CASE REPORT

An atypical case of chronic diarrhoea: olmesartan-induced sprue-like enteropathy

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Accepted 31 August 2015

SUMMARY

Olmesartan use has been associated with chronic diarrhoea and weight loss due to severe sprue-like enteropathy, yet this is still not well known among clinicians. We present the unique case of an 84-year-old Filipino woman diagnosed with olmesartan-induced sprue-like enteropathy after an extensive work up for chronic diarrhoea, and without improvement despite multiple empiric treatments for nearly 15 months. Withdrawal of olmesartan resulted in clinical and histological improvement. This case provides further evidence for olmesartan-induced sprue-like enteropathy, and emphasises the importance of its awareness and recognition among gastroenterologists and primary care physicians alike.

BACKGROUND

Olmesartan is one of several angiotensin II receptor blockers (ARB) and has been available for the treatment of hypertension since April 2002. Olmesartan use has been associated with chronic diarrhoea and weight loss due to severe sprue-like enteropathy. The evidence for olmesartan's association with sprue-like enteropathy has come from a series of case studies and case reports. The US Food and Drug Administration (FDA) identified 23 cases of late-onset diarrhoea with significant weight loss associated with olmesartan use, and several cases with biopsy showing villous atrophy as part of its Adverse Event Reporting System (FAERS). All patients clinically improved on stopping olmesartan and 10 patients had recurrent symptoms with rechallenge.¹ Olmesartan-induced sprue-like enteropathy was reported in June 2012 by Rubio-Tapia *et al*² of the Mayo Clinic, who published a case series of 22 patients between 2008 and 2011. In May 2013, DeGaetani *et al* published a case series of 72 patients with villous atrophy and negative serology for coeliac disease. The authors reported that 19 patients had developed villous atrophy from medications and of those, 16 patients were later found to have villous atrophy associated with olmesartan use.³ Based on this evidence, the FDA found a clear association between olmesartan use and sprue-like enteropathy, and issued a warning in July 2013 to make clinicians aware that olmesartan use can cause sprue-like enteropathy with symptoms of severe diarrhoea and significant weight loss.¹

CASE PRESENTATION

An 84-year-old woman with a history of sick sinus syndrome status post-atrial pacemaker and

hypertension, was evaluated for 15–20 episodes of watery, non-mucoid, non-bloody bowel movements a day that was not associated with food or abdominal pain, and had been ongoing for 15 months. The patient also had about 30 lbs of unintentional weight loss and denied nausea, vomiting, abdominal cramps, tenesmus, melena or haematochezia, steatorrhoea, or faecal incontinence.

Besides a pacemaker insertion, she had undergone cataract surgeries in both eyes. She was taking olmesartan 20 mg daily for her hypertension, potassium chloride 40 mEq two times a day and bimatoprost 0.01% ophthalmic solution 1 drop nightly. She had no known drug allergies. Her family history was negative except for glucose-6-phosphate dehydrogenase deficiency (G6PD) in her daughter. She was originally from the Philippines and came to the USA about 15 years earlier. She was widowed with three children and lived with her daughter. She was a lifetime non-smoker and did not use alcohol or recreational drugs. Three months prior to her presentation, she had made a return trip to the Philippines.

On examination, her blood pressure was 158/51 mm Hg, pulse 60 bpm, respiratory rate 16/min, oxygen saturation 99% on room air, temperature 36°C and her body mass index was (BMI) 17 kg/m². Besides a thin habitus, the remainder of the physical examination was unremarkable.

INVESTIGATIONS

An extensive evaluation was negative for infectious diseases, inflammatory bowel disease, ischaemic colitis, malignancy, maldigestion, and secretory and osmotic diarrhoea. The patient had had an extensive work up for her chronic diarrhoea, which had been initiated at an outside hospital by her local gastroenterologist. A colonoscopy was unremarkable. She also had an oesophagogastroduodenoscopy (OGD) with biopsy, which showed villous atrophy and inflammatory changes in the duodenum, very suggestive of sprue. Serology for tissue transglutaminase (tTG IgA and tTG IgG) was performed and was negative. The patient was placed on a gluten-free diet, which did not help her diarrhoea. Because she had recently travelled to the Philippines, the diagnosis of tropical sprue was also entertained. Treatment with 8 weeks of doxycycline had no significant clinical impact. She later underwent a sigmoidoscopy with biopsies to rule out microscopic colitis and inflammatory bowel disease. She was given budesonide empirically while waiting for her biopsy results. The biopsies showed no

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To cite: Naik DK, Martelli MG, Hernandez Gonzalo D, *et al*. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-212318

evidence of microscopic colitis or inflammatory bowel disease. She was also treated with octreotide empirically but failed treatment.

About 10 months prior to presentation to our institution, stool studies had been negative for enteric pathogens, ova or parasites, and testing for *Clostridium difficile* toxin had also been negative. The patient underwent a push enteroscopy up to 40 cm down the jejunum, on which the mucosa appeared grossly unremarkable. Several biopsies were taken, showing lymphoid aggregates within the lamina propria, devoid of germinal centres and without evidence of coeliac disease. Her VIP level at this time was normal and reducing substance in faeces was negative. She additionally underwent CT enterography and a CT of the abdomen, which showed no small bowel or colonic abnormalities.

On presentation to our institution, she underwent repeat EGD, which revealed duodenal mucosal atrophy, and the biopsies demonstrated a chronic active duodenitis with severe diffuse villous blunting, a mild increase in subepithelial collagen deposition, marked expansion of the lamina propria by chronic inflammation and crypt dropout in a sprue-like pattern suggestive of olmesartan-induced sprue-like enteropathy (figure 1A, B). There was no significant increase in intraepithelial lymphocytes. Antibody testing for coeliac disease was negative with anti-tissue transglutaminase IgA <2 U/mL (reference interval 0–3). On further review of the patient's medications, it was noted that she was taking olmesartan for hypertension. Based on the exclusion of other diagnoses as above, this was felt to be a case of olmesartan-induced sprue-like enteropathy.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for chronic diarrhoea includes osmotic diarrhoea due to lactose intolerance, secretory

diarrhoea (VIPoma, carcinoid, gastrinoma), malabsorption syndromes (coeliac disease, Whipple disease, tropical sprue), inflammatory bowel disease, ischaemic colitis, malignancy, infection (invasive bacterial infection, parasitic infection, *C. difficile* infection) and medication induced.

TREATMENT

Owing to the concern for sprue-like enteropathy associated with ARBs, the decision was made to avoid all drugs in this class. The patient was switched to amlodipine and lisinopril for her hypertension.

OUTCOME AND FOLLOW-UP

When followed up with a phone call 2 weeks after discharge, the patient reported that her diarrhoea had essentially resolved and that she started having one bowel movement a day. Four months later, she continued to be free of diarrhoea and had 10 lbs weight gain. Repeat endoscopy revealed a normal appearing duodenum without villous atrophy. Re-biopsy demonstrated normal histology and near complete recovery of the villous architecture (figure 2A, B).

DISCUSSION

The use of olmesartan has been associated with severe sprue-like enteropathy leading to symptoms of severe diarrhoea and weight loss. In May 2014, Ianiro *et al* published a systemic

Figure 1 (A) Low-power view demonstrating severe diffuse villous blunting and marked expansion of the lamina propria by chronic inflammation. (B) Higher magnification showing active duodenitis with neutrophils infiltrating the crypts.

Figure 2 (A) Low-power view demonstrating marked improvement in villous architecture, with normal histology. (B) Higher magnification demonstrating the recovered villous architecture and normal histology.

review on sprue-like enteropathy associated with olmesartan. The authors found 54 patients using olmesartan, who had presented with diarrhoea and weight loss but negative serology for coeliac disease. All the patients' signs and symptoms resolved once olmesartan was discontinued.⁴ The FDA had issued a warning in July 2013 to make clinicians aware that olmesartan use can cause sprue-like enteropathy. Despite the warning, many clinicians do not consider olmesartan-induced sprue-like enteropathy in the differential diagnosis for chronic diarrhoea. Although the association of enteropathy is more common with olmesartan, there have been cases apparently demonstrating an association with other ARBs as well. Marthey *et al*⁵ conducted a survey of French gastroenterologists to collect French cases of sartan-associated enteropathy. The authors reported 36 cases of olmesartan-associated enteropathy and one case of irbesartan-associated enteropathy.

Histologically, there is significant overlap between coeliac disease and ARB-induced sprue-like enteropathy. Clues to a diagnosis of the latter include active duodenitis, lack of a significant increase in intraepithelial lymphocytes, increased subepithelial collagen deposition and careful medication history in addition to a detailed clinical history.

Patient's perspective

A couple of years after I was put on 'Olmesartan' by my primary care physician, I started having diarrhoea. The initial diagnosis of my diarrhoea was stomach virus. However, my diarrhoea persisted even with the medication prescribed. I was then referred to a gastroenterologist who did extensive tests, but to no avail. Tropical sprue was ruled out. I was also hospitalised a couple of times at the local hospital due to severe diarrhoea and dehydration. I had lost about 30 pounds since I started having diarrhoea up to the time I was admitted to the University of Florida Shands hospital.

My hospitalisation at Shands was a result of bloodwork showing critical numbers. Medical records from my previous hospitalisations were brought and reviewed. Dr Naik came to see me in the hospital and inquired about listing of all my current medications. He later came back and told me that he had a suspicion olmesartan might be the cause of my diarrhoea, but needed to do more research to confirm the suspicion. They stopped giving me olmesartan and I saw immediate improvement of my diarrhoea. My diarrhoea quickly ceased and I have since gained weight and am very happy to be home again.

Learning points

- ▶ Olmesartan-induced sprue-like enteropathy should be considered in the differential diagnosis for chronic diarrhoea in patients taking olmesartan.
- ▶ For olmesartan-induced sprue-like enteropathy, withdrawal of the medication can result in not only clinical improvement but also histological improvement.
- ▶ This case highlights the importance of reviewing a patient's medication history when conducting the doctor–patient interview.
- ▶ Clinicians must be disciplined in obtaining a complete and effective history when trying to properly diagnose a patient's ailment.

The patient described in this report had an extensive work up for her chronic diarrhoea and was on multiple empiric treatments without improvement. Unfortunately, olmesartan-induced sprue-like enteropathy was not initially included in the differential diagnosis, resulting in substantial unnecessary testing and angst to the patient. Discontinuation of olmesartan resulted in resolution of her diarrhoea and in weight gain. Repeat biopsies the fourth month after discontinuation of olmesartan showed near complete recovery of villous architecture. This case provides further evidence for olmesartan-induced sprue-like enteropathy, and emphasises the importance of its awareness and recognition among gastroenterologists and primary care physicians alike.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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