

A Rare Case of Autoimmune Enteropathy Associated with Autoimmune Hepatitis

Francisca Correia¹, Isabel Garrido^{2,3}, Vanessa Chaves¹, Armando Peixoto^{2,3}, Joanne Lopes⁴, Guilherme Macedo^{2,3}, Jorge Almeida¹

1) Internal Medicine
Department, Centro
Hospitalar e Universitário de
São João, Porto;
2) Gastroenterology and
Hepatology Department,
Centro Hospitalar
Universitário de São João,
Porto;
3) World Gastroenterology
Organization (WGO) Porto
Training Center, Porto;
4) Pathology Department,
Centro Hospitalar
Universitário de São João,
Porto, Portugal

Address for correspondence:
Francisca Correia, MD
Internal Medicine
Department, Centro
Hospitalar e Universitário
de São João, Alameda Prof.
Hernâni Monteiro, 4200-319
Porto, Portugal;
[afranciscaazevedocorreia@
gmail.com](mailto:afranciscaazevedocorreia@gmail.com)

ABSTRACT

A 74-year-old woman was admitted for weight loss, abdominal pain and diarrhea for a year. Blood tests showed elevated transaminases, cholestasis and hyperbilirubinemia. Capsule endoscopy revealed extensively scattered lymphangiectasias, shortened villi and erosions in the jejunum and ileum. The histological examination of the small bowel mucosa biopsies evidenced severe mucosal atrophy and crypt hyperplasia, without significant intraepithelial lymphocytosis. The clinical picture, lack of response to a gluten-free diet and endoscopic and histopathologic findings were compatible with autoimmune enteropathy. Simultaneously, autoimmune hepatitis was also diagnosed. The patient showed significant improvement after starting treatment with prednisolone and azathioprine. To our knowledge, this is the first case of autoimmune enteropathy diagnosed simultaneously with autoimmune hepatitis.

Key words: autoimmune enteropathy – autoimmune hepatitis – malnutrition.

Abbreviations: ANA: antinuclear antibodies; Ig: immunoglobulin; PCR: polymerase chain reaction.

INTRODUCTION

Autoimmune enteropathy is a rare disease characterized by chronic diarrhea, villous atrophy of the small intestine and failed response to dietary manipulation [1]. It was first described in 1982 in a child who presented protracted diarrhea, vomiting and weight loss [2]. In fact, it is more common to be diagnosed in children in the first six months of life. Nevertheless, the incidence is estimated at less than 1 in 100,000 infants [3]. Over the years, autoimmune enteropathy has been increasingly recognized in adults.

The presence of anti-enterocyte or anti-goblet cell antibodies is supportive of the diagnosis, although their absence does not exclude a diagnosis of autoimmune enteropathy [4]. Exclusion of other causes of villous atrophy is essential,

including celiac disease, inflammatory bowel disease and intestinal lymphoma. Patients are typically treated with corticosteroids and immunosuppressive drugs.

The pathophysiology of autoimmune enteropathy is not completely understood but the available evidence suggests a hyperactive immune state due to a defect in regulatory T-cell homeostasis [5]. A predisposition to autoimmunity has been noted, as indicated by a variety of circulating autoantibodies and associated autoimmune disorders [6].

Herein, we describe the first case report of autoimmune enteropathy diagnosed simultaneously with autoimmune hepatitis. We found exuberant and extensive findings in the endoscopic studies, in a patient with abnormal liver tests, intractable diarrhea and severe weight loss for a year.

CASE PRESENTATION

A 74-year-old Caucasian woman, with arterial hypertension, dyslipidemia, and asthma, was admitted for asthenia, weight loss (10 Kg), abdominal pain and diarrhea for a year. The initial physical examination revealed signs of cachexia. Blood tests showed iron deficiency anemia (hemoglobin 10.3 g/dL, transferrin saturation 7%, ferritin 21.3 ng/mL), thrombocytopenia (platelet count 79×10^9 /L), severe hypoalbuminemia (20.8 g/L), hyponatremia, hypomagnesemia, folic acid and vitamin D deficiency. Furthermore, she had increased transaminases [aspartate aminotransferase 312

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U/L (normal range 10-37 U/L), alanine aminotransferase 481 U/L (normal range 10-37 U/L), cholestasis [gamma-glutamyl transferase 243 U/L (normal range 10-49 U/L), alkaline phosphatase 198 U/L (normal range 30-120 U/L)] and hyperbilirubinemia [total bilirubin 4.69mg/dL (normal range <1.20mg/dL), direct bilirubin 1.88 mg/dL (normal range <0.40mg/dL)], with normal coagulation tests.

The patient denied alcohol abuse, blood transfusion, high-risk sexual behaviors, tattoos, intravenous drug use or consumption of herbal preparations. The serology for hepatitis A virus, human immunodeficiency virus, Epstein-Barr virus, syphilis, parvovirus and herpes simplex virus type 1 and 2 were all negative. Polymerase chain reaction (PCR) for hepatitis B, C and E viruses was also negative. Ceruloplasmin was <18 mg/dL but 24-hour urinary copper was normal (28 µg per 24 hours). Alpha-1 antitrypsin were normal, as well as thyroid function. Antinuclear antibody (ANA) was positive (1:320, homogeneous pattern). Anti-mitochondrial, anti-smooth muscle, anti-liver-kidney microsomal, anti-soluble liver antigen and antineutrophil cytoplasmic antibodies were all negative. Furthermore, serum immunoglobulin A (IgA), immunoglobulin M (IgM) and immunoglobulin G (IgG) levels were all normal. Abdominal Doppler ultrasound showed hepatomegaly, without biliary dilation or portal vein thrombosis.

Stool cultures were all negative as well as serum *Tropheryma whipplei* PCR. The patient had an anti-transglutaminase IgA antibody <7 UI/L and normal fecal calprotectin. Computed tomography enterography showed no significant changes. Immunofixation and immunophenotyping of peripheral blood were normal, as well as bone marrow aspirate and biopsy.

The patient performed upper endoscopy and colonoscopy, without relevant findings. Molecular detection of *Tropheryma whipplei* by PCR in gastric, duodenal and colon biopsies was negative. Histological examination also excluded microscopic colitis. Then, the patient underwent capsule endoscopy, which revealed extensively scattered lymphangiectasias, areas with shortened villi and some erosions in the jejunum and ileum (Fig. 1). Upper double balloon enteroscopy was then performed with jejunal mucosa biopsies. The histological examination showed shortening and flattening of the villi, with severe mucosal atrophy, crypt hyperplasia and lymphoplasmacytic infiltration of the lamina propria, without significant

intraepithelial lymphocytosis (Fig. 2). Although we did not have access to the anti-enterocyte antibodies and anti-goblet cell antibodies, the clinical picture (chronic diarrhea, weight loss and malnutrition), lack of response to a gluten-free diet and endoscopic and histopathologic findings allowed us to establish the diagnosis of autoimmune enteropathy.

A percutaneous liver biopsy was also performed, revealing intense lymphoplasmacytic infiltrate in the portal spaces, involving lymphocytes, plasma cells and eosinophils, as well as focal lesions of interface hepatitis (Fig. 3). In addition, it was noted portal fibrosis and fibrous septation of the parenchyma, with the formation of bridges and occasional nodules (METAVIR score F3-F4). The score of the revised original pretreatment scoring system of the International Autoimmune Hepatitis Group was 19 (definitive diagnosis of autoimmune hepatitis).

Prednisolone 50 mg/day was started with a rapid improvement of symptoms. The corticosteroid dose was gradually tapered, and azathioprine 1mg/Kg was then added. Liver enzymes progressively improved (Fig. 4). One year after initial diagnosis, she was in an excellent general condition, with a weight gain of 5Kg and without nutritional deficits.

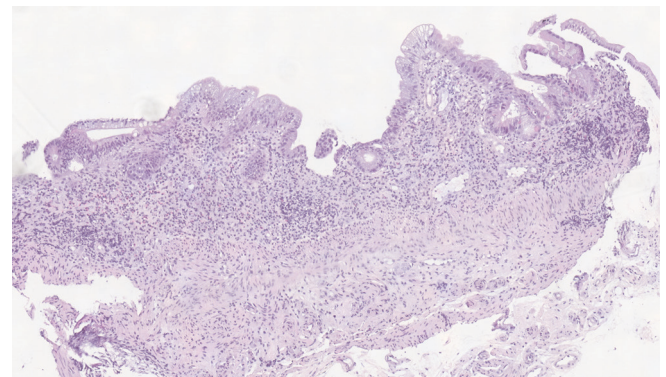


Fig. 2. Small bowel biopsy (HE, 10x): Enteric mucosa with enlargement and shortening of the villi; focal permeation of the crypts by inflammatory cells, without the formation of crypt abscesses; chorion with lymphoplasmacytic inflammatory infiltrate, with the participation of eosinophils and formation of lymphoid follicles, without significant intraepithelial lymphocytes (6-8 intraepithelial lymphocytes / 100 enterocytes).



Fig. 1. Videocapsule endoscopy with multiple lymphangiectasia and areas of villous atrophy scattered throughout the jejunum and ileum.

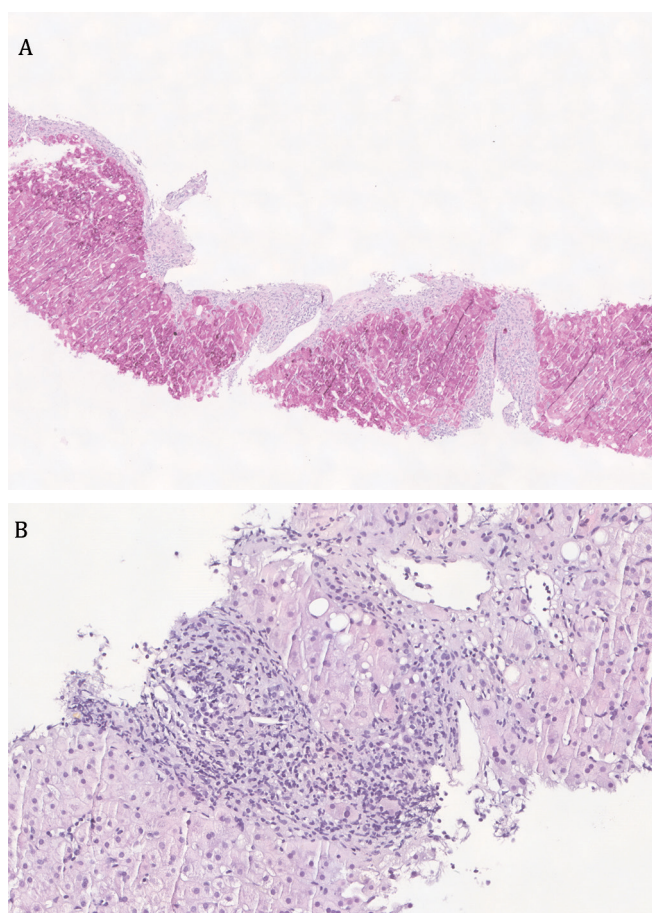


Fig. 3. Liver biopsy – (A) Portal fibrosis and fibrous septation of the parenchyma, with formation of bridges between vascular structures and occasional nodules (HE, 10x). (B) Marked portal tract inflammation with intense lymphoplasmacytic infiltrate and interface hepatitis (HE, 20x).

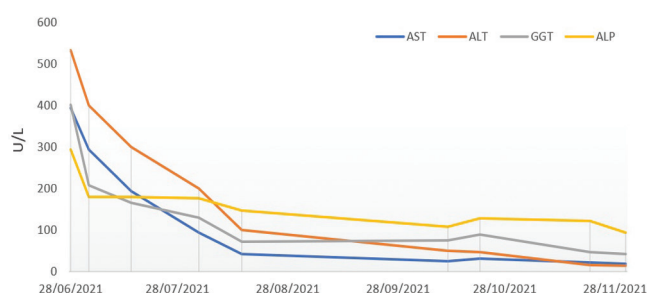


Fig. 4. Evolution of liver function tests during follow-up. AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; ALP: alkaline phosphatase.

DISCUSSION

Autoimmune enteropathy is a rare cause of intractable diarrhea associated with villous atrophy of the small intestine, circulating gut autoantibodies and a predisposition to autoimmunity. This is an emerging diagnosis in the adult population and should be included in the differential diagnosis for patients with chronic diarrhea. Prognosis varies

and is impacted by the degree of symptoms, the degree of gastrointestinal involvement and systemic manifestations [1]. Usually, these patients require immunosuppressive therapies.

The differential diagnosis of chronic diarrhea in adults with autoimmune enteropathy includes celiac disease, inflammatory bowel disease, lymphoma, eosinophilic enteritis, microscopic colitis, drug-associated enteropathy, common variable immunodeficiency, infections, and Whipple disease [7].

Neoplasia was excluded after absence of radiological changes in the computed tomography scan and endoscopic procedures. Immunofixation and immunophenotyping of peripheral blood, bone marrow aspirate and biopsy excluded hematology neoplasia, such as lymphoma. In our case, the diagnosis of eosinophilic enteritis and common variable immunodeficiency is unlikely because of the normal count of blood and tissue eosinophils, with normal immunoglobulin E levels. Inflammatory bowel disease and microscopic colitis were also excluded after colonoscopy, computed tomography enterography and histological examination did not show any alterations compatible with these entities.

The hypothesis of celiac disease was raised because of severe small bowel villous atrophy. However, histological results showed no intraepithelial lymphocytosis, anti-transglutaminase IgA antibody was negative (with no IgA deficit) and there was no response to a gluten-free diet. Whipple disease was also excluded.

Negative stool cultures make the diagnosis of infectious diarrhea unlikely. We also excluded drug-associated enteropathy, as the patient was not medicated with drugs that could justify her condition.

After exclusion of other etiologies, the study of the digestive tract was completed with capsule endoscopy and small intestine biopsies, which were compatible with the diagnosis of autoimmune enteropathy. It should be noted that despite not having available anti-enterocyte and anti-goblet cell antibodies, the ANA is the most common antibody observed in autoimmune enteropathy adult patients (8), as was observed in this case.

The diagnosis of autoimmune enteropathy is challenging. Our patient was diagnosed based on her symptoms, histopathologic findings, and the exclusion of other related conditions.

The most commonly reported first-line treatments for autoimmune enteropathy are steroids [9]. Other agents also induce remission, namely immunomodulators and biologic drugs. Our patient showed significant improvement after treatment with prednisolone and azathioprine.

Simultaneously, autoimmune hepatitis was diagnosed based on the scoring system of the International Autoimmune Hepatitis Group, after ruling out other causes for abnormal liver function tests. It is noteworthy that IgG levels were normal, which can be explained by mucosal atrophy and associated protein-losing enteropathy. This diagnosis reinforces the predisposition to autoimmunity in these patients. Indeed, associated autoimmune diseases are described in 55% of individuals with autoimmune enteropathy [6]. Hypothyroidism and hyperthyroidism are the most frequently reported.

Iaquinto et al. [7] have already described a case of autoimmune enteropathy in an adult with positive ANA, 7

years after a diagnosis of autoimmune hepatitis. Similarly, Bishu et al. [10] reported one case of autoimmune enteropathy associated with autoimmune hepatitis, but in that case, ANA were negative. To our knowledge, this is the first report in which the diagnosis of these two autoimmune diseases was made simultaneously.

CONCLUSIONS

The literature on autoimmune enteropathy is limited and much of it comes from case reports or small case series. It is necessary to encourage the reporting of more cases to promote a better understanding of this rare entity. Herein, the authors present the first case described in the literature of autoimmune hepatitis diagnosed simultaneously with autoimmune enteropathy. This report highlights the need for clinicians to be alert to other autoimmune diseases at the time of diagnosis.

Conflicts of interest: None to declare.

Authors' contribution: F.C. and I.G. reviewed the literature and drafted the manuscript. F.C., I.G., V.C., A.P., J.L., G.M. and J.A. critically revised the manuscript. All authors have approved the final version of the manuscript.

REFERENCES

1. Gentile NM, Murray JA, Pardi DS. Autoimmune enteropathy: a review and update of clinical management. *Curr Gastroenterol Rep* 2012;14:380-385. doi:[10.1007/s11894-012-0276-2](https://doi.org/10.1007/s11894-012-0276-2)
2. Walker-Smith JA, Unsworth DJ, Hutchins P, Phillips AD, Holborow EJ. Autoantibodies against gut epithelium in child with small-intestinal enteropathy. *Lancet* 1982;1:566-567. doi:[10.1016/s0140-6736\(82\)92076-1](https://doi.org/10.1016/s0140-6736(82)92076-1)
3. Montalto M, D'Onofrio F, Santoro L, Gallo A, Gasbarrini A, Gasbarrini G. Autoimmune enteropathy in children and adults. *Scand J Gastroenterol* 2009;44:1029-1036. doi:[10.1080/00365520902783691](https://doi.org/10.1080/00365520902783691)
4. Akram S, Murray JA, Pardi DS, et al. Adult autoimmune enteropathy: Mayo Clinic Rochester experience. *Clin Gastroenterol Hepatol* 2007;5:1282-1290. doi:[10.1016/j.cgh.2007.05.013](https://doi.org/10.1016/j.cgh.2007.05.013)
5. Ruemmele FM, Brousse N, Goulet O. Autoimmune enteropathy: molecular concepts. *Curr Opin Gastroenterol* 2004;20:587-591. doi:[10.1097/00001574-200411000-00014](https://doi.org/10.1097/00001574-200411000-00014)
6. Sharma A, Choung RS, Wang XJ, et al. Features of Adult Autoimmune Enteropathy Compared With Refractory Celiac Disease. *Clin Gastroenterol Hepatol* 2018;16:877-883. doi:[10.1016/j.cgh.2017.12.044](https://doi.org/10.1016/j.cgh.2017.12.044)
7. 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. doi:[10.1016/j.clinre.2021.101673](https://doi.org/10.1016/j.clinre.2021.101673)
8. Masia R, Peyton S, Lauwers GY, Brown I. Gastrointestinal biopsy findings of autoimmune enteropathy: a review of 25 cases. *Am J Surg Pathol* 2014;38:1319-1329. doi:[10.1097/PAS.0000000000000317](https://doi.org/10.1097/PAS.0000000000000317)
9. Ahmed Z, Imdad A, Connelly JA, Acra S. Autoimmune Enteropathy: An Updated Review with Special Focus on Stem Cell Transplant Therapy. *Dig Dis Sci* 2019;64:643-654. doi:[10.1007/s10620-018-5364-1](https://doi.org/10.1007/s10620-018-5364-1)
10. Bishu S, Arsenescu V, Lee EY, Vargas HD, de Villiers WJ, Arsenescu R. Autoimmune enteropathy with a CD8+ CD7- T-cell small bowel intraepithelial lymphocytosis: case report and literature review. *BMC Gastroenterol* 2011;11:131. doi:[10.1186/1471-230X-11-131](https://doi.org/10.1186/1471-230X-11-131)