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CASE REPORT

Significant Weight Loss in a Patient Taking Olmesartan: An Unusual Case Report

Andromachi Makri[1], Matilda Florentin[1,*], Moses S. Elisaf[1] and George Liamis[1]

[1]*Department of Internal Medicine, School of Medicine, University of Ioannina, Ioannina, Greece*

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Abstract: ***Objective*:** Olmesartan-induced enteropathy consists a syndrome that mimics celiac disease both clinically and histologically. Cases of this entity have sporadically been reported since 2012 and are usually characterized by severe diarrhea and malabsorption, followed by significant weight loss.

***Case Report*:** Herein, we report an uncommon case of this syndrome, where weight loss preceded several months the onset of gastrointestinal symptoms.

***Discussion and Conclusion*:** Physicians should be aware of unexplained weight loss in patients taking olmesartan, as prompt discontinuation of the drug may prevent the deleterious consequences of malabsorption.

Keywords: Enteropathy, olmesartan, weight loss, ARB, computed tomography, IgA.

1. INTRODUCTION

Olmesartan is a commonly used Angiotensin II Receptor Blocker (ARB) with an excellent safety profile and antihypertensive effect [1]. In 2012, Rubio-Tapia *et al* first reported diarrhea and weight loss in 22 patients taking olmesartan for a mean of 13 years [2]. Since then, an increasing number of cases with this syndrome, known as olmesartan-induced enteropathy, have been reported. This clinical entity is characterized by chronic diarrhea and weight loss, while the histologic findings range from intraepithelial lymphocytosis and lymphocytic proliferation of the lamina propria to marked villous atrophy [3]. Herein, we present a case, where significant weight loss was the first clinical manifestation of olmesartan- associated enteropathy, followed by severe diarrhea after several months.

2. CASE PRESENTATION

A 71-year-old woman was evaluated in the Internal Medicine Department for a 15 kg-weight loss during the preceding 14 months and a 20-day history of watery diarrhea. Laboratory studies, including blood tests and urinalysis, carried out a few days before presentation were normal. Moreover, computed tomography (CT) of the abdomen as well as upper and lower gastrointestinal endoscopy performed seven months and one year before presentation, respectively were unremarkable. The patient had a medical history of hypertension for the last 5 years and depression since the age of 25. Her medication included olmesartan 40 mg and amlodipine 5 mg which were stable for the past 5 years, whereas there was a recent modification in her antidepressant medication (venlafaxine 75 mg was replaced by amitriptyline 50 mg, duloxetine 40 mg and clorazepate 15 mg) about 15 days before presentation. However, there was no change in her symptoms with this treatment modification. She denied using tobacco, alcohol or illicit drugs. Her father died at 67 from lung cancer and her sister at 47 from breast cancer; the rest family history was insignificant.

At presentation the temperature was 36°C, the blood pressure was 143/82 mmHg, the heart rate was 69 beats per minute, the respiratory rate was 16 breaths per minute and the oxygen saturation was 98%, while the patient was breathing ambient air. Her height was 1.60 m and her weight was 43 kg (body mass index 17 kg/m^2). Bilateral pitting edema was detected on her lower extremities, while the remainder physical findings were unremarkable. The electrocardiogram was normal. Laboratory (Table **1**) and imaging studies were obtained.

The laboratory exams were significant for International Normalized Ratio (INR) prolongation, which was corrected with vitamin K administration, hypoalbuminemia without albuminuria and hypokalemia. Stool was negative for clostridium difficile, parasites or other enteropathogens. Chest radiograph and CT of brain, chest and abdomen were normal. The remainder thorough investigation for underlying infections, endocrinopathies, immunological diseases and malignancy was negative. Upper endoscopy demonstrated an edematous, reddish duodenal mucosa with reduced mucosal folds. Duodenal biopsies demonstrated the increased presence of inflammatory cells and crypt cell proliferation with substantial

*Address correspondence to this author at the Department of Internal Medicine, Medical School, University of Ioannina, Ioannina, 45110, Greece, Tel: +30-26510-99462, +30-6944662406; Fax: +30-26510-07016; E-mail: matildaflorentin@yahoo.com

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Table 1. Laboratory examinations on admission and after drug discontinuation.

Variable	Reference Range	On Admission	A Few Months Later
Hematocrit %	41-53	36,6	42,1
Hemoglobin (g/dl)	13,5-17,5	12,5	13,7
White cell count (per mm^3) Neutrophils (%)	4,000-11,000 54-62	4,120 47,6	5,560 45,5
Platelet count (per mm^3)	150,000-450,000	156,000	194,000
Red cell count (per mm^3)	4,000,000-5,900,000	4,030,000	4,690,000
MCV(fL)	80-100	90,8	89,8
Erythrocyte sedimentation rate (mm/hr)	0-15	2	2
International normalized ratio	0,9-1,1	1,3	1,1
Creatinine (mg/dl)	0,6-1,2	0,89	0,94
Urea (mg/dl)	11-54	30	40
Alanine aminotransferase (IU/L)	10-35	25	23
Aspartate aminotranferase (IU/L)	10-35	31	16
Alkaline phosphatase (IU/L)	30-125	100	89
Total bilrubin (mg/dl)	0,1-1	0,7	
Direct bilrubin (mg/dl)	0-0,2	0,16	
Ferritin (ng/mL)	11-306,8	65	
B12 (pg/μL)	145-914	675	
Creatinine kinase (IU/L)	25-160	83	83
Amylase (IU/L)	0-90	44	44
Glucose (mg/dl)	70-125	83	82
C-reactive protein(mg/L)	<6	12	
TSH (mIU/L)	0,38-5,33	2,65	2,63
FT4 (ng/dL)	0,6-1,37	1,10	
Sodium (mEq/L)	136-146	136	137
Potassium (mEq/L)	3,5-5,3	3,47	4,43
Total protein (g/dl)	6-8,4	4,7	7,2
Albumin (g/dl)	3,4-5	2,5	4,1

villous atrophy. Lower endoscopy was insignificant**.** Tissue transglutaminase antibodies (IgA) and deaminated gliadin peptide antibodies (IgA and IgG) were negative, while a gluten-free diet was found to be ineffective.

Taking into account the aforementioned examinations and by excluding almost with certainty celiac disease and neoplasia, we considered the possibility of olmesartan-induced enteropathy and discontinued olmesartan. Ten days after drug removal diarrhea resolved completely. Few months later, complete recovery of weight was observed along with normalization of laboratory tests (Table **1**). The patient denied a new upper endoscopy to confirm resolution of the lesions. As all symptoms disappeared and the patient returned to her usual condition after olmesartan withdrawal, we decided not to re-introduce the drug; in fact, we substituted olmesartan with a blood pressure lowering drug from another class.

3. DISCUSSION

This case highlights an uncommon clinical manifestation of olmesartan-induced enteropathy, where unexplained weight loss occurred over a year before the patient experienced diarrhea, whereas usually gastrointestinal symptoms prevail with or without accompanying weight loss. A severe form of intestinal injury with chronic diarrhea due to olmesartan was first described by Rubio-Tapia *et al.* in 2012

[2]. Numerous other reports of olmesartan-associated enteropathy have since appeared in the literature, several of which during the last few years [4-15], suggesting that this clinical entity is eventually being more and more recognized. In fact, in 2013, the Food and Drug Administration (FDA) approved label changes to include updated data about the association of olmesartan with sprue-like enteropathy [16].

The largest experience comes from a French cohort of 4,546,680 patients who initiated therapy with olmesartan, a different ARB or an angiotensin-converting enzyme inhibitor (ACE-I) [17]. Intestinal malabsorption severe enough to cause hospitalization was more frequent in patients taking olmesartan for one to two years [adjusted risk ratio 3.7, 95% Confidence Interval (CI) 1.8-7.3] and for over two years (adjusted risk ratio 10.6, 95% CI 5.0-22.5) compared with those treated with ACE-I [18]. Of note, no excess risk was observed with other ARBs. However, a class effect cannot undoubtedly be ruled out, as reports of sprue-like enteropathy attributed to other ARBs have been described [19-21]. A recent multidatabase large scale study found a higher rate of enteropathy in patients taking olmesartan versus other ARBs and severe diarrhea was the most common manifestation; however, the absolute incidence rate was low in both groups [22].

Symptoms of this syndrome include severe chronic diarrhea, weight loss, fatigue, nausea and vomiting, abdominal pain, bloating, and, less commonly, reflux symptoms and loss of appetite [23]. This disorder seems to affect the whole gastrointestinal tract [2]. Laboratory evaluation is usually indicative of malabsorption with normocytic anemia, hypoalbuminemia and multiple electrolyte abnormalities. Dehydration and acute renal failure are the most frequent causes of hospitalization, even in the Intensive Care Unit (ICU) [6, 15]. Other unusual cases of this entity include colonic perforation [24], Wernicke-Korsakoff syndrome due to vitamin B1 malabsorption with minimal gastrointestinal symptoms [25], nonalcoholic steatohepatitis [26] and simultaneous olmesartan-associated uveitis with enteropathy [27]. Furthermore, a case with severe diarrhea, weight loss and a cutaneous lesion histologically indicative of pemphigoid or acquired bullous epidermolysis-like lesions has been reported [28]. Both the aforementioned unusual manifestations of olmesartan-induced enteropathy, as well as our case highlight the clinical diversity of this syndrome. Therefore, physicians should think of it even if it does not manifest with its most typical clinical signs and symptoms.

The pathophysiology of this disorder is unclear; two mechanisms appear to prevail. ARBs may inhibit transforming growth factor β (TGFβ), which is involved in gut immune homeostasis and maintains the balance between proinflammatory and anti-inflammatory factors. Furthermore, there seems to be a disproportionate activation of angiotensin II receptor type 2 (AT2) receptors by angiotensin II after blocking AT1 receptors with olmesartan. Angiotensin II promotes enterocyte apoptosis, suggesting that olmesartan-associated enteropathy results from excess apoptosis of enterocytes. The high affinity of olmesartan for AT1 receptors may explain the greater incidence of enteropathy with this ARB [13-29].

The long latency period between initiation of olmesartan and development of symptoms is suggestive of cell-mediated immune damage. Rubio-Tapia *et al*. found a prevalence of HLA-DQ2 in 68% of patients with olmesartan-induced enteropathy, which is significantly higher than the expected for the general population. Anti-nuclear antibodies have also been noted in several cases [2]. These findings raise the suspicion of a genetic predisposition in such patients.

A French survey including 36 patients with olmesartan-induced enteropathy indicated that the latter may be immune-mediated, as most of the affected individuals responded to treatment with steroids and/or immunosuppressants. Furthermore, it is likely that those with a history of autoimmune disease have a higher risk of developing this syndrome [19].

Olmesartan-induced enteropathy not only resembles celiac disease in terms of symptoms, but these two disorders probably share common immunopathogenic pathways, such as an increase in CD8+ cells and overexpression of interleukin 15 by epithelial cells, as suggested by duodenal biopsies of patients taking olmesartan [29]. Therefore, we should consider olmesartan-associated enteropathy in patients with a presumptive diagnosis of celiac disease who do not respond to a gluten-free diet.

CONCLUSION

In our case, the patient was losing weight for over a year without having any other (gastrointestinal) symptom; it was, therefore, difficult to think of olmesartan as the culprit for weight loss. In this context, physicians should be alert in patients who receive olmesartan and complain about unexplained weight loss, especially if there are indications of malabsorption, even if they do not have diarrhea. After excluding other more common diseases associated with weight loss, they should consider early discontinuation of the drug in their diagnostic approach in order to avoid serious malabsorption and its consequences on patients' well being.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Written and informed consent was obtained from the the patient for this study.

STANDARD FOR REPORTING

The CARE guidelines and methodologies were followed in this study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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