Case Report

Olmesartan: An overlooked cause for non-celiac sprue like enteropathy

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Abstract

Objective: Chronic diarrhea is a frequently encountered clinical problem and is often challenging to diagnose. During the evaluation of chronic diarrhea, enteropathy is commonly found, but a specific etiology is not achieved. A drug-induced enteropathy is overlooked quite often. **Methods:** Olmesartan is an angiotensin II receptor blocker (ARB), and is frequently prescribed by physicians in India. We present a case of 51 years female; who was managed for repeated episodes of sever diarrhea requiring repeated hospital admission for dehydration and acute kidney injury. **Results and conclusion:** On evaluation she was found to have enteropathy for which no cause could be elicited. She remained undiagnosed for months with persisted symptoms until an observation between her symptoms and olmesartan was observed. Her symptoms and enteropathy promptly resolved after discontinuing olmesartan. In this article a short review for the possible differential diagnosis for sprue like enteropathy will also be discussed.

Keywords: Olmesartan, chronic diarrhea, non-celiac enteropathy

Introduction

Celiac disease is the most common cause of enteropathy (Fasano et al., 2012). Despite the availability of diagnostic tests such as celiac serology, genetic typing, flow cytometry, open access to endoscopy, and wireless capsule endoscopy, the aetiology of enteropathy remains unclear in a substantial portion of patients. Non-celiac enteropathy can occur due to several diseases tropical sprue, Giardia, HIV, autoimmune enteropathy, etc (Pallav et al., 2012) and should be ruled out in undiagnosed cases. Severity of symptoms of enteropathy may vary, but can be severe and sometimes life-threatening. Extensive diagnostic work-up and hospitalization can cause substantial morbidity and cost for these patients.

Drug induced enteropathy is rare and have been previously reported with few drugs like azathioprine, mycophenolate mofetil (Ziegler et al., 2003; Weclawiak et al., 2011). Olmesartan is a selective antagonist of angiotensin II, widely used in the treatment of essential hypertension. It is popular first line treatment for hypertension in India. Here we will discuss a case of non-celiac enteropathy which was related to olmesartan with a short review understanding about various differential diagnosis.

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Methods/Case Study

A 51-year female started with diarrhea in February 2015. She described her diarrhea as; large volume, painless, not associated with meal intake, non-bloody, without any fever or vomiting's. Apart from being diagnosed to have hypertension 12 years back her medical history was unremarkable. She was currently being managed with Nebivolol and Olmesartan for last one year. She was managed with antibiotics, and antidiarrheal agents and was advised for follow up by her physician.

Subsequently, In March she persisted to have multiple episodes of diarrhea, each episode lasted for 2-3 days, severe enough and requiring hospitalization for I/V fluids. After hospital admissions her symptoms used to improve within 24-48 hours but she presented with relapse in her symptoms after 3-4 days. During hospital admissions her antihypertensive medicines used to be withheld and were re-introduced on discharge when her symptoms used to improve.

In April 2015, she presented at our center with severe dehydration, acute kidney injury and metabolic acidosis, require intensive care and a session of hemodialysis. After initial fluid management and supportive care her AKI improved. Simultaneously we also started evaluating her for a cause of her painless small bowel chronic diarrhea.

Results

Her physical examination revealed pallor, and systemic examination was unremarkable. Her routine blood investigations suggested anemia (Hb-11.1 g/dl). Stool examination for ova and cyst and stool C & S were negative. Her IgA TtG (tissue transglutaminase) and immunoglobulins levels were normal. Her serum chromogranin was normal. D-Xylose test was suggestive of malabsorption. An upper gastrointestinal endoscopy was done and multiple biopsies were taken from the second part of the duodenum. Duodenal biopsy revealed partial villous atrophy with crypt hyperplasia and increased IEL's (Figure 1). Colonoscopy with random colonic biopsies also revealed features of lymphocytic infiltrates suggestive of lymphocytic colitis. To rule out celiac disease HLA DQ2/DQ8 was done which was negative. HIV serology was negative. Small intestinal bacterial overgrowth was ruled out as patient had already received multiple courses of antibiotics with no improvement.

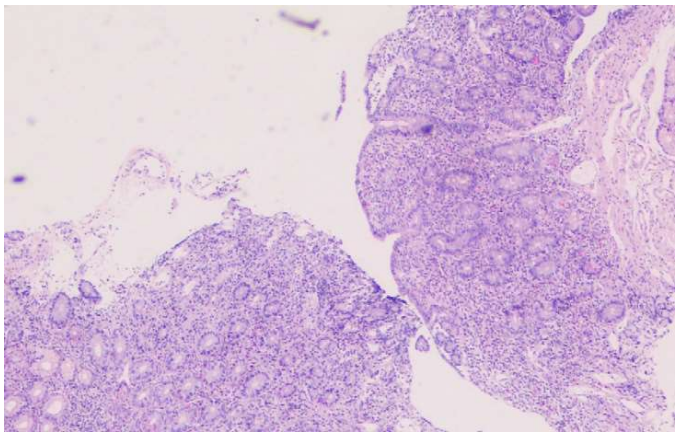

Figure 1. Duodenum biopsy showing partial villous blunting, lamina propria inflammation extending down to the base of mucosa (hematoxylin-eosin, original magnification x 40).

As no obvious cause of enteropathy was elicited and patient had persisted with her symptoms an observation was made between re-introduction of olmesartan and episodes of diarrhea. We reviewed the literature and found the report by (Rubio-Tapia et al., 2012) and hypothesized the same in our patient. Olmesartan was replaced by amlodipine for hypertension. Our patient reported back in 1 week with no further diarrheal episodes. Her duodenal biopsy was repeated after a month with normal villous pattern.

Discussion

In Northern India celiac disease is the most common cause of enteropathy associated with villous atrophy (Yadav et al., 2011). In a patient with suspected enteropathy, a diagnostic work up includes tests such as celiac serology, genetic typing, flow cytometry, upper gastrointestinal endoscopy, and wireless capsule endoscopy. Even after an extensive evaluation the aetiology of enteropathy remains unclear in a substantial portion of patients.

An undiagnosed case of enteropathy can lead to extensive repeated workups, recurrent hospitalization, ultimately amounting to high cost burden on the patient. Our patient had recurrent episodes of painless small bowel diarrhea with negative etiological work up for celiac disease and other common causes of enteropathy. The patient had recurrent hospital admissions in a short time span with disease severity causing kidney injury and requiring hemodialysis. Our patient had a prompt resolution of diarrhea when olmesartan was omitted and had recurrence of symptoms on re-introduction.

A clinico-pathological association between olmesartan and sprue like enteropathy was first observed by Rubio-tapia at Mayo clinic in 2012 (Rubio-tapia et al., 2012). They identified 22 patients who presented with diarrhea, weight loss, negative anti-transglutaminase antibodies with evidence of enteropathy, and no clinical response to gluten-free diet. Possible, other causes of enteropathy were also ruled out and patients finally responded both clinically and histologically to olmesartan discontinuation.

A national survey was done in France few years back and 36 cases were reported with olmesartan-induced enteropathy, accounting olmesartan as a cause of severe immune mediated enteropathy; with or without villous atrophy (Marthey et al., 2014). Another French study survey observed that that a duration of more than 1 year of consuming olmesartan is more related to the effect of enteropathy (Basson et al., 2015).

FDA announced a warning on olmesartan for causing sprue like diarrheal illness in 2013. A systemic survey done in 2014 found around 11 publications with olmesartan-induced enteropathy. Amounting to a global reporting of the incidence, olmesartan induced enteropathy is now considered as a distinct clinical entity (Ianiro G et al, 2014). Subsequently an Indian series was published involving seven patients with chronic painless diarrhea and villous atrophy. All patients were on olmesartan and responded to drug withdrawal (Bhat et al., 2014).

Olmesartan induced enteropathy can affect almost the entire gut. Clinical manifestations can be severe, such as life-threatening diarrhea with dehydration, acute renal failure, electrolyte abnormalities and metabolic acidosis (Rubio-Tapia et al., 2014). The pathological mechanism remains unclear. The long latency period between drug exposure and symptoms makes Type 1 hypersensitivity unlikely. A possible role of cell mediated delayed

hypersensitivity reaction has been considered. Rubio-Tapia found a significant increase in the numbers of CD8+ cells in the duodenal biopsies from these patients while still taking olmesartan. An alternate hypothesis suggested is the inhibition of the transforming growth factor beta (TGF-β) which is an important mediator of intestinal immune homeostasis, as seen with all ARBs (Marthey et al., 2014).

Olmesartan is the only drug been reported widely for causing enteropathy between ARB's. The association between other ARB's (Irbesartan and Valsartan) is rare and only two cases have been reported (Marthey et al., 2014; Herman et al., 2015). Thus, a drug specific mechanism seems more realistic than class specific as other ARB's rarely cause similar symptoms.

Olmesartan must be considered as a cause of severe diarrhea in order to facilitate an early identification of patients with enteropathy, particularly those with severe diarrhea, duodenal villous atrophy, and negative celiac serology. Other causes of villous atrophy with negative celiac serologies should also be excluded according to regional endemicity (Table 1). Drug discontinuation is vital for confirming suspected olmesartan-induced sprue-like enteropathy and it will result in rapid clinical improvement. A re-introduction of the drug will cause symptoms to relapse.

Table 1. Causes of villous atrophy with negative celiac serologies

Condition	Work up
Tropical sprue	Endemic area, Folate
HIV enteropathy	HIV, CD4+ cells
Giardia	Giardia antigen in stool, Duodenal biopsy
Small bowel bacterial overgrowth	Breath test, small bowel fluid culture
Collagenous sprue	Subepithelial collagen deposition
Hypogammaglobulinaemic sprue	Serum immunoglobulins
Seronegative celiac disease	HLA genotyping, gluten challenge
Eosinophilic gastroenteritis	Eosinophilic infiltration
Autoimmune enteropathy	Antienterocyte antibodies
Common variable immune deficiency	Serum immunoglobulins
Drug induced enteropathy	Drug discontinuation and re-introduction

Conclusion

It is critical to keep olmesartan in mind when evaluating patients with unexplained chronic diarrhea. If a patient is non-responsive to conventional treatment with suggested enteropathy and no obvious etiology, we propose a high index of suspicion and omitting olmesartan medication for those who are currently on this medicine. The timing of the improvement of symptoms promptly after stopping olmesartan and recurrence with re-introduction will indicate that olmesartan associated sprue like enteropathy is the likely etiology.

References

Basson M, Mezzarobba M, Weill A, Ricordeau P, Allemand H, Alla F, Carbonnel F. 2016. Severe intestinal malabsorption associated with olmesartan: a French nationwide observational cohort study. Gut 65(10):1664-9.

Bhat N, Anupama NK, Yelsangikar A, Vizhi K. 2014. Olmesartan-related sprue-like enteropathy. Indian Journal of Gastroenterology 33(6):564–7.

Fasano A, Catassi C. 2012. Clinical practice. Celiac disease. The New England Journal of Medicine 367(25):2419–26.

Herman ML, Rubio-Tapia A, Wu T-T, Murray JA. 2015. A Case of Severe Sprue-Like Enteropathy Associated With Valsartan. ACG Case Reports Journal, 2(2):92–4.

Ianiro G, Bibbò S, Montalto M, Ricci R, Gasbarrini A, Cammarota G. 2014. Systematic review: Sprue-like enteropathy associated with olmesartan. Alimentary Pharmacology and Therapeutics 40(1):16–23.

Marthey L, Cadiot G, Seksik P, Pouderoux P, Lacroute J, Skinazi F, Mesnard B, Chayvialle JA, Savoye G, Druez A, Parlier D, Abitbol V, Gompel M, Eoche M, Poncin E, Bobichon R, Colardelle P, Wils P, Salloum H, Peschard S, Zerbib F, Méresse B, Cerf-Bensussan N, Malamut G, Carbonnel F. 2014. Olmesartan-associated enteropathy: results of a national survey. Alimentary Pharmacology and Therapeutics 40(9):1103–9.

Pallav K, Leffler DA, Tariq S, Kabbani T, Hansen J, Peer A, Bhansali A, Najarian R, Kelly CP. 2012. Noncoeliac enteropathy: the differential diagnosis of villous atrophy in contemporary clinical practice. Alimentary Pharmacology and Therapeutics 35(3):380–90.

Rubio-Tapia A, Herman ML, Ludvigsson JF, Kelly DG, Mangan TF, Wu TT, Murray JA. 2012. Severe Spruelike Enteropathy Associated With Olmesartan. Mayo Clinic Proceedings 87(8):732–8.

Rubio-Tapia A. 2014. Sprue-like enteropathy associated with olmesartan - broadening the differential diagnosis of enteropathy. Alimentary Pharmacology and Therapeutics 40(11–12):1362–3.

Weclawiak H, Ould-Mohamed A, Bournet B, Guilbeau-Frugier C, Fortenfant F, Muscari F, Sallusto F, Dambrin C, Esposito L, Guitard J, Abbal M, Rostaing L, Kamar N. 2011. Duodenal villous atrophy: a cause of chronic diarrhea after solid-organ transplantation. American Journal of Transplantation 11(3):575–82.

Yadav P, Das P, Mirdha BR, Gupta SD, Bhatnagar S, Pandey RM, Makharia GK. 2011. Current spectrum of malabsorption syndrome in adults in India. Indian

Journal of Gastroenterology 30(1):22–8.

Ziegler TR, Fernández-Estívariz C, Gu LH, Fried MW, Leader LM. 2003. Severe villus atrophy and chronic malabsorption induced by azathioprine. Gastroenterology 124(7):1950–7.