocytes / 100 epithelial cells). Immunostaing for CD3 **(C-D).**

During follow-up, patients with PIDs presented several clinical complications such as recurrent respiratory infections, but also herpetic mucositis, atypical systemic mycobacteriosis, chronic mucocutaneous candidiasis. In addition, 2 PID patients developed systemic cytomegalovirus (CMV) infection (Table 1).

Concomitant conditions observed in our cohort included hepatic involvement in eight cases, autoimmune pathologies such as type I diabetes mellitus (1/40), thyroiditis (1/40), chronic pancreatitis (1/40), uveitis (1/40) and celiac disease (1/40), splenomegaly (4/40), lymphoadenopathies (2/40), alopecia (1/40), adrenal insufficiency (1/40), and glomerulopathy (1/40) (Table 1).

Besides altered laboratory results related to the protracted diarrhea and consequent malabsorption, additional laboratory abnormalities included increased values of C reactive protein (5/40), increased levels of fecal calprotectin (4/40 tested). Autoantibody determination showed positivity for anti-nuclear antibodies (ANA) (3/40), anti-smooth muscle antibodies (ASMA) (1/40), anti-neutrophil cytoplasmic antibodies of the perinuclear type (pANCA) (1/40). Finally, anti-enterocyte antibodies were searched in 28 cases and only 4 resulted positive.

3.2. Endoscopic and pathologic features: duodenum

With respect to the endoscopic appearance of the duodenal mucosa at the time of diagnosis, the majority of patients 47.5% (19/40) cases displayed a normal macroscopic aspect (Fig. 1A). Macroscopic alterations included mild mucosal hyperemia (17.5%)(7/40 cases), atrophy in 12.5% (5/40 cases), nodular/granular appearance of the mucosa in 10% (4/40 cases), scalloping of the plicae (10%) (4/40 cases, 10%), cobblestoning mucosal appearance (7.5%) (3/40), edema (5%)(2/40) and ulcers (5%)(2/40) (Fig. 1A).

Histologically, the classification of the duodenal mucosa alterations in our cohort based on the patterns proposed by Masia et al. [16] showed that the most frequent observed pattern was the so-called "celiac disease-like" pattern (50%) (20/40 cases), (Figs. 1B and 2). The second most frequently pattern was the "mixed" pattern (simultaneous presence of two or more main patterns), described in 14 (35%) cases; of these, 7 showed the pattern "active duodenitis + acute graft versus-host disease (GvHD)-like", 4 the pattern "celiac disease + active duodenitis "and 3 the pattern" celiac disease-like + acute GvHD-like". Finally, other described patterns were "chronic active duodenitis" (10%) (4/40 cases) and "acute GvHD-like" (5%)(2/40 cases). The cases with "chronic active duodenitis" were characterized by villous atrophy and increased inflammatory component in the lamina propria with cryptitis. Cryptic abscesses was reported in only one case. In cases displaying the "acute GVHD-like" pattern, in addition to villous atrophy, a marked increase in the number of apoptotic bodies in hyperplastic glandular crypts (> 1 apoptotic body/10 crypts) was found, in the presence of a minimum infiltrate of predominantly mononuclear type (plasma cells, lymphocytes) (Figs. 3 and 4).

Additional morphological alterations included the presence of follicular lymphoid aggregates in the lamina propria (17.5%) (7/40 cases), an increased number of eosinophils in the lamina propria (40%) (16/40 cases), and overlapping CMV infection (5%) (2/40).

To evaluate whether the histological pattern of AIE showed differences based on age at presentation, we confronted the histological features observed in AIE in adults and children. The "celiac disease-like" pattern was observed in 58.8% (10/17 cases) of adult patients and 43.4% (10/23 cases) of pediatric ones (Fig. 1C). The mixed pattern was observed in 35.2% (6/17 cases) of adult patients and in 34.7% (8/23 cases) of pediatric ones (Fig. 1C). The "acute GvHD-like" pattern was observed in 5.8% (1/17 cases) of adult patients and in 4.3% (1/23 cases) of pediatric patients. Finally, only pediatric patients showed the

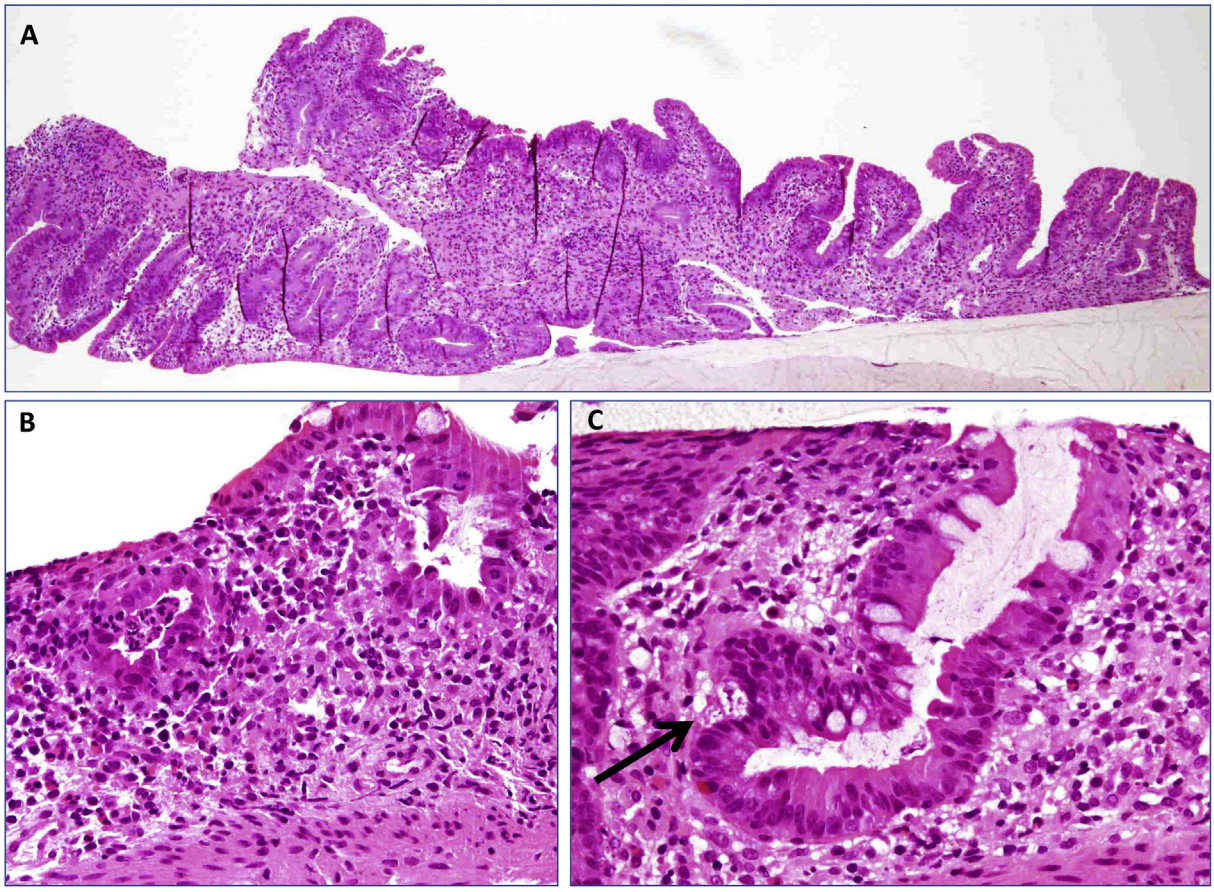

Fig. 3. Mixed pattern "chronic active duodenitis + acute GvHD-like": histologically we observe the simultaneous presence of the two main patterns "chronic active duodenitis" (increase of the inflammatory component in the lamina propria and cryptitis with presence of cryptic abscess indicated by the star in B) and "acute GvHD-like" (presence of apoptotic bodies in the glandular crypts, one of which is indicated by the arrow in C).

exclusive active duodenitis pattern (17.3%) (4/23 cases) ($p < .0001$, Fisher's exact test) (Fig. 1C). No other significant differences were observed in the distribution of histological patterns between adult and pediatric patients.

We then investigated the histological pattern distribution among AIE patients with (PIDs) or without primary immunodeficiency (no PIDs) (Fig. 1D). The "celiac disease-like" pattern was that most frequently found among PID patients (72.7%) (16/22 cases), while only one patient among the no PIDs group showed this pattern (5,55%) (1/18 of cases) ($p < .0001$, Fisher's exact test). The mixed pattern was present only in 13.6% (3/22 cases) of PIDs patients, while it was the most represented one within the no PIDs group (61.1%) (11/18 cases) ($p < .0001$, Fisher's exact test). Active duodenitis was present in similar percentages between the two groups: PIDs 9% (2/22 cases) versus no PIDs 11.1% (2/18 cases). The GVHD like pattern was equally distributed as well among the two groups: PIDs 4.5% (1/22 cases) versus no PIDs 5.55% (1/18 cases) (Fig. 1D).

3.3. Endoscopic and pathologic features: other segments of the gastrointestinal (g-i) tract

Previous studies on AIE have focused on the duodenum findings [16]. In order to evaluate whether other parts of the g-i tract may be involved in the case of AIE, we investigated available bioptic specimens from affected patients in our cohort (Esophagus:18 cases; stomach: 32 cases; ileum: 15 cases; colon: 27 cases). More in detail, esophagitis was observed in 73.2% (13/18 cases), while mild acanthosis was diagnosed in 16.7% (3/18 cases).

Regarding gastric biopsies, 90.6% (29/32 cases) resulted abnormal. Fifty per cent of sampels (16/32 cases) showed chronic quiescent gastritis, while 40.6% (13/32 cases) showed chronic active gastritis (Fig. 5A). Additional observed features included follicular gastritis (15.6%)(5/32 cases), lymphocytic gastritis (9.4%)(3/32 cases), presence of apoptotic bodies (9.4%) (3/32 cases) and increased eosinophilic count (12.5%) (4/32 cases) (Fig. 5B).

Ileum specimens from AIE patients presented abnormal findings in 73.3% (11/15 cases) (Fig. 5C). These findings included simil-celiac disease (CD) (20%) (5/15 cases), chronic active ileitis (33.3%)(5/15 cases), CD + chronic active ileitis (6.7%) (1/15) and chronic active duodenitis + simil-GVHD (13.3%) (2/15). Additional findings included the presence of follicular lymphoid aggregates in the lamina propria (20%)(3/15 cases) and increased presence of eosinophilic granulocytes in the lamina propria (26.7%)(4/15 cases).

Histological specimens from colon biopsies were available from 27 AIE patients. Alterations were observed in 92.6% (25/27 cases) in terms of acute (74.1%) (20/25 cases) or chronic inflammation (18.5%)(5/27 cases) (Fig. 5D). Additional histological findings included the presence of apoptotic bodies (51.9%) (14/27), increased eosinophil infiltrate (44.4%) (12/27 cases), follicular lymphoid aggregates (22.2%) (6/27 cases) and CMV infection (7.4%) (2/27 cases).

3.4. Comparison of histological patterns in different locations of the g-i tract in patients with AIE

Considering the abnormal pattern observed in segments other than the duodenum in patients with AIE, we decided to compare the histological findings between duodenum and other districts of the g-i tract in these patients, when samples were available. By analyzing the main

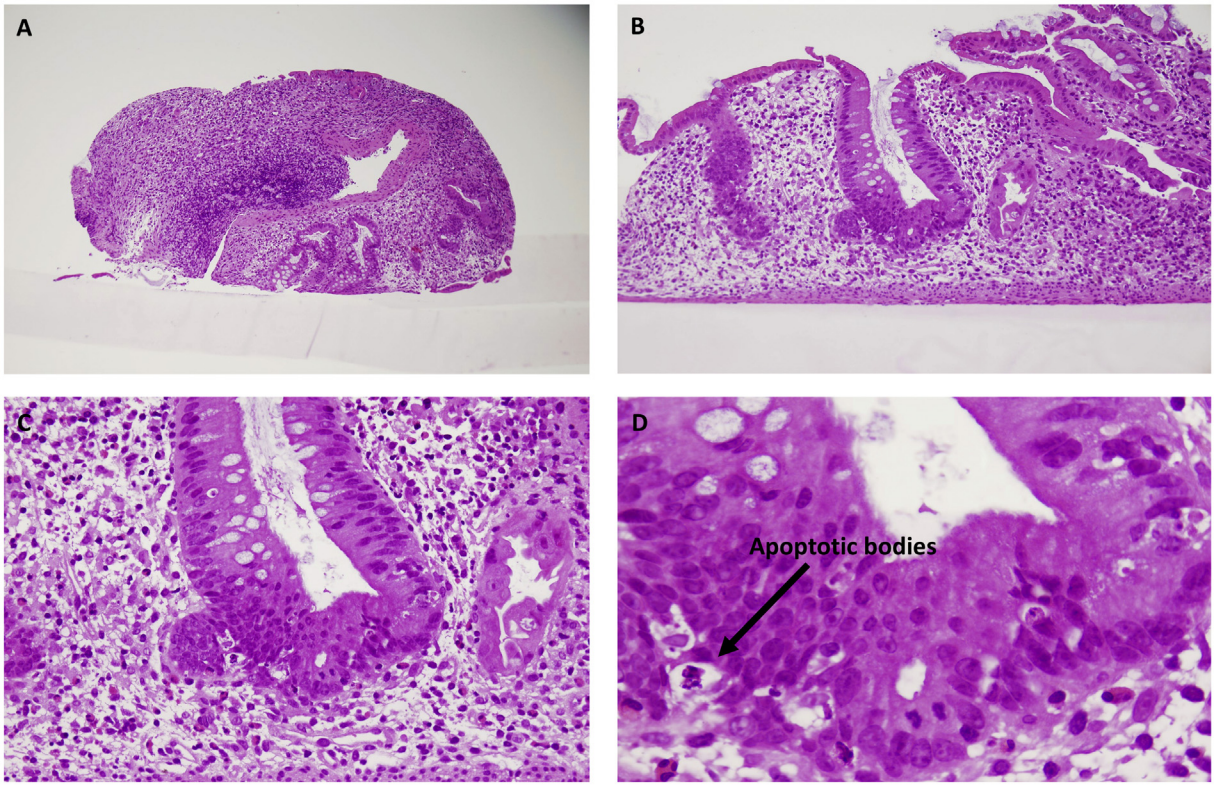

Fig. 4. "Acute GVHD-like" pattern; marked atrophy and hyperplasia of colonic crypts and increase in apoptotic bodies (arrows) at the level of glandular crypts (> 1 apoptotic body / 10 crypts).

morphological alterations observed (normal mucosa /acute inflammation/chronic inflammation), our data showed that the total concordance between the duodenum and all other districts present in 33.3% of samples (12/36 cases), while a partial concordance (defined by the concordance of the duodenal pattern with at least one other district) was present in 30.5% of samples (11/36 cases).

We then compared the different g-i segments for additional histological findings and found that lymphoid aggregates resulted concordant between duodenum and other g-i segments in 53.8% of available samples (7/13 cases), while the increased presence of eosinophils was concordant between duodenum and other g-i segments in 50% of analyzed samples (3/6 cases). Finally, the presence of apoptotic bodies suggestive of GVHD-like pattern was concordant between duodenum and other g-i districts in 50% of analyzed samples (5/10 cases).

4. Discussion

Although the pathogenesis of AIE is still largely unknown, there is evidence that an abnormal activation of the immune system, mainly of the T cell compartment, may play an important role in the pathogenesis of the condition [3].

The rarity of this condition and the limited available data in the literature, based mainly of single case reports, renders difficult a better understanding of the pathophysiology of AIE. Cohort studies in terms of clinical and histological findings in AIE are limited [12–16]. Timely and accurate histopathologic diagnosis of AIE is crucial since it drives patients' clinical management, affecting thus prognosis and clinical outcome.

The present study reports the largest series of AIE patients, adult and pediatric, reported to date, including clinical and pathological data from 40 subjects, observed during a time span of 15 years. As previously reported in literature [3], AIE was most frequently observed in children (57.5% of cases).

Concerning the clinical presentation, all patients displayed protracted secretory-type diarrhea, according to the original proposed diagnostic criteria [1] and the subsequent modifications [13].

In our cohort, primary immunodeficiencies (PIDs) co-existed with AIE in 55% of cases (22/40), with CVID being the most represented form (9/22, 41%), in accordance with previously reported data (13, 16, 22–23) (Table 1). Similarly, the previously reported association of AIE and autoimmune manifestations [13,16,22,23], was confirmed in our cohort. Of note, our cohort included syndromic forms such as IPEX and IPEX-like syndrome, already reported previously, as well as patients affected with tricho-hepato-enteric syndrome and the Silver-Russell syndrome (Table 1), that have not been reported before, suggesting that genetic abnormalities may play some role in these pathological conditions.

It has previously been underlined that the presence of autoantibodies against enterocytes should not be always considered suggestive or necessary for the diagnosis of (pediatric) AIE, since they can be present in other conditions such as allergy to milk proteins, chronic inflammatory bowel disease, HIV infection, etc.) [24,25]. In our cohort, the limited number of patients that were tested for such antibodies showed only a minor positivity (Table 1). Macroscopic alterations were also not suggestive for AIE (Fig. 1AB).

Histological evaluation of our cohort of 40 patients based on previously reported criteria [16] showed that the most frequent pattern, encountered in 50% of cases, was the "celiac disease-like" followed by the "mixed" pattern (chronic active duodenitis + acute GvHD-like 35% of cases) (Fig. 1B). While our findings are in accordance with previous studies (13,22), showing that the mixed pattern is far more frequent than the chronic duodenitis, suggesting that the latter finding alone may not be sufficient for diagnosis of AIE, this is not true for the study by Masia et al. [16] where active duodenitis was reported in > 50% of patients.

On the other hand, the presence of follicular lymphoid aggregates (found in 17.5% of cases) and the relative increase of eosinophils in the lamina propria (found in 40% of patients) are in accordance with

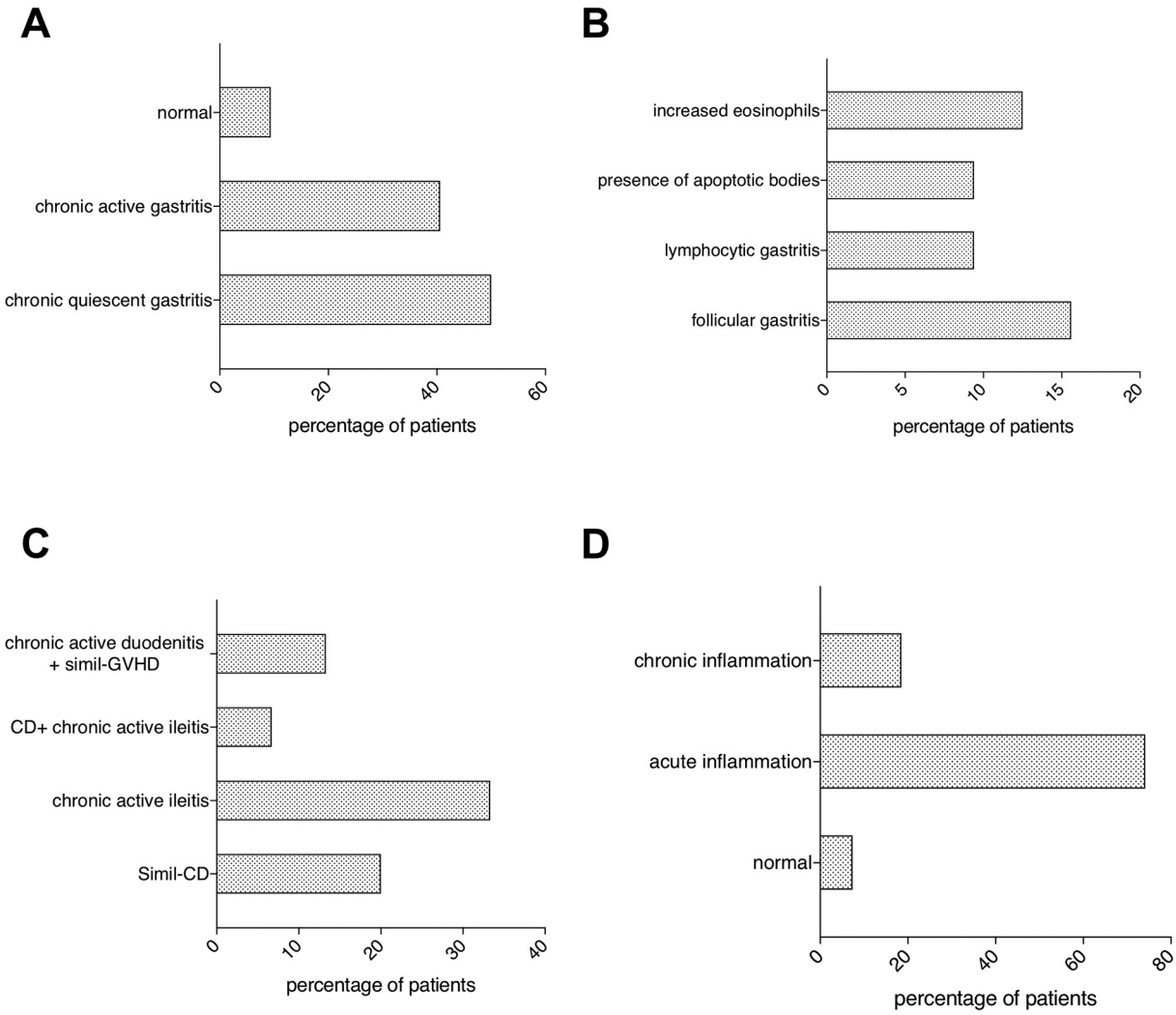

Fig. 5. Histological findings in gastric (A and B), ileal (C) nd colic biopsies (D) from AIE patients.

previously reported data [26].

The inclusion of both pediatric and adult patients with AIE confirmed that the CD-like and the mixed pattern show a similar trend in both groups, while the chronic active duodenitis phenotype was only observed in the pediatric cohort (Fig. 1 C), a finding that has to be validated in larger cohort studies.

The comparison of AIE between patients with and without an associated PID revealed an inverse and statistically significant trend in terms of pattern presentation: while among PID patients the CD-like pattern was the most prevalent, among non-PID patients the mixed pattern was the one mostly represented ($p < .0001$, Fisher's exact test) (Fig. 1D). This finding has not been reported before and underlines an important histologic feature of AIE in PIDs that has to be taken into consideration each time the suspicion of AIE arises in patients with PIDs.

The majority of available esophageal samples form AIE patients showed pathologic findings, mainly esophagitis, in accordance with previously reported data [22]. Similarly, histology of gastric specimens in our cohort of patients revealed data in accordance with previously reported abnormalities [16,22]. The incidence of lymphocytic gastritis was lower in our cohort, maybe due to the mixed age groups. Of note, follicular lymphoid aggregates in the lamina propria ("follicular gastritis"), were found in 5 (17.2%) of our AIE patients, a finding that has not been reported before.

Evaluation of ileal biopsies, available in 15 patients showed histological abnormalities in 73.3% of cases, similarly to the study by Masia et al. [16]. Finally, evaluation of colonic biopsies presented variable aspects.

4.1. Conclusions

In conclusion, AIE is an infrequent pathological condition with different possible patterns of histologic presentation, and can interest both adults and children either as a sporadic or a syndromic form [27]. Our data show that AIE in PIDs in particular presents mainly with a CD-like pattern, in contrast with non PID patients where the mixed pattern is prevalent, a finding that has not been reported before. Protracted diarrhea should always arise the suspicion of AIE and the direct involvement of the pathologist is warranted, since timely and precise diagnosis is of paramount importance for early and targeted therapeutic approaches that may result in positive clinical outcomes for affected patients.

Authors contribution

V.V., V.L., G.B. designed the study; V.L., A.R., E.B., T.S., P.L., S.M., C.D.G. D.F, G.P. contributed with clinical data and histological samples; V.V. and M.S. performed histological studies; V.V. and V.L. analyzed data and wrote the paper; all authors approved the final version of the manuscript.

Declaration of Competing Interest

None declared.

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