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CHRONIC DIARRHEA DUE TO AUTOIMMUNE ENTEROPATHY

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ABSTRACT
Chronic diarrhea is a common symptom attended in a Gastroenterology office. Occasionally, the diagnosis is a real challenge as there are multiple entities which their symptomatology is unremitting diarrhea. Herein we present a patient affected of intractable diarrhea who was transferred to our Department. After many laboratory, endoscopy and radiological tests, she was diagnosed with autoimmune enteropathy (AE). She achieved clinical remission with corticosteroids and azathioprine.

Keywords
Chronic diarrhea, autoimmune enteropathy.

CLINICAL CASE
A 72-year-old woman was admitted to our hospital for 15-20 days of intractable diarrhea. Her medical history included high blood pressure and chronic obstructive pulmonary disease treated with inhaled bronchodilators, proton pump inhibitors and dozasoxine. An upper endoscopy with duodenal biopsies and an ileo-colonoscopy with random biopsies were performed which disclosed normal results. Fecal exam was positive for cryptosporidium spp, therefore paromomycin 500 mg tid was administered and she was discharged.
One month later she was re-admitted for persistent symptoms and 8-kg unintentional weight loss. She referred up to 10-15 watery bowel movements per day (Bristol 6-7), which occurred mainly after meals without fever or abdominal pain.
She was put on intravenous fluids associated with bicarbonate, potassium and magnesium infusions. Yet, she developed severe metabolic acidosis, hypokalemia and renal failure so she was transferred to intensive care unit (ICU) for resuscitation and total parenteral nutrition. After a 7-day stay in ICU she was moved back to our department. A complete fecal infectious workup which included gastrointestinal virus and bacteria, clostridium difficile toxin, and parasites, disclosed negative results. Blood gastrointestinal peptides (gastrin, somatostatin and vasoactive intestinal peptide), TSH, fecal calprotectin and urine 5 hydroxy-indol-acetic acid were within normal values. Alimentary allergic tests for wheat, milk, eggs, fish and nuts were negative. Fecal elastase (44 mg/g, normal > 200 µg/g feces) and D-xilose test (9.5 mg normal > 25 mg) revealed abnormal results. Abdominal computed tomography (CT) with intravenous contrast showed no abnormalities with normal pancreas. Meanwhile, the patient was put on a lactose and gluten free diet which had no beneficial effect on her bowel movements. We also added oral pancreatic enzymes, rifaximin 200 mgrs tid, bile salt chelators and loperamide with unsatisfactory results. Therefore, we focused on the abnormal levels of D-xilose test and blood test: hemoglobin 9.2 gr/dl (nv 12-18), iron 15 µg/dl (nv 59-158), folic acid 2 ng/ml (nv 3-16), total blood protein 5.2 mg/dl (nv 6-8), albumin 3 mg/dl (nv 4-5), pre-albumin 11.6 mg/dl (nv 20-40), cholesterol 80 mg/dl (nv 120-220), calcium 7.5 mg/dl (nv 8.5-10.5), magnesium 1 mg/dl (nv 1,2-2,6), zinc 50 µg/dl (nv 73-127). We therefore had suspicion that we could be dealing with malabsorptive syndrome. Subsequently the patient was summited to a capsule endoscopy (Fig 1). The procedure revealed extensive mucosal atrophy associated with diffuse superficial ulcerations. In order to obtain samples for histopathology study, an upper endoscopy was repeated which showed clear duodenal atrophy (fig 2). Multiple biopsies were performed which disclosed blunting and villous atrophy, plasma cell infiltration (fig 3A) and severe lymphocytic infiltration in the crypt epithelium (fig 3B). Lipid-containing vacuoles were not found in the specimens. There were no macrophages with gram positive bacilli suggestive of Tropheryma Whipplei (DNA for T. Whipplei in the samples was negative). Intraepithelial lymphocytes did not suggest celiac disease (CD45+ 55.2 %, CD3- 6 %, CD3+ TCR γδ 6.4 %). Several attempts to feed the patient with enteral nutrition failed so total parenteral nutrition was maintained.
Her diarrhea only ceased when fasting. The histological exam had ruled out the most common etiologies of intractable diarrhea. We considered that her clinical profile could be consistent with autoimmune enteropathy. Consequently, she was administered intravenous prednisone (1mg/Kg weight) associated with 50 mg azathioprine. She tested negative for anti-enterocyte and anti-goblet cell antibodies. Her clinical response was slow but steady. Oral feeding was gently reassumed and bowel movements were progressively reduced. She was discharged after 45 days on tapering corticosteroids with 50 mg azathioprine. After a 6-month follow-up period she remains symptom free with only azathioprine treatment. A new D-xilose test was normal as well as fecal elastase (the previous result was considered a secondary exocrine pancreatic insufficiency due to enterokinase lost).

Autoimmune Enteropathy (AE) is a rare cause of intractable diarrhea (1). AE was initially described in infants (2); however, there are several published cases affecting adult patients over the last few years (3,4,5). The pathophysiology remains complex and it is not fully understood. There is a dysregulation in both humoral and cell-mediated immunity (1). The overexpression of MHC-II molecules results in the proliferation of CD4+ and CD8+T lymphocytes that exert their effect either through direct cytotoxicity by secreted lymphokines or through indirect antibody-dependent cytotoxicity. (3,6). Some other autoimmune diseases such as diabetes or hypothyroidism can also be found in patients affected with AE. (1,3-7)

The diagnosis of AE is a clinical challenge. Patients suffer from persistent diarrhea with no dietary response and with a specific intestinal histology. Several other entities must be ruled out, such as celiac disease, drug enteropathy (e.g. Olmesartan), inflammatory bowel disease, collagenous colitis, intestinal lymphoma or common variable immunodeficiency (8). Antibodies against intestinal epithelium (anti goblet cells and anti-enterocyte) can help in the diagnosis (1,7,9,10); however, their absence do not rule out the diagnosis of AE (3,5,12). The association between epithelial antibodies and the pathology of AE is a subject of ongoing debate; furthermore, they can be found in some other diseases such as inflammatory bowel disease, HIV infection, and allergic enteropathy (11, 6, 10). In fact, in large series such as the one by Sharma et al, only 55% or their patients tested positive for antibodies (8). Villanacci et al only found 4
out of their 28 patients positive for antibodies. (13).

AE is considered to have male predominance (3,8); however, some other authors do not find a sex tendency (13,10). Mean age is around 40-50 years of age in some publications (13,10); nonetheless, there are cases described affecting all ages (3,4).

Intestinal mucosa can be normal at endoscopy (11,13,15). However, features such as duodenal scalloping (2,12), ulcerations and edema (10,13), mosaic pattern and villous atrophy are frequently seen along the small intestine. Furthermore, mucosa changes can occur in the whole digestive system; Masia et al, demonstrated the presence of mucosa alterations in colon (64 %), stomach (68 %) and esophagus (28 %). In cases where capsule endoscope was performed, as in the series from Mayo Clinic, edema, fissures and villous atrophy was seen all through the small bowel (10).

Histological findings are similar to those found in several other entities e.g. graft versus host disease, food allergies, drug enteropathies and celiac disease (3,8); therefore, the diagnosis of AE can not only rely on histological specimens. Both biopsies abnormalities and clinical symptoms, must go together. Complete or partial villous atrophy, intraepithelial lymphocytes , crypt hyperplasia and plasmatic cells infiltration in lamina propria are the main hallmarks in AE (8,10). Nevertheless, these histological features can be absent in early phases of the disease, as happened with our patient. Lundhom et al (5) suggest that histological changes can be subtle and scattered at the beginning of the disease and therefore difficult to find.

Treatment of AE is based on corticosteroids (budesonide/prednisone) (1,4,8) with or without azathioprine/mercaptopurine (10, 3). We prescribed combination therapy because in literature patients treated with corticosteroids alone did not fulfill complete response (e.g. less than 25 % in Sharma’s series) ( 8 ) or suffered from an early recurrence with subsequent immunomodulator addition as described by Akram et. al. (10). Nevertheless, there are patients who do not respond to the initial treatment which worsens prognosis. Thus, severe desnutrition is developed and total parenteral nutrition must be administered for long periods of time (7,10). Refractory AE can respond to the use of anti-TNF alfa (infliximab 12,14 adalimumab 11) . Vedolizumab which is a monoclonal antibody against intestinal integrins can also be a good option in selected patients (9).
Little is known about the progression in AE. There are very few cases followed over a long period of time published in literature. Ciccocioppo et al (16) described an interesting clinical case of AE who developed intestinal lymphoma after a 20-year follow up period. They suggest that patients affected with AE can progressively accumulate genotypical changes which lead to the development of lymphoma. The authors advise a close follow-up of AE patients even if they have no symptoms.

In summary, we present a challenging case of chronic diarrhea where we learn the importance to keep in mind all the diagnostic possibilities. Even though AE is a rare cause of unmanageable diarrhea, it must be present in the differential diagnostic of patients with persistent symptoms after ruling out the most common disorders. As shown in our clinical case, sometimes endoscopic procedures which are initially normal, if repeated, can disclose pathological findings.

REFERENCES
Figure 1. Small bowel mucosa with blunt villous, erythema, edema and ulcerations

Figure 2. Atrophic distal duodenal mucosa.
Figure 3. Villous atrophy, plasma cell and lymphocytic infiltration HE 10X (A). Hyperplasic crypts with intraepithelial lymphocytosis. No goblet cells were present HE 20X (B).