Chronic diarrhea due to autoimmune enteropathy

María Lourdes Ruiz Rebollo¹, Daniel Corrales Cruz², Sandra Izquierdo Santervás¹, Reyes Busta Nistal³, Miguel Dirá Gil¹ and Beatriz Burgueño Gómez¹

¹Digestive Diseases and ²Anatomic Pathology Services. Hospital Clínico Universitario. Valladolid, Spain

Received: 06/05/2020
Accepted: 8/9/2020
Correspondence: María Lourdes Ruiz Rebollo. Digestive Diseases Service. Hospital Clínico Universitario. Av. de Ramón y Cajal, 3. 47003 Valladolid, Spain
e-mail: ruizrebollo@hotmail.com

The authors declare no conflict of interest.

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

Key words: Chronic diarrhea. Autoimmune enteropathy.

CASE REPORT
A 72-year-old female was admitted to our hospital due to 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 were normal. A fecal exam was positive for *Cryptosporidium spp.* Therefore, paromomycin 500 mg three times daily (tid) was administered and she was discharged. One month later, she was re-admitted due to 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 placed on intravenous fluids associated with bicarbonate, potassium and magnesium infusions. Yet, she developed severe metabolic acidosis, hypokalemia and renal failure and was transferred to the 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, including gastrointestinal virus and bacteria, *Clostridium difficile* toxin and parasites, was negative. Blood gastrointestinal peptides (gastrin, somatostatin and vasoactive intestinal peptide), TSH, fecal calprotectin and urine 5 hydroxy-indol-acetic acid were within the 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) were abnormal. Abdominal computed tomography (CT) with intravenous contrast showed no abnormalities with a normal pancreas. Meanwhile, the patient was put on a lactose and gluten free diet, which had no beneficial effect on her bowel movements. Oral pancreatic enzymes, rifaximin 200 mg tid, bile salt chelators and loperamide were also added with unsatisfactory results. Therefore, we focused on the abnormal levels of D-xilose test and the following blood test results: hemoglobin 9.2 gr/dl (nv12-18), 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) and zinc 50 µg/dl (nv 73-127). Thus, there was a suspicion of malabsorptive syndrome. Subsequently, the patient underwent a capsule endoscopy (Fig. 1). The procedure revealed extensive mucosal atrophy associated with diffuse superficial ulcerations. Upper endoscopy was repeated in order to obtain samples for a histopathology study, which showed clear duodenal atrophy (Fig. 2). Multiple biopsies were performed,
which showed blunting and villous atrophy, plasma cell infiltration (Fig. 3A) and severe lymphocytic infiltration in the crypt epithelium (Fig. 3B). There were no lipid-containing vacuoles in the specimens. There were no macrophages with gram-positive bacilli suggestive of *Tropheryma whipplei* (DNA of *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. The diarrhea only ceased when fasting. The histological exam had ruled out the most common etiologies of intractable diarrhea and we considered that her clinical profile could be consistent with autoimmune enteropathy (AE). Consequently, she was administered intravenous prednisone (1 mg/kg weight) associated with 50 mg azathioprine and 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 fecal elastase was normal (the previous result was considered as a secondary exocrine pancreatic insufficiency due to enterokinase loss).

**DISCUSSION**

AE is a rare cause of intractable diarrhea (1). AE was initially described in infants (2), although there are several published cases over the last few years in adult patients (3-5). The pathophysiology remains complex and 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 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 and 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 the subject of ongoing debate. Furthermore, they can be found in some other diseases such as inflammatory bowel disease, HIV infection and allergic enteropathy (6,10,11). In fact, in large series such as the one by Sharma et al., only 55% of patients tested positive for antibodies (8). Villanacci et al. only found four out of 28 that were patients positive for antibodies (13). AE is considered to have male predominance (3,8). However, some other authors do not find a gender tendency (10,13). The mean age is around 40-50 years of age in some publications (10,13). 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 the colon (64%), stomach (68%) and esophagus (28%). In cases that underwent capsule endoscope, as in the series from Mayo Clinic, edema, fissures and villous atrophy were seen throughout the small bowel (10). Histological findings are similar to those found in several other entities, such as graft versus host disease, food allergies, drug enteropathies and celiac disease (3,8). Therefore, the diagnosis of AE cannot only rely on histological specimens. Both biopsy 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 in 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 (3,10). We prescribed combination therapy
because in the literature, patients treated with corticosteroids alone did not fulfill a complete response (e.g., less than 25% in Sharma’s series) (8) or suffered 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 leads to a poor prognosis. Thus, severe malnutrition 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 the literature. Ciccocioppo et al. (16) described an interesting clinical case of AE who developed intestinal lymphoma after a 20-year follow-up. They suggest that patients affected with AE can progressively accumulate genotypical changes, which lead to the development of lymphoma. The authors advised 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 of keeping 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, when repeated, can disclose pathological findings.

REFERENCES


Fig. 1. Small bowel mucosa with blunt villous, erythema, edema and ulcerations.
Fig. 2. Atrophic distal duodenal mucosa.
Fig. 3. A. Villous atrophy, plasma cell and lymphocytic infiltration (HE 10x). B. Hyperplastic crypts with intraepithelial lymphocytosis; no goblet cells were present (HE 20x).