

CASE REPORT

Olmesartan-induced enteropathy associated with cutaneous lesions

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Funding Information

No sources of funding were declared for this study.

Received: 9 November 2015; Revised: 6

January 2016; Accepted: 10 February 2016

Clinical Case Reports 2016; 4(4): 379–382

doi: 10.1002/ccr3.531

Key Clinical Message

Olmesartan is an angiotensin II receptor antagonist which may cause severe sprue-like enteropathy with duodenal villous atrophy. Skin lesions may be associated as reported for the first time in our case. Clinicians should be informed of this side effect and its reversibility after suspension of the drug.

Keywords

Enteropathy, Olmesartan, side effect, skin lesions.

Introduction

Olmesartan, an angiotensin II receptor antagonist, is commonly used to control benign hypertension [1]. Recently, three case series [2–4] and several case reports [5, 6] reported that olmesartan could induce severe sprue-like enteropathy revealed by chronic diarrhea with malabsorption syndrome and weight loss. In these series, duodenal biopsies always demonstrated histological abnormalities (moderate or severe duodenal villous atrophy in almost all cases). A gluten-free diet had no effect on diarrhea for these patients, but clinical and histological improvement occurred quickly as soon as the treatment by olmesartan was stopped.

We report the case of a 58-year-old female patient treated for 5 years by olmesartan who developed a severe chronic diarrhea with malabsorption, but without villous atrophy and skin lesions.

Case History

In December 2013, a 58-year-old female consulted for chronic diarrhea and weight loss. She had a past history of pulmonary embolism during a pregnancy. She

progressively developed overweight and arterial hypertension. In 2008, treatment with olmesartan (20 mg per day) was introduced and well tolerated. She was not taking any other medicine. Blood pressure returned to normal value under treatment. In September 2013, she experienced progressive diarrhea (4 to 6 liquid stools mainly postprandial), nausea, and abdominal pain. She had progressive weight loss (15 kg within 3 months) and no other clinical symptoms. In October 2013, standard biology (blood count, serum electrolytes, liver enzymes, albuminemia, CRP) remained in the normal ranges. Upper gastrointestinal endoscopy and colonoscopy with ileoscopy were performed in November 2013 and did not evidence any morphological abnormality. Ileal and colonic biopsies were considered as normal, duodenal biopsies demonstrated a slight increase in intraepithelial lymphocytes without villous atrophy. A second expert advice was sought and finally duodenal biopsies were considered as normal.

In November 2013, pruritus on the forearms and neckline appeared, associated with papulo-erythematous lesions and scabs (Fig. 1A and B).

In December 2013, she was referred to our unit for further investigations. The mean daily stool weight was

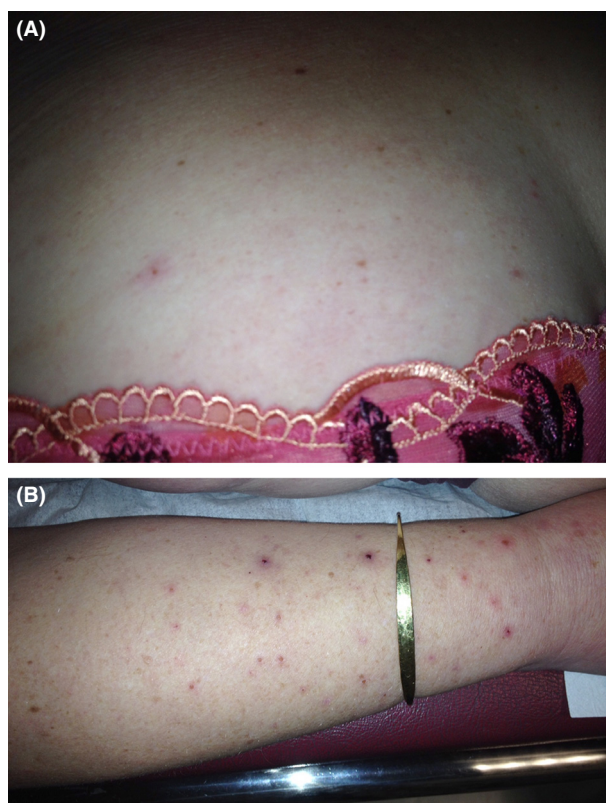


Figure 1. (A) Neckline papulo-erythematous lesions and scabs. (B) Forearms papulo-erythematous lesions and scabs.

increased at 1000 g/24 h associated with a steatorrhea at 36.4 g/24 h (normal value <7 g/24 h). Alpha-1 antitrypsin clearance and fecal elastase were normal, laxative research was negative, fecal calprotectin was not performed. Further biological etiologic assessment included TSH, chromogranin-A, gastrinemia, thyrocalcitonin, seric immunoglobulins, IgA endomysial and anti-transglutaminase antibodies, and 5-HIAA urinary excretion. All proved to be normal. An abdominal CT-scan did not evidence any abnormality. A forearm skin biopsy was performed and showed a moderate dermic lymphocytic infiltrate. Immunofluorescence with anti-C3 antibody demonstrated a linear marking of the dermo-epidermic junction pemphigoid like lesions or acquired bullous epidermolysis. In late December 2013, her symptoms didn't show any improvement and she was hospitalized for dehydration and arterial hypotension due to increasing diarrhea (10 to 15 liquid stools per day). No infection was evidenced in the analysis performed. Considering hypotension, olmesartan was stopped on admission. Rehydration and symptomatic treatment were provided. Diarrhea and skin lesions quickly disappeared, respectively within 3 and 5 days. She was discharged without any abdominal or dermatological symptoms. As hyper-

tension reappeared, treatment by olmesartan was reintroduced. Nausea, abdominal pain, and diarrhea all reappeared within 2 days. The diagnosis of olmesartan-induced diarrhea was then hypothesized. Olmesartan was stopped and symptoms rapidly disappeared, which gave further evidence for this hypothesis. After the definitive cessation of olmesartan, digestive symptoms and cutaneous lesions rapidly improved within a few days and never reoccurred after an 18-month follow-up. Hypertension was well controlled by a calcium antagonist treatment (Amlodipine).

Using the Naranjo algorithm (score calculated: 8), accountability of olmesartan in the symptoms observed in our patient was considered as highly probable.

Discussion

Drug-induced enteropathy has been previously reported with a lot of medications such as ticlopidine [7], methotrexate [8], azathioprine [9], or mycophenolic acid [10]. Recently several cases series reported olmesartan-related severe sprue-like enteropathy. Rubio Tapia and al [2] first reported 22 cases of this drug-induced pathology regressive after withdrawal of the treatment. Thereafter, two French series [3, 4], with respectively 39 and seven patients, confirmed these findings. Patients presented chronic diarrhea, weight loss, and abdominal pain after a long-term treatment with olmesartan (extremes 2–10 years). Duodenal biopsies were performed in all patients. Duodenal atrophy (partial or total) was found in almost all samples except for four patients of the Marthey and co-workers cohort that were not included in the cases description [3]. Histologic abnormalities such as an increase in intraepithelial lymphocytes and a lymphocytic infiltrate of the lamina propria were found. All these lesions had disappeared when a control endoscopy was performed after withdrawal of the drug.

In our case, after a second expert advice, duodenal biopsies were considered as normal with a normal lymphocytic infiltration. However, a recent retrospective study in patients taking olmesartan and having moderate abdominal pain, without diarrhea, could have normal duodenal biopsies in 50% of cases [11]. Other recent articles reported olmesartan-induced enteropathy without villous atrophy, which support our diagnosis [12, 13].

In our patient, the symptom's severity including a life-threatening diarrhea and a malabsorption syndrome associated with steatorrhea contrasts with the absence of histological duodenal lesions. However, lesions of the whole small intestine could cause similar symptoms. A case of severe sprue-like enteropathy associated with valsartan in whom a capsule endoscopy had been performed, showed extensive villous atrophy in 75–90% of the small bowel

[14]. Capsule endoscopy was planned for our patient in early 2014 but eventually not performed because the patient refused it after the final diagnosis was made. Other sartans do not seem to be responsible for this kind of severe side effects or it seems to be very rare. A French nationwide patient cohort compared the risk of hospitalization for intestinal malabsorption associated with olmesartan with other angiotensin receptor blockers [15]. Olmesartan users had an increased risk of hospitalization, and its duration was prolonged especially when the exposure to the drug was longer. Cases of severe diarrhea, weight loss, and acute renal failure associated with irbesartan and valsartan have been reported in the literature [3, 14].

The enteropathy of our patient occurred after 5 years of olmesartan treatment, which confirm the fact that a long-term treatment is usual to induce this sprue-like enteropathy. The long duration between the initiation of olmesartan therapy and the development of symptoms seem to involve cell-mediated immunity damage rather than type I hypersensitivity responsible of allergic reactions. Clinicians should be aware of this particularity.

To the best of our knowledge, this case report is the first detailed description of skin lesion associated with sprue-like olmesartan enteropathy. Some cutaneous reactions had previously been described in patients taking olmesartan [16], but its association with digestive symptoms had never been reported. The lesions of our patient appeared almost simultaneously with the digestive symptoms and regressed rapidly after drug withdrawal. This ascertainment strongly suggests olmesartan-related toxicity. The observed lesion type could remind us of those observed in the case of dermatitis herpetiformis associated with celiac disease, but the histological findings we found were more pemphigoid or acquired bullous epidermolysis-like lesions.

More series, case reports, and studies could permit to describe more precisely skin lesions associated with olmesartan use in terms of topography and pathophysiology.

In conclusion, we report a case of sprue-like enteropathy responsible of diarrhea and weight loss induced by olmesartan without any duodenal histological abnormalities and with skin lesions associated with the digestive symptoms. Clinicians should be informed of this side effect, its potential severity, the possible association with skin lesions and its reversibility after drug withdrawal.

Conflict of Interest

None declared.

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