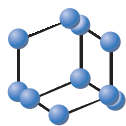


CASE REPORT

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SCIENCE

Olmesartan Associated Enteropathy: Usefulness of Video Capsule Endoscopy in a Case With Doubtful Upper Endoscopic/Histological Picture



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Abstract: Background: Olmesartan, an antihypertensive drug, may be associated with a severe “sprue-like enteropathy”.

Objectives: To report a case of Olmesartan enteropathy demonstrated by video capsule endoscopy distally from the second duodenum along with the whole small bowel before and after drug withdrawal.

Case Presentation: A 81-years-old man was referred for asthenia, chronic watery diarrhea and anasarca (ascites, pleural effusion and edemas of superior and inferior limb). The only comorbidity was hypertension treated with Olmesartan. All causes of infective and inflammatory chronic diarrhea were investigated and excluded. Upper endoscopy was normal; histological examination of the second portion of the duodenum showed moderate and patchy infiltration of lymphocytes at mucosal and intra-epithelial level with intermittent partial villous atrophy. The possibility of adverse drug reaction, estimated by Naranjo scale, showed a score of 7, indicating a strong probability. Olmesartan was then withdrawn. However, because of severe clinical general condition, we preferred to corroborate our diagnostic work-up by a non-invasive investigation, *i.e.* video capsule endoscopy, which showed jejunal and ileal mucosal alterations (mosaic pattern, diffuse hyperemia, severe edema, consequent apparent reduced lumen, diffuse thickening of intestinal folds, multiple erosions, patchy lymphangectasia). After 14 days, the resolution of anasarcatc state and hydroelectrolytic imbalances was observed. Nine months later, small-bowel video-capsule demonstrated mild mucosal hyperaemia and mosaic pattern.

Conclusion: Our case could give new insights in the field of Olmesartan associated enteropathy by highlighting the possibility of distally main lesion location and, therefore, the usefulness of video capsule endoscopy in the presence of doubtful diagnostic features.

Keywords: Olmesartan, malabsorption, sprue-like enteropathy, video capsule endoscopy, anasarca, diarrhea.

1. INTRODUCTION

Olmesartan, an antihypertensive drug, that blocks the angiotensin receptor II, may be associated with a severe “sprue-like enteropathy” with chronic diarrhea and weight loss. Symptoms are due to severe intestinal malabsorption, described for the first time by Rubio-Tapia *et al.*, in 2012 [1]. Authors observed that diarrhea may occur after a mean period of Olmesartan assumption of 3,1 years (range 0.5 - 7). This adverse effect is rare, and its exact incidence is unknown. Olmesartan-associated enteropathy shares many features with coeliac disease. Indeed, the clinical presentation is associated with histological/duodenal aspects characterized

by severe or total villous atrophy with increased number of intraepithelial lymphocytes (especially CD8), enhanced sub-epithelial collagen and inflammation of the lamina propria [2]. Bhat *et al.* in a series of seven patients found less severe histological patterns, such as mild villous blunting [3]. Sporadic reports demonstrated similar enteropathies triggered by angiotensin-receptor blockers other than Olmesartan, thus suggesting a class-effect adverse reaction [4-7]. A recent systematic review by Kamal *et al.*, [8] enclosed 248 cases of sartanic users: 233 Olmesartan, 5 Telmisartan, 4 Irbesartan, 3 Valsartan, 2 Losartan and 1 Eprosartan.

The pathophysiology is unclear. Marietta *et al* proposed a role for overexpression of IL15 by epithelial cells reflecting increased CD8 and consequent tight junction destruction similar to the innate effect of gluten on the enterocytes of coeliac patients [9].

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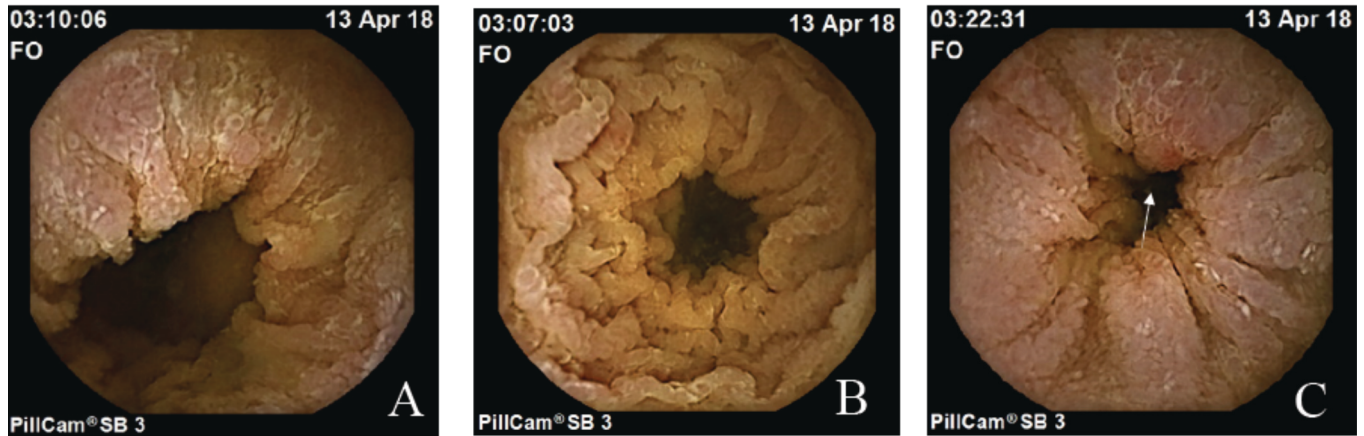


Fig. (1). A: mosaic pattern; B: severe edema with thickening of intestinal folds; C: severe edema and erosion (arrow) with consequent apparent reduced lumen.

Diagnosis is based on the histological picture of the duodenum associated with the exclusion of all other causes of malabsorption and chronic diarrhea [1], especially celiac disease. Diagnosis confirmation and treatment are constituted by clinical and damage complete reversal after Olmesartan withdrawal [1].

Since, the wide-ranging systematic review [8] states that retrospective studies performed until now had inconsistent study designs (*e.g.* differences in periods of study and case definition) and findings, it is possible that some aspects of this clinical entity still have to be observed. Therefore, herein, we report a singular case of “sartanic enteropathy” in which video capsule endoscopy was used to corroborate the diagnosis since upper endoscopy did not demonstrate substantial alterations. At the best of our knowledge, this is the first iconographic demonstration of the whole small bowel mucosal damage during Olmesartan assumption and after its withdrawal.

2. CASE PRESENTATION

An 81-years-old man was referred for asthenia and chronic watery diarrhea (four bowel movements/day) persisting for about 2 years. The only comorbidity was hypertension treated with a combination of Olmesartan and hydrochlorothiazide (20/12 mg/die). At hospitalization, the patient was in an anasarctic condition (moderate ascites, bilateral pleural effusion and severe edema of superior and inferior limbs) with a paradoxical BMI value of 28.6 kg/m² due to massive water retention. In this context, laboratory investigations showed severe hypoalbuminemia (1.8 g/dL), hypokalaemia (2.9 mmol/l) poorly responsive to external supplementation, moderate hypernatraemia, multifactorial anemia with decreased serum values of iron, folates and vitamin B12 (haemoglobin: 9.7 g/dL, red blood cell count: 3.27 x 10⁶ cells/ μ L, mean corpuscular volume: 90.1 fL), increased C-reactive protein and erythrocyte sedimentation rate.

All the causes of both infective and inflammatory chronic diarrhea were investigated. In detail, anti-transglutaminase, anti-gliadin and anti-endomysium were negative as well as stool search of *Salmonellae*, *Shigelle*, *E. Coli*, *Yersinia*, *Campylobacter jejuni*. Indices of thyroid and liver function

as well as oncological markers (including *neuron-specific enolase*, chromogranin A, alphafeto-protein, carcinoembryonic antigen and Carbohydrate Antigen 19) were negative. Upper endoscopy was a normal and histological examination of the second portion of the duodenum showed moderate and patchy infiltration of lymphocytes at mucosal and intra-epithelial level with intermittent partial villous atrophy. Colonoscopy revealed just uncomplicated sigmoid diverticula. Histology did not reveal any specific inflammatory alteration of both the large bowel and terminal ileum.

Naranjo scale [10] was used to estimate the possibility of an adverse drug reaction. The final score was 7, thus indicating a strong probability of Olmesartan related enteropathy. Therefore, Olmesartan was withdrawn.

However, because of severe hypoalbuminemia, anasarctic state and hydroelectrolytic imbalances, we decided to corroborate our diagnostic work-up by investigating the small bowel avoiding an invasive investigation such as enteroscopy. Thus, video capsule endoscopy by Pillcam SB3 (Medtronic, Dublin, Ireland) was performed.

The total duration of the video was 12 hours and 17 minutes.

The main small bowel mucosal alterations were (Fig. 1):

- mosaic pattern (Figs. 1A and 2),
- diffuse hyperemia (Fig. 2),
- severe edema and consequent apparent reduced lumen (Fig. 1B),
- diffuse thickening of intestinal folds (Fig. 1B),
- multiple erosions with fibrin clots (Fig. 1B and 1C)
- patchy lymphangiectasia

Diuretics (furosemide and potassium canrenoate) were temporarily introduced. Successively, a cardiologist was consulted and slow-release nifedipine 20 mg daily was administered. The complete symptoms recovery was achieved in about ten days after sartanic treatment discontinuation.

After 14 days of hospitalization, the patient was discharged with the complete resolution of anasarctic state and hydro-electrolytic imbalances.

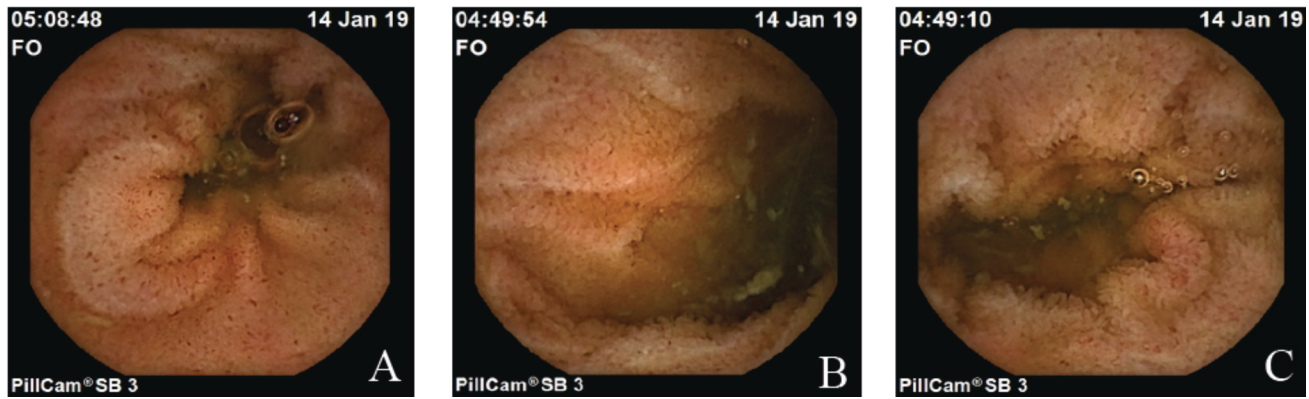


Fig. (2). (A-C): mosaic pattern and mucosal hyperaemia.

Nine months later, upper endoscopy and histology of distal duodenum showed a normal picture. However, small-bowel video-capsule demonstrated a persistent mucosal hyperaemia and mosaic pattern even if with an evident improvement when compared to the previous investigation (Fig. 2).

3. DISCUSSION

The first description of Olmesartan induced enteropathy is from Rubio-Tapia *et al.*, who described 22 cases [1]. In all the main diagnostic finding was a histological picture of distal duodenum characterized by villous atrophy, intraepithelial lymphocyte massive infiltration, enhanced subepithelial collagen and inflammation of the lamina propria in the absence of celiac disease. In this as well as in successive series and/or case reports, very few data were reported about the macroscopic aspect of this condition. In detail, Shenbagarajand Swift [11] described a nonspecific picture of mucosal inflammation and Mandavdhare *et al.* [12] a more detailed feature of scalloping and grooving of the duodenum. Moreover, the exact extension of small bowel involvement has not been investigated despite a case report of Desruisseaux *et al.*, [13] who interestingly described a collagenous sprue observed in the duodenum and terminal ileum with villous atrophy and increased intraepithelial lymphocytes. These controversial aspects have been confirmed by a recent systematic review [8] including 248 patients and highlighting that retrospective studies performed until now had inconsistent study designs and findings.

In this scenario, a singular case of Olmesartan related enteropathy is described, where severe symptoms, mainly due to malabsorption (hypoalbuminemia and anemia) lasted for two years and had given rise to severe complications of malnutrition, *i.e.* massive and diffuse anasarca. Despite this dramatic clinical picture and the reliable suspicion of “sartan enteropathy”, confirmed by the score obtained using Naranjo scale [10], surprisingly upper endoscopy did not demonstrate any alteration. Moreover, histological examination of the second portion of the duodenum showed minor changes such as a mild and patchy infiltration of lymphocytes at a mucosal and intra-epithelial level without a clear diffuse villous atrophy. This non-specific endoscopic-histological aspect led us to perform video capsule endoscopy in order to demonstrate

the presence of supposed enteropathy as well as its site and extension. Despite video capsule endoscopy has the limit of the unfeasibility of collecting biopsy samples, we avoided to perform invasive investigations (enteroscopy) for both the general clinical conditions and old age of the patient. On the other hand, Naranjo score suggested us to suspend Olmesartan and symptom improvement immediately occurred.

The main peculiarity of our case is that video capsule endoscopy showed a large spectrum of alteration along the whole small bowel (diffuse hyperemia, severe oedema and consequent apparent reduced lumen, multiple erosions with fibrin clots, diffuse thickening of intestinal folds, mosaic pattern and patchy lymphangiectasia) thus revealing, for the first time, both the severity and diffuse location of intestinal Olmesartan-induced damage. A significant suggestion from our case is that an extensive small bowel involvement may be observed distally from the second portion of the duodenum even in the absence of upper endoscopic alterations and in the presence of minimal histological changes. We are conscious that this finding is unusual and disagrees with most of the reports. Nevertheless, we believe that a medical error is highly unlikely since endoscopic and histological examinations were performed by experienced operators. Rather, it is possible that Olmesartan enteropathy could share with celiac disease the patchiness and duodenal-jejunal variations of the mucosal abnormalities [14]. On the other hand, also in celiac disease, video capsule endoscopy has been indicated in the case of discordant results between serological and histological investigations as well as in patients with nonresponsive or refractory disorder [15].

Finally, the same investigation showed the persistence of mucosal hyperemia and mosaic pattern nine months after Olmesartan withdrawal despite a complete symptomatic and biochemical resolution. These alterations, even if clinically not significant, could indicate that Olmesartan enteropathy, similarly to symptom onset, may require a long time also for complete mucosal healing.

CONCLUSION

In conclusion, the case we observed gives new insights to what was reported until now, in a recently observed rare condition such as Olmesartan associated enteropathy, thus stimulating a vigilant approach of clinicians [8]. Moreover, it

highlights even for this purpose the usefulness of video capsule endoscopy in the presence of doubtful features or in the need to obtain information regarding the whole small bowel involvement.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

The patient gave informed consent to the anonymous publication of this case report.

STANDARD FOR REPORTING

The study has followed the CARE guidelines.

FUNDING

None.

CONFLICT OF INTEREST

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

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Declared none.

REFERENCES

- [1] Rubio-Tapia A, Herman ML, Ludvigsson JF, *et al.* Severe spruelike enteropathy associated with olmesartan. *Mayo Clin Proc* 2012; 87(8): 732-8. [http://dx.doi.org/10.1016/j.mayocp.2012.06.003] [PMID: 22728033]
- [2] Burbure N, Lebowl B, Arguelles-Grande C, Green PHR, Bhagat G, Lagana S. Olmesartan-associated sprue-like enteropathy: A systematic review with emphasis on histopathology. *Hum Pathol* 2016; 50: 127-34. [http://dx.doi.org/10.1016/j.humpath.2015.12.001] [PMID: 26997446]
- [3] Bhat N, Anupama NK, Yelsangikar A, Vizhi K. Olmesartan-related sprue-like enteropathy. *Indian J Gastroenterol* 2014; 33(6): 564-7. [http://dx.doi.org/10.1007/s12664-014-0506-7] [PMID: 25303875]
- [4] Herman M, Rubio-Tapia A, Marietta E, Wu T, Murray J. Severe enteropathy in a patient on valsartan. *Am J Gastroenterol* 2013; 108(Suppl. 1): S302.
- [5] Cyrany J, Vasatko T, Machac J, Nova M, Szanyi J, Kopacova M. Letter: Telmisartan-associated enteropathy - is there any class effect? *Aliment Pharmacol Ther* 2014; 40(5): 569-70. [http://dx.doi.org/10.1111/apt.12850] [PMID: 25103353]
- [6] Cammarota G, Ianiro G, Bibbò S, Gasbarrini A. Letter: Telmisartan associated enteropathy - is there any class effect? Authors' reply. *Aliment Pharmacol Ther* 2014; 40(5): 569-70. [http://dx.doi.org/10.1111/apt.12870] [PMID: 25103354]
- [7] Marthey L, Cadiot G, Seksik P, *et al.* Olmesartan-associated enteropathy: Results of a national survey. *Aliment Pharmacol Ther* 2014; 40(9): 1103-9. [http://dx.doi.org/10.1111/apt.12937] [PMID: 25199794]
- [8] Kamal A, Fain C, Park A, *et al.* Angiotensin II receptor blockers and gastrointestinal adverse events of resembling sprue-like enteropathy: A systematic review. *Gastroenterol Rep (Oxf)* 2019; 7(3): 162-7. [http://dx.doi.org/10.1093/gastro/goz019] [PMID: 31217979]
- [9] Marietta EV, Nadeau AM, Cartee AK, *et al.* Immunopathogenesis of olmesartan-associated enteropathy. *Aliment Pharmacol Ther* 2015; 42(11-12): 1303-14. [http://dx.doi.org/10.1111/apt.13413] [PMID: 26423313]
- [10] Naranjo CA, Busto U, Sellers EM, *et al.* A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; 30(2): 239-45. [http://dx.doi.org/10.1038/clpt.1981.154] [PMID: 7249508]
- [11] Shenbagaraj L, Swift G. Olmesartan-associated severe gastritis and enteropathy. *BMJ Case Rep* 2018; 11(1): pii: e226133. [http://dx.doi.org/10.1136/bcr-2018-226133]
- [12] Mandavdhare HS, Sharma V, Prasad KK, Kumar A, Rathi M, Rana SS. Telmisartan-induced sprue-like enteropathy: A case report and a review of patients using non-olmesartan angiotensin receptor blockers. *Intest Res* 2017; 15(3): 419-21. [http://dx.doi.org/10.5217/ir.2017.15.3.419] [PMID: 28670240]
- [13] Desruisseaux C, Bensoussan M, Désilets E, *et al.* Adding water to the mill: Olmesartan-induced collagenous sprue-A case report and brief literature review. *Can J Gastroenterol Hepatol* 2016; 2016: 4837270. [http://dx.doi.org/10.1155/2016/4837270] [PMID: 27446843]
- [14] Scott BB, Losowsky MS. Patchiness and duodenal-jejunal variation of the mucosal abnormality in coeliac disease and dermatitis herpetiformis. *Gut* 1976; 17(12): 984-92. [http://dx.doi.org/10.1136/gut.17.12.984] [PMID: 1017719]
- [15] Alimetov AY, Poliakov PP, Onopriev AV, Avakimyan AV, Zanin SA, Kade AK. Capsule endoscopy for diagnosis of celiac disease. *Ter Arkh* 2019; 91(2): 91-6. [PMID: 31094178]