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Case Report

Duodenal Villous Atrophy and Diarrhea Associated with Chronic Olmesartan Intake

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Abstract: Olmesartan is an angiotensin II receptor blocker (ARB) approved for the treatment of hypertension since 2002. Olmesartan-associated enteropathy (OAE), first described in 2012 by Rubio-Tapia, has seldom been considered as a diagnosis in patients with villous atrophy and negative serology for celiac disease. The clinical presentation could be extremely heterogenous. In contrast to celiac disease, there is no response to a gluten-free diet. The exact mechanism of intestinal injury still remains unknown. The histological pattern, at the upper gastrointestinal endoscopy, usually reveals a variable degree of villous atrophy and a moderate infiltration of lymphocytes at mucosal level. Symptoms usually improve upon olmesartan discontinuation and the repeat endoscopy could demonstrate complete resolution of inflammatory change with normal villous architecture. The differential diagnosis for this kind of clinical and pathological features include celiac disease, tropical sprue, autoimmune enteropathy, inflammatory bowel disease, and drug induced enteropathy. With this background, we report the case of a patient with a clinical picture compatible with seronegative celiac disease and symptoms that rapidly improved clinically and histologically after olmesartan discontinuation. In conclusion, although this condition is rare, physicians should be consider this medication in the differential diagnosis of this enteropathy.

Keywords: Olmesartan, Celiac Disease, Enteropathy, Diarrhea, Weight Loss, Nausea

1. Introduction

Celiac disease (CD) is the most common cause of villous atrophy and intraepithelial lymphocyte infiltrates in the small bowel [1-3]. These histological findings may be present in different disorders reproducing this condition, such as tropical sprue, autoimmune enteropathy, inflammatory bowel diseases and drug-induced enteropathy, the latter being especially observed in association with the intake of mycophenolate mofetil, methotrexate, azathioprine, colchicine and non-steroidal antiinflammatory drugs [4-6].

Olmesartan [7-8], an angiotensin II receptor blocker (ARB) used for the management of hypertension [9] has been included in the class of medications causing drug-induced enteropathy, after a spruelike enteropathy associated with this drug was first described in 2012 by Rubio-Tapia [10]. In the last few years other cases have been described, with duodenal biopsies showing variable degrees of villous atrophy with or without intraepithelial lymphocytosis [11].

Here a case of a severe villous atrophy in an old woman who was taking olmesartan for a year and whose clinical and histological manifestations improved after the discontinuation of this drug.

2. Case Report

A 70-year-old woman presented to our medical department complaining of a 5-month history of nausea, diarrhea, fatigue and hyporexia associated with a 10 kg weight loss. Her past medical history was relevant for diabetes mellitus type II complicated by polineuropathy, hypothyroidism and hypertension, and so she was on chronic therapy with metformin, levothyroxine, gabapentin and olmersartan. She had failed an empiric treatment with metoclopramide prescribed one month before she came to our attention, and denied recent travels, sick contacts, dietary changes or consumption of spoiled or at risk food. Two weeks before admission she had performed a colonoscopy which showed a normal mucosa except for a villous polyp in the colon, that on histological examination was a tubular adenoma with low grade dysplasia. Laboratory tests showed no definite abnormality: hemoglobin was 12 g/dl, mean corpuscular volume (MCV) 80 fl [normal value (n. v.) 78-99], albumin 3.9 g/dl, creatinine 0.58 mg/dl, sodium 138 mmol/L, potassium 4 mmol/l, aspartate aminotransferase 41 U/L [n. v. 5-31], alanine aminotransferase 33 U/l [n. v. 5-32], TSH 3.9 mU/L [n. v. 0.28-4]. However, there was laboratory evidence of malabsorption, with low serum levels of folic acid (2.1 mcg/l, normal value [4.6-18.7 mcg/l] and 25-hydroxyvitamin D (6.7 mcg/l, normal value [> 30 mcg/l]). Serology for celiac disease showed normal IgA levels (204 [n. v. 70-400mg/dl] and negative tissue transglutaminase antibodies (Ttg-IgA 1.3 U/mL [n. v. 0-20]). The human leukocyte antigen (HLA) DQ2 was positive, HLA DQ8 was negative. The fecal blood occult test was negative, as well as coproculture.

During hospitalization she performed an esophagogastroduodenoscopy (EGDS) that showed macroscopically scalloping of the duodenal mucosal folds. Biopsies (both in the bulb and in the descending duodenum) showed epithelial changes in association with a severe duodenal villous atrophy (villous/crypt ratio: 1/1), accompanied by a moderate intraepithelial lymphocytosis (CD3 lymphocytes) [figure 1].

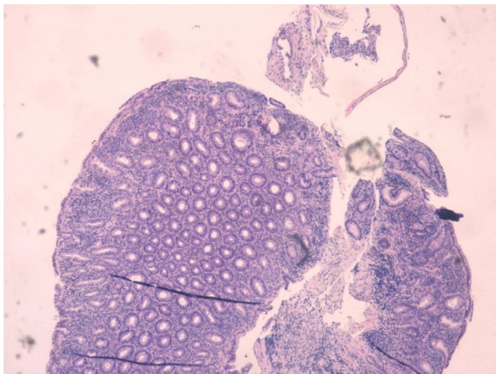

Figure 1. *In the biopsy sample obtained at the time of olmesartan intake, superficial fragments of duodenal mucosa show severe atrophy of the villi, hyperplasia of the crypts, no evidence of increased intraepithelial lymphocytes (< IELs 8-10 / 100 epithelial cells evaluated by immunohistochemistry with anti-CD3 monoclonal antibody) and normal lymphocyte distribution along the villus, with a small lymphoplasmacellular infiltrate in the lamina propria. (EE, CD3, 18-I-4811).*

An intestinal ultrasound examination failed to demonstrate thickening of the intestinal wall but a videocapsule endoscopy confirmed the presence of macroscopic signs of villous atrophy throughout the small bowel. In addition, a CT scan of the chest and abdomen showed inflammatory lymphnodes in the celiac area and in the mesenterial fat. Furthermore, she was positive for antinuclear antibodies (ANA 1: 640) with a speckeled granular pattern, and for anti-extractable nuclear antigens (ENA) antibodies (86 UA [n. v 0-20UA]), particularly antiRNP/Sm antibodies (119 UA [n. v 0-20]).

After a detailed review of the patient's medication and evaluation of the histology, olmesartan was discontinued and the patients symptoms improved within four months, with resolution of nausea and diarrhea and an increase of body weight. No antihipertensive therapy was introduced since her blood pressure maintained normal values. Two months after discharge, the patient repeated the EGDS, that confirmed villous atrophy in the second portion of the duodenum, but there was an improvement of the histological picture (villous/cript ratio: 3/2) [figure 2], thus reinforcing the diagnosis of enteropathy induced by olmesartan.

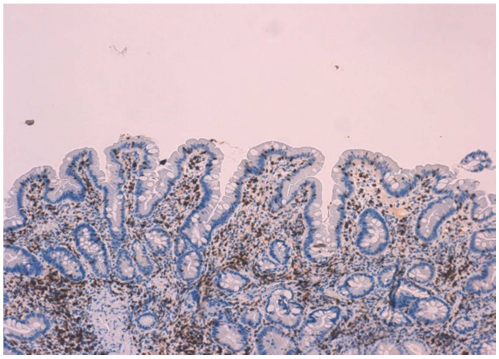

Figure 2. *After olmesartan suspension, biopsy of superficial fragments of the duodenal mucosa shows moderate villous atrophy, villus / crypt ratio (1/2), no evidence of increased of intraepithelial lymphocytes (<IELs 10-12 / 100 epithelial cells evaluated by immunohistochemistry with anti-CD3 monoclonal antibody) nor their abnormal distribution along the axis of the villus and only slight lymphoplasmacellular infiltrate in the lamina propria. (EE, CD3 18-I-9094).*

3. Discussion

Olmesartan [12-15] has been associated with the development of a sprue-like enteropathy, characterised by diarrhea, weight loss and a variable degrees of duodenal mucosa damage. The clinical presentation may be variable, spanning from mild to severe symptoms, including dehydration, acute renal failure and electrolyte abnormalities in a small percentage of cases. In patients who undergo endoscopy, non specific findings such as villous atrophy in the duodenum along with intraepithelial lymphocytosis are often found [11]. Most described patients are usually in the sixth to eighth decade of life and there is no special gender predisposition [15]. Although the time between olmesartan exposure and onset of symptoms is highly variable (from less than a few months to 5 years), it is thought that olmersartan -

induced enteropathy develops slowly [15]. In our patient, the symptoms indeed appeared after one year of drug intake, suggesting, that a long-term treatment with olmesartan is usually needed to induce the sprue - like enteropathy. Celiac serology -- including anti-transglutaminase, anti-gliadin or anti-endomysium antibodies -- are usually negative, but the prevalence of HLADQ2 is higher (68%) than in the general population (25.30%), indicating that this biomarker may be associated with an increased risk of immune mediated damage [13]. The association between autoimmunity and olmesartan enteropathy is consistent, suggesting that olmesartan may trigger changes in the intestinal epithelial cells similar to those induced by gluten in patients with CD [15]. In our case negative serology for CD, presence of HLA-DQ2 haplotype, villous atrophy with lymphocyte infiltrates at the endoscopy was suggestive for the presence of seronegative CD, but the clinical improvement after olmesartan discontinuation established a diagnosis of a drug-induced complication.

4. Conclusion

In the last few years, gastrointestinal drug-induced adverse effects are increasingly seen.

The small intestine is one of the most frequent sites of drug-induced undesirable effects, accounting for 20–40% of all adverse reactions [16].

The clinical picture may range from subtle and innocent symptoms to life-threatening presentations [16].

In particular, olmesartan-associated sprue-like enteropathy may be considered in the differential diagnosis of seronegative villous atrophy. In most cases the prompt discontinuation of the drug, is associated with the resolution of symptoms. Thus physicians must be aware of the possibility of this rare drug-induced side effect that it is potentially reversible after discontinuation of the medication.

References

[1] Ludvigsson JF, Brandt L, Montgomery SM, et al. Validation study of villous atrophy and small intestinal inflammation in Swedish biopsy registers. BMC Gastroenterol 2009; 9: 19.

[2] Ludvigsson JF, Ludvigsson J, Ekbom A, Montgomery SM. Celiac Disease and Risk of Subsequent Type 1 Diabetes: A general population cohort study of children and adolescents. Diabetes Care. 2006; 29: 2483–2488.

[3] Ludvigsson JF, Reutfors J, Osby U, Ekbom A, Montgomery SM. Coeliac disease and risk of mood disorders–a general population-based cohort study. J Affect Disord. 2007; 99: 117–126.

[4] T. R. Ziegler, C. Fernández-Estívariz, L. H. Gu, M. W. Fried, L. M. LeaderSevere villus atrophy and chronic malabsorption induced by azathioprine Gastroenterology, 2003, pp. 1950-1957.

[5] N. Kamar, P. Faure, E. Dupuis, et al. Villous atrophy induced by mycophenolate mofetil in renal-transplant patients Transpl Int, 2004, 463-467.

[6] H. Weclawiak, A. Ould-Mohamed, B. Bournet, et al. Duodenal villous atrophy: a cause of chronic diarrhea after solid-organ transplantation Am J Transplant, 2011, pp. 575-582.

[7] Burbure N, Lebwohl B, Arguelles-Grande C et al: Olmesartan-associated sprue-like enteropathy: A systematic review with emphasis on histopathology. Hum Pathol, 2016; 50: 127–34.

[8] Zhao D, Liu H, Dong P. A meta-analysis of antihypertensive effect of telmisartan versus candesartan in patients with essential hypertension. Clin Exp Hypertens 2019; 41: 75–9.

[9] The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Bethesda, MD: National Institutes of Health, National Heart, Lung, and Blood Institute, US Department of Health and Human Services; 2004. NIH Publication No. 04-5230.

[10] Rubio-Tapia A, Herman ML, Ludvigsson JF, et al. Severe spruelike enteropathy associated with olmesartan. Mayo Clin Proc 2012; 87: 732–8.

[11] Choi E-YK, McKenna BJ: Olmesartan-associated enteropathy: A review of clinical and histologic findings. Arch Pathol Lab Med, 2015; 139: 1242–47 15.

[12] Fuchs FD, DiNicolantonio JJ. Angiotensin receptor blockers for prevention of cardiovascular disease: where does the evidence stand? Open Heart 2015; 2: e000236.

[13] Abdelghany M, Gonzalez L 3rd, Slater J, Begley C: Olmesartan associated sprue-like enteropathy and colon perforation. Case Rep Gastrointest Med, 2014; 2014: 494098 16.

[14] Adike A, Corral J, Rybnicek D, et al. Olmesartan-induced enteropathy. Methodist DeBakey Cardiovasc J. 2016; 12: 230–3.

[15] Marthey L, Cadiot G, Seksik P et al: Olmesartan–associated enteropathy: Results of a national survey. Aliment Pharmacol Ther, 2014; 40: 1103-9.

[16] Zeino Z, Sisson G, Bjarnason I. Adverse effects of drugs on small intestine and colon. Best Pract Res Clin Gastroenterol. 2010; 24: 133–41.