



Nota clínica

Olmesartan-induced enteropathy

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The association between sprue-like enteropathy and olmesartan is described in recent literature and is an entity that manifests with chronic diarrhea and should be considered in its differential diagnosis. Olmesartan is a commonly used antihypertensive and the recognition of this entity may reduce the overuse of expensive complementary means of diagnosis. We present 2 cases of chronic diarrhea without blood, one with severe metabolic acidemia that motivated intensive care and renal replacement therapy. No evidence of infection, negative stool cultures, anti-transglutaminase was negative. In both cases, there were no macroscopy alterations, and biopsy was performed in one of the cases. It was considered olmesartan-associated enteropathy, and with its suspension, the clinic did not recur. Being a reversible side effect of a common drug, we should consider their suspension before initiating an extensive investigation of chronic diarrhea.

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Enteropatía inducida por olmesartán

R E S U M E N

La asociación entre la enteropatía tipo esprue y el olmesartán está descrita en la literatura reciente y es una entidad que se manifiesta con diarrea crónica y debe ser considerada en su diagnóstico diferencial. El olmesartán es un antihipertensivo de uso común y el reconocimiento de esta entidad puede reducir el uso excesivo de medios complementarios costosos de diagnóstico. Presentamos dos casos de diarrea crónica, uno de ellos con acidemia metabólica grave que motivó cuidados intensivos y terapia renal sustitutiva. No había evidencia de infección, los coprocultivos fueron negativos y la antitransglutaminasa fue negativa. En ambos casos no había alteraciones macroscópicas y en uno de ellos se realizó biopsia. Se consideró enteropatía asociada a olmesartán, y con su suspensión, la clínica no recurrió. Al ser un efecto secundario reversible de un fármaco común, debemos considerar su suspensión antes de iniciar una investigación exhaustiva de la diarrea crónica.

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Palabras clave:

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olmesartán

diarrea crónica

enteropatía

Introduction

Drug-associated small bowel enteropathy has been previously reported in association with olmesartan, an angiotensin II type 1 receptor blocker (ARB), since 2012.¹ Although clinically it is similar to celiac disease, they diverge once celiac serology is negative and there is absence of response to a gluten-free diet.¹ We can find anemia, hydroelectrolyte disturbances, and endoscopic changes may be nonspecific.^{2–5} Treatment involves discontinuation of the drug with clinical and histological

regression and improvement.⁵ We report the cases of 2 patients medicated with olmesartan who presented with chronic diarrhea and weight loss, being both diagnosed with olmesartan-induced enteropathy.

Case presentation

Case 1

We present the case of 70-year-old female who had arterial hypertension and had been medicated with amlodipine/olmesartan 5/20 mg once daily for 10 years, that presented with watery diarrhea, 6–10 stools a day, without blood, with abdominal pain, anorexia, and

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weight loss of 10%. She lived in the city and did not consume non-drinking water. She had no history of allergies, alcohol intake, contact with animals, or recent travels abroad. The patient went to the emergency room multiple times in 2018, the examination was unremarkable, and was medicated with ciprofloxacin for possible small bowel bacterial overgrowth, without improvement. In 2 of these episodes, the patient was admitted in intensive care with severe metabolic acidemia (pH 7,00 e HCO_3^- 1,4 mmol/L), hypoalbuminemia and hypokalemia, in need of renal therapy replacement. Blood tests did not reveal leukocytosis or elevation of the C-reactive protein, the erythrocyte sedimentation rate was normal. Bacteriological, mycobacteriological, parasitological, and clostridium stool tests were persistently negative. Colonoscopy and upper gastrointestinal endoscopy were both macroscopically normal, biopsy was not performed. An extended workup revealed normal thyroid function, cortisol level, and protein electrophoresis. Antinuclear antibodies and coeliac auto-antibodies were negative. Gastrin and VIP levels were normal. Stool osmolality was normal, and tests for reducing sugars and fat were negative. During 2 of the episodes that required hospitalization, due to a controlled arterial pressure profile, she suspended the ARB, and the diarrhea did not recur in 3-year follow-up.

Case 2

We present the case of a 61-year-old female with arterial hypertension who had been medicated with olmesartan/hydrochlorothiazide 20/25 mg for 2 years who presented 6 stools a day of watery diarrhea, without blood. She was admitted for acute kidney injury KDIGO 1 and weight loss of about 7%. She described similar episodes with 1 year of evolution. No identifiable epidemiological risk, nor history of allergies. Extensive workup excluded other causes, such as infectious etiology, inflammatory, and cancer. Colonoscopy (Fig. 1) and upper gastrointestinal endoscopy were macroscopically normal, but colon biopsy was performed revealing histological findings compatible with enteropathy

due to olmesartan, such as increased intraepithelial lymphocytes and flattened villous mucosa. She suspended the ARB, and the diarrhea did not recur in 3-month follow-up.

Discussion

The differential diagnosis of a chronic diarrhea include celiac disease, tropical sprue, autoimmune enteropathy, inflammatory bowel disease, and drug-induced enteropathy. Other clinical conditions which need to be excluded include infections disorders such as clostridioides colitis, small intestinal bacterial overgrowth, intestinal lymphomas, and combined variable immunodeficiency disease. A careful medication history is vital as certain medications of current use cause enteropathies, such as non-steroidal anti-inflammatory and anti-hypertensive drugs. Drug-associated small bowel enteropathy has been reported in association with olmesartan, and the clinical manifestations include chronic diarrhea and loss of weight.¹⁻⁵ Symptoms may be very severe and sometimes life-threatening. A latency time of 6-120 months has been described from first exposure to the onset of symptoms. Anemia and electrolyte abnormalities are also frequent.¹⁻⁴ Drug-induced enteropathy usually shows increased crypt apoptosis and may also show villous atrophy.⁵ Serology for celiac disease is negative and a gluten-free diet is not beneficial, but these patients may carry the HLA-DQ2 and/or DQ8 haplotypes, present in many patients with coeliac disease.¹ The mechanisms underlying ARB-associated enteropathy are still unknown, but the delay between the onset of symptoms after initial ARB treatment suggests a cell-mediated immunity damage, rather than a type I hypersensitivity.¹⁻² Our clinical cases report such causality relation. Discontinuation of olmesartan results in clinical and histologic improvement, and in severe cases, may require oral or intravenous steroids to alleviate the symptoms.¹⁻⁵ More studies need to be done to reveal the underlying mechanisms of ARB-associated enteropathy and to evaluate the newer classes of ARBs such as azilsartan.⁵ A complete workup and

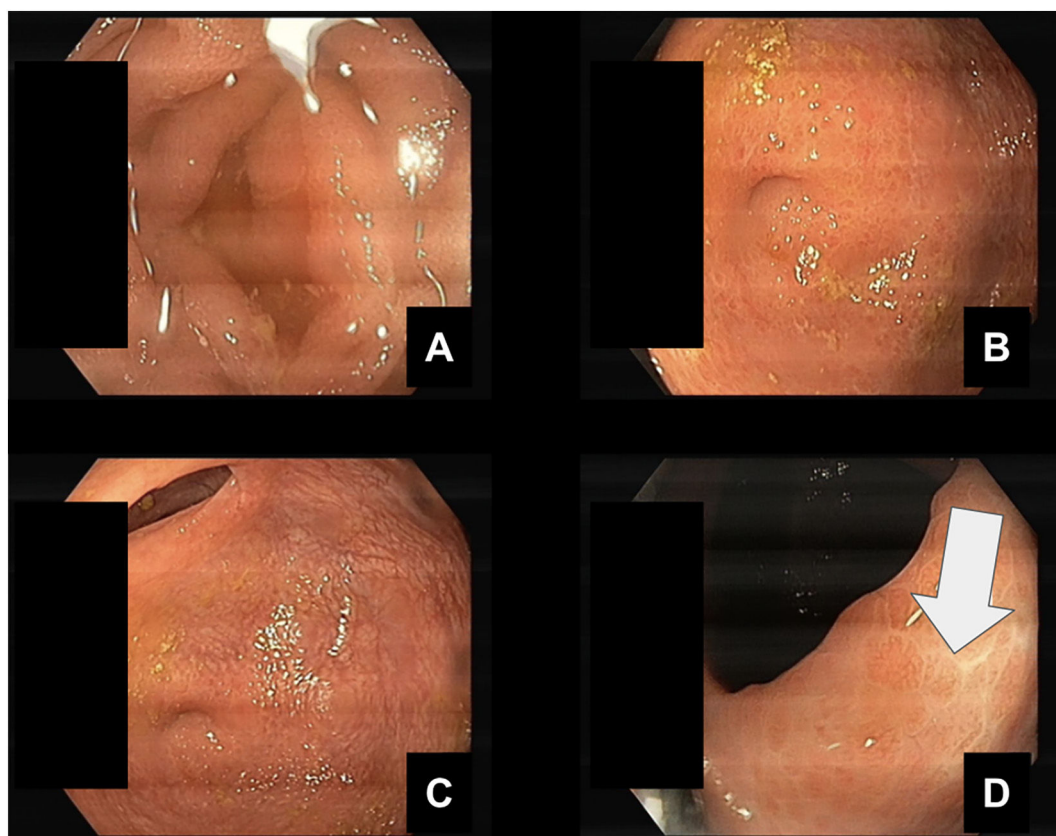


Fig. 1. Colonoscopy performed with adequate bowel preparation. Biopsies were made in the right and left colon (D).

review of medications was made to study these cases of chronic diarrhea, with negative results for all most-known conditions. The fact that there was no recurrence of symptoms, in the older patient after more than 2 years of follow-up with suspension of olmesartan, led us to believe that these were indeed cases of olmesartan-induced enteropathy. Olmesartan-induced enteropathy is uncommon but should be kept in mind when patients present with chronic diarrhea and are medicated with a ARB, and additionally, there is evidence of villous atrophy. Since coeliac disease is the most common cause of villous atrophy, it must always be excluded.²⁻³

Conclusions

Olmesartan-induced enteropathy is an entity with increasing awareness and recognition. Being a reversible and potentially fatal side effect of a commonly used antihypertensive medication, these cases highlight the need to consider their suspension before initiating an extensive investigation of chronic diarrhea.

Conflict of Interest

None

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