European Journal of Case Reports in Internal Medicine

Olmesartan-Induced Enteropathy: A Case of Recurrent Diarrhoea

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Doi: 10.12890/2020_001614 - European Journal of Case Reports in Internal Medicine - © EFIM 2020

Received: 03/03/2020
Accepted: 29/04/2020
Published: 15/05/2020

How to cite this article: Fernandes Matos AR, Coelho E, Caridade S. Olmesartan-induced entheropathy: a case of recurrent diarrhoea. *EJCRIM* 2020;**7**: doi:10.12890/2020_001614.

Conflicts of Interests: The Authors declare that there are no competing interests.

ABSTRACT

A 77-year-old man with arterial hypertension and dyslipidaemia, treated with olmesartan/hydrochlorothiazide and simvastatin, was admitted with a 3-week history of anorexia, nausea, vomiting, profuse diarrhoea and weight loss. He was dehydrated and blood tests showed acute kidney injury. The aetiological study was inconclusive. The patient had a favourable clinical evolution during hospitalization and was discharged. However, after about 10 days at home, he was re-admitted to hospital with the same clinical presentation. It was noticed that olmesartan had not been prescribed during the previous admission but had been restarted on an outpatient basis. Biopsy examination showed duodenal mucosa with villous atrophy and polymorphic inflammatory infiltrate. Antibody testing for coeliac disease was negative. Based on these facts, it was hypothesized that the patient had olmesartan-induced enteropathy, which was subsequently confirmed.

LEARNING POINTS

- Drug-induced sprue-like enteropathy must be considered in the differential diagnosis of patients with diarrhoea, weight loss, and villous atrophy of the duodenal mucosa of unknow origin.
- Olmesartan has been associated with the development of enteropathy.
- Olmesartan-induced enteropathy can happen years after drug initiation.

KEYWORDS

Olmesartan, diarrhoea, sprue-like enteropathy

CASE DESCRIPTION

We report the case of a 77-year-old Caucasian man with arterial hypertension and dyslipidaemia treated with olmesartan / hydrochlorothiazide (20/5 mg) and simvastatin (40 mg) for more than a year. He was admitted to the emergency department with a 3-week history of anorexia, nausea, vomiting, profuse watery and non-bloody diarrhoea (about five times a day) and weight loss of 7.5 kg. He denied having abdominal pain or fever. Despite living in a rural environment, he drank public potable water. He also denied consumption of contaminated food, changes in diet or medication, recent travel, or contact with toxic products or with animals. His physical examination was unremarkable except for severe dehydration. He was hospitalized for stabilization and investigation.

Blood tests showed prerenal acute kidney injury, which was corrected with fluid administration. Antihypertensive treatment was stopped. An aetiological study was inconclusive. Immunological tests (namely antibody testing for coeliac disease) were negative, as were the serological tests and endocrinological panel. Stool cultures, stool ova and parasites and a *Clostridium difficile* toxin assay were unremarkable. Abdominal-pelvic CT was unremarkable. Endoscopic studies (upper digestive endoscopy and colonoscopy) revealed diffuse erythematous gastric mucosa; random biopsies of the gastric, duodenal and colonic mucosa were performed. The clinical evolution during hospitalization was favourable: the patient had no further episodes of vomiting, the diarrhoea resolved, and there was a gradual increase in appetite. The patient remained in hospital for about 5 days after clinical normalization, without relapse of symptoms, and was then discharged.

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However, after about 10 days at home, the patient was re-admitted to hospital with the same symptoms, which he reported had started the day immediately after discharge. Diagnostic hypotheses relating to environmental and/or toxic exposures were considered. We also noticed that olmesartan had not been prescribed during the previous admission but had been restarted on an outpatient basis. We also accessed the results of the biopsies which showed duodenal mucosa with villous atrophy and polymorphic inflammatory infiltrate in the chorion. Based on these facts, it was hypothesized that the patient had olmesartan-induced enteropathy. This diagnosis was confirmed by clinical and histological responses after drug withdrawal: the clinical signs resolved completely within 1 week and 6 months after suspension of olmesartan, a second biopsy showed normalization of the structural architecture of the mucosa.

DISCUSSION

Olmesartan-induced enteropathy (OIE) is a new clinical entity [1,2], characterized by diarrhoea and weight loss [3], which should be included in the differential diagnosis of seronegative villous atrophy with negative coeliac serology [1,2]. Although the frequency of this disease seems to be low, it is very important to rapidly identify it as complications may be severe [4], and discontinuation of the causative drug leads to the resolution of symptoms and mucosal healing [1,3–6]. In addition, physicians may carry out extensive unnecessary testing [3]. Drug-induced sprue-like enteropathy must be considered in the differential diagnosis of patients with diarrhoea, weight loss, and villous atrophy of the duodenal mucosa of unknow origin [1]. Olmesartan, which is an angiotensin II receptor antagonist widely used for the treatment of hypertension [2,4,5,7,8], has been associated with the development of enteropathy [1–3,5–7]. This association was first reported by Rubio-Tapia [9] et al. in 2012, leading the FDA to issue a safety alert in 2013 [1, 3]. Other similar cases have since been described [1–3,6,7,10].

OIE can occur years after drug initiation [1]. The most frequent symptom is severe chronic diarrhoea with weight loss [3], but nausea, vomiting, fatigue and abdominal pain can also occur [1,4]. These symptoms may be complicated by severe dehydration, electrolyte abnormalities and acute renal failure [3]. This pathology is characterized histologically by severe intestinal villous atrophy with more variable intraepithelial lymphocytosis, as seen in coeliac disease [1,3,6,7]. However, sprue-like enteropathy can be distinguished from coeliac disease by the absence of antibodies and the lack of response to a gluten-free diet [1,3,7]. The differential diagnosis can be challenging because a variable degree of villous atrophy can be found in other conditions, such as autoimmune enteropathy, common variable immune deficiency, parasitic infection, small bowel bacterial overgrowth, intestinal lymphoma, HIV-related enteropathy, Whipple´s disease and tropical sprue [1,10].

The pathogenesis of this enteropathy remains unclear [1,2,6]. One proposed mechanism involves a cell-mediated immune response that damages the small intestinal brush border [1,7]. Angiotensin receptor blockers have also been suggested to have inhibitory effects on transforming growth factor, which is implicated in gut immune homeostasis [1,7]. The clinical and histological features completely resolve after drug cessation [1,3–6], allowing unnecessary investigation to be avoided [1]. In our case, the patient experienced clinical improvement during his first hospitalization due to the discontinuation of olmesartan. Since an association between the drug and the clinical presentation was not established at that time, olmesartan was restarted on an outpatient basis. However, we noticed recurrence of symptoms, which disappeared again when the drug was stopped.

This report is intended to alert clinicians to the importance of timely recognition of this cause of sprue-like enteropathy. Olmesartan is a widely used drug for the treatment of high blood pressure and the correct diagnosis of OIE can avoid unnecessary and costly diagnostic investigations and the complications associated with this disease. In conclusion, cautious medication review is imperative because some drugs can cause enteropathy [3].

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