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Case Report

Olmesartan Associated Enteropathy, an easily overlooked etiology of bowel disturbance: report of three cases

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Abstract:

Olmesartan medoxomil is one of eight marketed Angiotensin II Receptor Blocker for the treatment of high blood pressure. Olmesartan Associated Enteropathy has been described in several case reports, subsequently, the United states Food and Drug Administrationincluded severe sprue-like enteropathy as an adverse effect of Olmesartan. Olmesartan Associated Enteropathy mimics celiac disease clinically and pathologically. The pathologic findings are villous atrophy and increased intraepithelial lymphocytes. Clinical presentation of Olmesartan Associated Enteropathy includes nausea, bloating, diarrhea and weight loss.

In contrast to celiac disease, tissue transglutaminase is not elevated, and there is no response to a gluten-free diet. Several case reports have described the effects of olmesartan on gut, giving rise to the term of Olmesartan Associated Enteropathy. Clinicians should always be aware that Olmesartan can cause an enteropathy clinically and histologically similar to celiac disease since replacing Olmesartan with an alternative antihypertensive drug can simplify the diagnostic workup and provide both clinical and histologic improvement. We report three cases of Olmesartan Associated Enteropathy in this article.

Keywords: *Olmesartan, Coeliac disease, Olmesartan Associated Enteropathy.*

Background:

Olmesartan medoxomil is one of eight marketed Angiotensin II Receptor Blocker (ARB) for the treatment of high blood pressure[1]. It was approved in 2002 in the USA, and in 2003 in the European Union, for the treatment of hypertension. Olmesartan Associated Enteropathy (OAE) was first described in a case series by Rubio-Tapia et al[2] in 2012; subsequently, the United States Food and Drug Administration[1] included severe sprue-like enteropathy as an adverse effect of Olmesartan. The diagnosis of OAE relies on high clinical suspicion, demonstration of histological changes associated with enteropathy, and negative coeliac disease (CD) serology.[3] Patients with OAE typically present with diarrhea, weight loss, nausea, vomiting, and low albumin. Although biopsy findings mimic celiac disease, OAE can be distinguished from celiac disease by the presence of normal celiac serologies and by the absence of a response to a gluten-free diet.[2]

The presence of small bowel villous atrophy and negative serologic testing for celiac disease represents a difficult dilemma in clinical practice[4]. The differential diagnoses include several intestinal disorders (e.g., bacterial overgrowth, ulcerative jejunitis, protein-losing enteropathy, T-cell lymphoma, and tropical sprue)[5], even though in recent years, similar findings have also been reported following the use of drugs[6-9]. Among the drugs, Olmesartan has recently been reported to be responsible for enteropathy and malabsorption mimicking celiac disease[2]. OAE is increasingly being recognized as a major differential diagnosis in patients with villous atrophy and negative coeliac disease serology. We report three cases of Olmesartan Associated Enteropathy in this article.

Case 1:

A 63-year-old woman was admitted to the Gastroenterology department of Jahurul Islam Medical College & Hospital, Kishoreganj, Bangladesh with complaints of dyspepsia, abdominal bloating & chronic diarrhoea for last 6 months. On query, she gave a history of weight loss of about 10 kg in last 6 months. She gave no history of abdominal pain, fever or passage of bloody stool. She was hypertensive & was on Amlodipine-Olmesartan combination for last 2 years with optimal control of blood pressure. On examination, she was mildly dehydrated. Other system examinations, including abdominal examination, revealed no abnormality. Except for

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mild hypokalemia, the blood count, hepatic & renal function & serum albumin were within normal limit. Stool studies including faecal leukocytes, faecal fat staining, Clostridium difficile toxin PCR, rotavirus ELISA, bacterial cultures, and Giardia and Cryptosporidium antigen testing all returned negative. Tests for other ova & parasites were negative as well. Serologicaltest for HIV was negative.

She attempted to avoid several potential food triggers like wheat products, milk products, salads & fibre containing foods with no effect on her symptoms. Endoscopy of upper gastrointestinal tract was done, which showed gross scalloping of mucosa at the second part of duodenum. Biopsy from the second part of duodenum revealed villous atrophy along with increased Intra Epithelial lymphocytes (IEL). Based on these reports, antit TG IgA was sent along with serum IgA level & a glutenfree diet was started. Serum IgA level was 284 mg/dl (70-400 mg/dl) & anti tTG IgA was negative (<3U/ml). And the clinical condition did not improve at all even after strictly sticking to a glutenfree diet for a month. Colonoscopy with terminal ileoscopy was performed, which revealed no abnormality. Moreover, biopsy samples were also negative for microscopic colitis.

A trial of tetracycline also failed to resolve symptoms. An empirical course of prednisolone was prescribed, targeting the gut inflammation. Symptoms resolved rapidly within few days, but relapse of symptoms occurred as soon as prednisolone was weaned.

A critical review of patient's food & medication history was done. And subsequently, Olmesartan was discontinued following different reports of enteropathy induced by Olmesartan worldwide. Olmesartan was replaced by losartan. After about two weeks of discontinuation of Olmesartan, symptoms started getting better & she became symptom-free after about a month of discontinuation of Olmesartan. A repeat endoscopy UGI was done 6 months after the discontinuation of Olmesartan, which showed complete resolution of the endoscopic findings at the second part of duodenum. She continued to feel absolutely symptom free on losartan, after about a year of discontinuation of Olmesartan, with a gain of 7 kg weight during this period.

Case 2:

A 57-year-old asthmatic, hypertensive male, presented to the Gastroenterology OPD of same hospital with complaints of nausea & passage of recurrent unformed stool for last 3years. He also complained of weight loss. He lost about 7 kg in last 1 year. There was no history of passage of blood with stool. He was on salbutamol inhaler & montelukast tablet for his asthma and was having Olmesartan 20mg daily as an antihypertensive. On examination, he was dehydrated. Other system examinations revealed no abnormality. The blood count, hepatic & renal function were within normal range. Stool studies, including routine examination and culture results, were normal. Stool study was negative for *Clostridium difficile* toxin, rotavirus, Giardia and Cryptosporidium. No ova or parasites were found. Serological test for HIV was also negative.

He tried ciprofloxacin & metronidazole for his bowel upset with little temporary effect. He avoided wheat products, milk products & fibre containing foods with no effect on his symptoms. Endoscopy UGI was done, which showed focal scalloping of mucosa at the second part of duodenum. Biopsy from the second part of the duodenum revealed partial villous atrophy with increased Intra Epithelial lymphocytes. Colonoscopy with terminal ileoscopy was performed, which revealed no abnormality. Colonoscopic biopsy was negative for microscopic colitis. Antit TG IgA and serum IgA levelwere within normal limit. Moreover, a gluten free diet didn't seem to be helping.

After hearing about several reports of OAE, Olmesartan was discontinued & replaced by Amlodipine. After about one month of discontinuation of Olmesartan, symptoms started getting better. The patient denied a repeat endoscopy of UGI to be done, and he continued to be symptom-free after about 1 year of discontinuation of Olmesartan.

Case 3:

A 46-year-old diabetic, hypertensive woman presented with the complaints of lethargy, chronic diarrhoea and weight loss for last 2 years. She lost about 15 kg in last 2 years. She had no fever, abdominal pain or history of passage of blood with stool. She was on Olmesartan for last 3 years with optimal control of blood pressure. She tried rifaximin, metronidazole and food restrictions with very little impact on the clinical course. On examination, she was dehydrated. The routine investigations, including complete blood count, hepatic, renal & thyroid function & serum albumin were within normal limit, except for a low serum potassium level. Stool studies, including Clostridium difficile toxin PCR, bacterial cultures, and Giardia & Cryptosporidium antigen testing were negative. Tests for other ova & parasites were negative as well. Serological test for HIV was negative. An endoscopy UGI was done, which showed gross scalloping of mucosa at the second part of duodenum. Biopsy from the second part of duodenum revealed villous atrophy with increased intraepithelial lymphocytes.

An anti tTG IgA was sent along with serum IgA level. Serum IgA level was 197 mg/dl (70-400 mg/dl) & anti tTG IgA was negative. Colonoscopy with terminal ileoscopy was performed, which revealed no abnormality. A trial of an oral course of prednisolone was given empirically, targeting the gut inflammation. Symptoms resolved within few days, but symptoms relapsed as soon as the prednisolone was stopped. Due to financial constraints, the patient had to discontinue Olmesartan. Olmesartan was replaced by Amlodipine. The patient started feeling better & she became symptomfree after about a month of discontinuation of Olmesartan. A repeat endoscopy UGI was done 1 year after discontinuation of Olmesartan, which showed complete resolution of the endoscopic findings at the second part of duodenum. She continued to feel symptom free after about a year of discontinuation of Olmesartan, with a gain of 5 kg weight during this period.

Discussion:

Olmesartan medoxomil is one of eight marketed ARB for the treatment of high blood pressure[1]. It was approved in 2002 in the USA, and in 2003 in the European Union, for the treatment of hypertension. Olmesartan Associated Enteropathy was first described in a case series by Rubio-Tapia et al[2] in 2012; subsequently, the United States Food and Drug Administration[1] included severe sprue-like enteropathy as an adverse effect of Olmesartan. The diagnosis of OAE relies on high clinical suspicion, demonstration of histological changes associated with enteropathy and negative coeliac disease serology.[3] Dong et al[10] reported a higher incidence of gastrointestinal adverse events with Olmesartan when compared with other ARBs in a cohort of over 1.5 million patients, of whom 350,790 were on Olmesartan.

At present, the mechanisms responsible for the onset of enteritis after Olmesartan use are unknown[2]. The effect of Olmesartan on the intestinal mucosa is thought to be immune-mediated.[11] Transforming growth factor-β (TGF-β) is a multifunctional cytokine that plays a role in gut haemostasis.[11] Olmesartan has a higher affinity to block angiotensin II receptor (ATR) type-1, leaving angiotensin free to bind ATR type-2. This results in modulation of TGF-β, which in turn leads to histological changes on the small bowel mucosa.[11]Two pathways have been proposed, including (1) the inhibitory effects of angiotensin II receptor blockers (ARBs) on transforming growth factor β, and (2) a disproportionate activation of angiotensin II receptor type 2 (AT2) receptors by angiotensin II after blocking AT1 receptors with Olmesartan, which results in apoptosis of enterocytes.[2,12]

Patients with OAE typically present with diarrhea, weight loss, nausea, vomiting, and low albumin. Although biopsy findings mimic those of celiac disease, OAE can be distinguished from celiac disease by the presence of normal celiac serologies and, importantly, by the absence of a response to a gluten-free diet.[2] Histological changes described in OAE can range from intraepithelial lymphocytosis and lymphocytic proliferation of the lamina propria to marked villous atrophy.[13] Steroids may ameliorate symptoms in 95% of cases.[13] In 2012, Rubio-Tapia et al identified 22 patients on Olmesartan who developed clinical features of chronic diarrhea, weight loss, and sprue-like enteropathy, evidenced by villous atrophy and mucosal inflammation on intestinal biopsy.[2] Notably, all 22 patients experienced resolution of symptoms upon withdrawal of Olmesartan and discontinuation of a gluten-free diet.[1]

In the cases we discussed, the patients presented with dyspepsia, nausea, bloating, lethargy, chronic diarrhoea and weight loss, mimicking a spruelike illness. Initial investigations were almost normal in all the cases. Stool studies including fecal leukocytes, fecal fat staining, Clostridium difficile toxin PCR, rotavirus ELISA, bacterial cultures, and Giardia and Cryptosporidium antigen testing were negative. Tests for other ova & parasites were negative as well. Serological test for HIV was negative. UGI endoscopy revealed scalloping of duodenal mucosa at the second part& biopsy showed the presence of villous atrophy along with raised intraepithelial lymphocytes. Serum IgA levels were normal & anti tTG IgA was negative in all three cases. Glutenfree diet did not seem to be working. The patients tried empirical courses of metronidazole, ciprofloxacin, rifaximin and prednisolone with only short-term benefit with recurrence of symptoms after discontinuing the drugs. Colonoscopy with terminal ileoscopy was also normal along with a normal biopsy report, excluding microscopic colitis in all three cases. Dramatic improvement of symptoms was observed after discontinuation of Olmesartan. Repeat endoscopies revealed a complete histological resolution in the affected part of the gut, establishing the diagnosis of OAE.

Conclusion:

Small intestinal villous atrophy and inflammatory infiltrates with negative celiac serologies (sprue-like enteropathy) presents a diagnostic challenge. The differential diagnosis is broad and includes autoimmune and drug-induced enteropathies, malignancies, infections, post-infectious enteropathy, and immunodeficient disorders. Several case reports have described the effects of Olmesartan on gut, giving rise to the term of Olmesartan Associated Enteropathy. Clinicians should always be aware that Olmesartan can cause an enteropathy clinically and histologically similar to celiac disease; since replacing Olmesartan with an alternative drug can simplify the whole process and provide rapid resolution of clinical symptoms along with complete histological resolution.

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