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Case Report

Olmesartan Induced Enteropathy- Common Drug Uncommon Side-Effect

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ABSTRACT

Olmesartan-Induced Enteropathy (OIE) is a newly detected entity, typically presenting with chronic diarrhoea, weight loss, and villous atrophy on biopsy.

Early recognition of this adverse event is usually delayed due to clinical and histologic similarities with celiac disease. We report a case of a 60 -year-old female, known hypertensive, presenting with persistent/chronic diarrhea and vomiting. She had undergone multiple rounds of antibiotics and non-invasive procedures for her symptoms but to no avail. Her duodenal biopsy with negative tissue transglutaminase (Anti-TTG) and a history of olmesartan use clinched the diagnosis. Stopping olmesartan resulted in a dramatic and rapid reversal of symptoms. Clinicians should be aware of the adverse drug reactions of this commonly used antihypertensive drug. Alternative antihypertensive drugs can simplify the diagnostic workup and provide both clinical and histologic improvement rapidly.

Keywords: Enteropathy; Villous atrophy; Chronic diarrhoea; Olmesartan induced adverse effects

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INTRODUCTION

Olmesartan is an angiotensin II receptor antagonist first approved for the treatment of hypertension in 2002. OIE is a recently detected condition, first reported in a case series of 22 patients by Mayo Clinic in 2012,the largest case series so far.[1] Since then, many case reports have been published across the world. Similar side effects with telmisartan, irbesartan, valsartan, losartan, and eprosartan are also reported.[2] Food and Drug Administration (FDA) has issued a warning for the risk of enteropathy in 2013, however olmesartan continues to be a popular antihypertensive in the Indian subcontinent. This is likely because it demonstrates a promising response in lowering blood pressure and bears a favorable drug-drug interaction profile.[3] OIE causes villous flattening and reduces the

effective absorption surface area causing enteropathy. Unabsorbed nutrients cause osmotic diarrhoea. Diagnosis of OIE should therefore be considered in cases of villous atrophy with negative celiac serology. Resolution of symptoms after olmesartan withdrawal almost confirms the diagnosis. Mucosal recovery usually occurs in 3 to 6 months of olmesartan withdrawal. Follow-up duodenal biopsy is reasonable and shows histologic resolution.

CASE REPORT

We report a case of a 60 -year-old female with complaints of non-bloody diarrhea and vomiting. She had been experiencing 5-10 episodes of large watery stools for 6 weeks; it was associated with occasional episodes of bilious vomiting and mild spasmodic abdominal pain. She was earlier being treated at a local hospital with intravenous and oral antibiotics. When she presented to us, she had already received multiple trials of empirical antibiotics and had tried multiple sessions of hydroponic therapy, an alternative form of medicine. None of these provided her any relief. Due to excessive fluid loss, she had developed hypokalaemia and acute kidney injury. Her stool routine microscopy, culture, and hanging drops were negative. USG abdomens with pelvis, CECT abdomen were normal. Her laboratory findings revealed normal hemogram, liver functions, thyroid, and sugars.

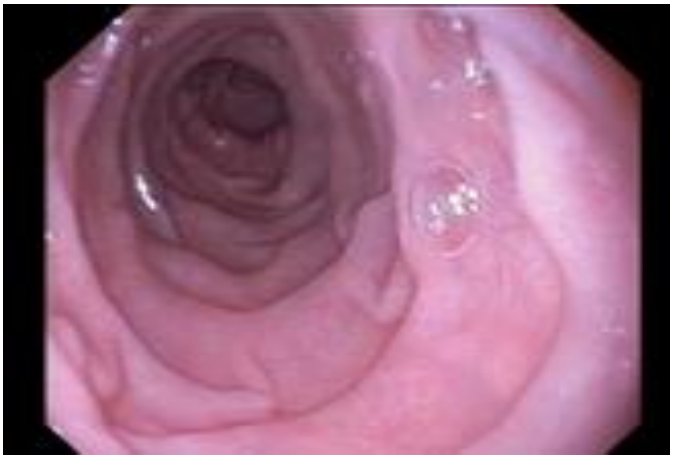
A gastroenterology consultation was obtained. On reviewing her history, she was found to be a known case of hypertension, being treated with olmesartan and amlodipine for about 2 years. She had no associated complaints or other comorbidities and had a short history, with presentation at an elderly age of 60. Differentials of drug induced enteropathy, celiac disease, tropical sprue, and other aging infections were made.

Immediately olmesartan was stopped. Ig A anti-TTg(tissue transglutaminase) was sent.

After correction of the electrolyte imbalance, the patient was planned for an Esophagogastroduodenoscopy(EGD) and ilio-colonoscopy.

EGD revealed partial blunting of villi in the D2 (Figure 1), however the ileo-colonoscopy was normal.

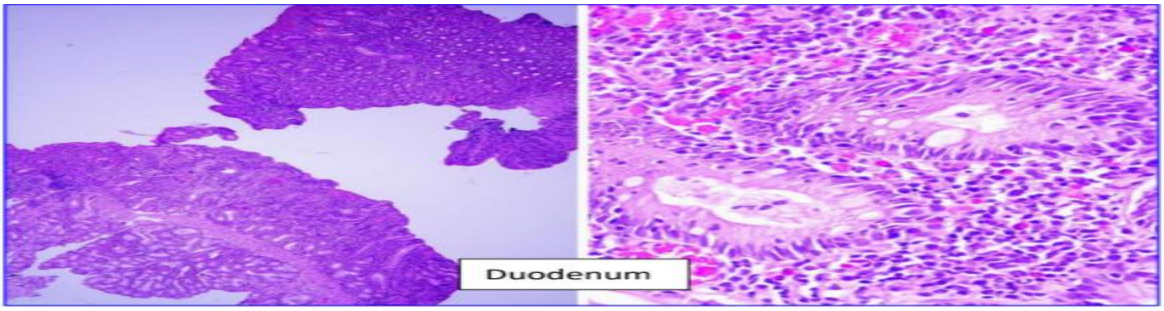
Figure 1



Mapping biopsies were obtained both from the duodenum & the colon.

Endoscopic duodenal biopsy revealed sprue-like enteropathy with diffuse villous blunting, crypt hyperplasia, and an increase in intraepithelial lymphocytes. (Figure 2) Mapping colonic biopsies revealed nonspecific inflammatory changes.

Figure 2



By day 5 of admission, her majority of symptoms had improved, and the patient was discharged.

In the meanwhile, her IgA Anti-TTg report came out to be negative.

Two weeks after discharge, although repeat endoscopy was not performed, the patient reported complete resolution of symptoms and olmesartan had not been reinitiated.

DISCUSSION

The most common cause of villous atrophy is celiac disease.[4] The diagnosis is by classical histopathology findings with positive IgA anti-TTG. The diagnosis is further solidified by a gluten free diet resulting in complete resolution of symptoms. Other causes of villous atrophy were ruled out and a diagnosis of OIE was established. Previously published data shows the onset of enteropathy can take anywhere between 6 - 60 months. Our patient had a history of 24 months intake. The mean age of onset has been 69 years.[5,6] Clinical presentation can be as varied as chronic diarrhea, vomiting, abdominal pain, bloating, weight loss, and fatigue. Our patient was fortunately diagnosed early before signs and symptoms of chronic malabsorption developed.

Human Leukocyte Antigen (HLA) assessments have shown a higher prevalence of DQ2 or DQ8 haplotypes than expected for the general population. This may suggest a genetic susceptibility to the drug.

The patients may go undiagnosed for years, developing hypoalbuminemia, anemia and many cases report severe weight loss. It can cause a significant reduction in quality of life to the patient. Patients have a history of multiple admissions with extensive investigations, causing significant loss of valuable resources in resource poor countries like India and an added economic burden on the patient.

The exact mechanism of OIE is still unknown. It has been postulated that villous atrophy has been caused by AT2 receptors activated by Angiotensin II. Sun et al.?? Have shown that angiotensin II promotes apoptosis of enterocytes through binding to AT2 receptors and consequent upregulation of proapoptotic proteins (Bax and GATA-6) associated with a down regulation of Bcl-2, an antiapoptotic protein. Drug-induced AT1 receptor blocking causes translocation of AT2 receptors from the cytosol to the external membrane in the presence of high concentrations of

angiotensin II in rat smooth muscle cells; such behaviour may favour the binding of angiotensin II to AT2 receptors.[5] Olmesartan shows high affinity for AT1 receptors. In case of AT1 receptor saturation by olmesartan, circulating angiotensin II could bind only AT2 receptor, with a consequent proapoptotic effect. Apoptosis of enterocytes may ultimately lead to villous atrophy without inflammatory reaction and an increase in intraepithelial lymphocytes.[6]

The most common histopathological finding is intestinal villous atrophy (either total or partial), which may be associated with variable degrees of mucosal inflammation. Some authors have reported involvement of the stomach and colon with lymphocytic aggregation[7], it is likely that the entire gastrointestinal tract may get involved.

Multiple case series have reported complete reversal of symptoms on stopping the drug[8], including a series of 7 patients published in India[9] celiac may take years to reverse the histopathology findings after gluten withdrawal, in contrast OIE responds rapidly to drug withdrawal(almost eight months from the suspension of the drug to follow-up biopsies).[1]

CONCLUSION

The purpose of writing this article is for the physician community to be aware of this adverse drug reaction. Most case reports in the literature have a prolonged interval between symptoms and diagnosis, highlighting the need for awareness. This is especially true in India since very few case reports and case series are reported from the country. Further research into the class effect of the drug and genetic make-up of susceptible individuals is the need of the hour.

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