CASE REPORT

Case of olmesartan-associated enteropathy and transient positive antitissue transglutaminase serology

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SUMMARY

Olmesartan-associated enteropathy (OAE) is increasingly being recognised as a major differential diagnosis in patients with villous atrophy and negative coeliac disease (CD) serology. OAE and positive coeliac markers have rarely been reported. We report a case of diarrhoea and small bowel villous blunting associated with a transient elevation of antitissue transglutaminase antibody (ATTG). On discontinuation of olmesartan, symptoms improved, repeat biopsies were normal and levels of ATTG also returned normal. We discuss a possible explanation for the transient elevation in ATTG and the significance of considering OAE/CD overlap.

BACKGROUND

Olmesartan is an angiotensin II receptor blocker (ARB) that has been available in Canada since 2008. The Randomized Olmesartan and Diabetes Microalbuminuria Prevention study followed patients on olmesartan for a median of 3.2 years and reported no significant gastrointestinal side effects when compared with placebo.

Olmesartan-associated enteropathy (OAE) was first described in a case series by Rubio-Tapia et al in 2012; subsequently, the US Food and Drug Administration 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. It is unclear if there is a relationship between OAE and CD; however, given the pathogenesis of OAE, an overlap between the two conditions may be possible. In our case report, we describe a challenging case of OAE with a transient elevation of antitissue transglutaminase antibodies (ATTG) and human leukocyte antigen (HLA) typing often associated with CD.

CASE PRESENTATION

A 62-year-old woman with a medical history of hypertension, irritable bowel syndrome (IBS), spinal stenosis and osteoporosis presented to the gastroenterology clinic with a 1-year history of diarrhoea. Her medications included olmesartan, calcium and vitamin D. She reported six to seven daily episodes of watery stool without mucus or blood. The patient was treated for possible IBS-diarrhoea flare with low fermentable oligosaccharides, disaccharides, monosaccharides and polyols diet, loperamide, eluxadoline and rifaximin, all of which have failed to control her diarrhoea.

INVESTIGATIONS

A complete blood count revealed normal leucocytes, haemoglobin and platelet count. Electrolytes, creatinine, liver function tests, thyroid function and immunoglobulin levels were within the normal range. Clostridium difficile B gene PCR, stool culture and faecal calprotectin were negative. An initial ATTG at presentation was measured at 45 U/mL, and the repeat level was 19 U/mL (ATTG measurement interpretation: negative <9 U/mL, borderline 9–16 U/mL, positive >16 U/mL). HLA DQ2 test was positive but negative for HLA DQ2. Magnetic resonance enterography reported normal duodenum, jejunum and colonic mucosa but with a rectocele. The patient was started on a gluten-free diet but without response to treatment; therefore, coeliac sprue was excluded. Colonoscopy demonstrated rectal prolapse but was otherwise normal. Colonic biopsies eliminated microscopic colitis. A gastroscopy was grossly normal except for possible loss of valvulae conniventes in the second portion of the duodenum (figure 1). The original duodenal endoscopic biopsy showed partial blunting of the villous architecture with increased CD3+ intraepithelial lymphocytes at the tip of the villi. The collagen table thickness was within normal limit on trichrome stain. The findings in the duodenal mucosa at that stage are reminiscent of CD in the appropriate serological and clinical context (figure 2).

FOLLOW-UP

Finally, OAE was suspected and olmesartan was discontinued. The patient’s symptoms improved substantially and the frequency of watery diarrhoea had decreased remarkably but not completely. Residual diarrhoea was likely related to underlying IBS and compounded by rectal prolapse. Following 3 months of cessation, repeat small bowel biopsies showed duodenal mucosa with preserved villous architecture. The number of intraepithelial lymphocytes, as well as the thickness of collagen tables, are all within normal limit. Comparing the two biopsies, there is a complete histological reversal to a normal duodenal mucosa (figure 3). A repeat ATTG level was also negative (ATTG level=6 U/mL).
Unusual presentation of more common disease/injury

**DISCUSSION**

Since 2012, more cases and studies have linked olmesartan with a diarrhoeal illness induced by villous atrophy. Dong et al\(^5\) 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.

We found 312 cases of OAE reported in the literature. The mean age was 68, with a female predominance. The average time to clinical presentation was 2.1 years after being placed on olmesartan. Of the reported cases, only three tested positive for ATTG. Interestingly one patient had ATTG deposits on duodenal biopsy.\(^6\)–\(^9\)

The effect of olmesartan on the intestinal mucosa is thought to be immune-mediated.\(^10\) Transforming growth factor-β (TGF-β) is a multifunctional cytokine that plays a role in gut haemostasis.\(^10\) 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.\(^10\) The distinctive side effects of olmesartan are likely related to (1) its prodrug that converts to an active form in the small intestines, (2) olmesartan's high efficacy and (3) its long half-life.

CD and OAE are entities that have similar clinical presentations and mechanism of enterocyte injury. Genetic predisposition is a major determinant of the pathophysiology as HLA DQ2/DQ8 is reported positive in 95% of CD cases.\(^11\) Around 73% of patients with OAE reported by Rubio-Tapia et al\(^2\) carried HLA DQ2/DQ8. OAE is distinguished from CD by negative CD markers and failure to respond to gluten-free diet.

Our patient had a transient elevation of ATTG level at the onset of symptoms, which subsequently normalised. Additionally, her symptoms had improved on cessation of olmesartan despite being on a gluten-rich diet. The diagnosis of OAE was established after failure to respond to a gluten-free diet and improvement of symptoms and histopathology on repeat biopsies. Testing for HLA DQ2/DQ8 in our patient did not help exclude CD.

Although false-positive ATTG results are not uncommon, separating CD and OAE in our case was difficult given the excellent sensitivity and specificity of the Eurospital ATTG IgA assay kit.\(^12\) ATTG expression has been described as a sign of intestinal injury reflecting villous atrophy in non-CD, which makes the interpretation of a positive ATTG difficult given the almost identical presentation of CD and OAE.\(^13\)

In conclusion, we describe a case of OAE with transient ATTG positivity. To our knowledge, an overlap syndrome between the two conditions has not been reported, and definite recommendations on the use of olmesartan in patients with CD are not available. Therefore, avoiding olmesartan in patients diagnosed with CD seems like a reasonable measure. Expanding on what we know about OAE's pathogenesis may help identify new pathways in the pathobiology of CD and the possibility of immunogenic overlap.

**Learning points**

- Olmesartan-associated enteropathy (OAE) should be included in the differential diagnoses of diarrhoea associated with villous atrophy.
- Positive coeliac disease serology does not inevitably rule out OAE.
- Avoid prescribing olmesartan in a patient with established coeliac disease or undiagnosed enteropathies.
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REFERENCES
1 Menne J, Haller H. Olmesartan and intestinal adverse effects in the ROADMAP study. *Mayo Clin Proc* 2012;87:1230–1.
2 Rubio-Tapia A, Herman ML, Ludvigsson JE, et al. Severe spruelike enteropathy associated with olmesartan. *Mayo Clin Proc* 2012;87:732–8.
3 FDA. *FDA Drug Safety Communication: FDA approves label changes to include intestinal problems (sprue-like enteropathy) linked to blood pressure medicine olmesartan medoxomil [Internet]*: U.S. Department of Health and Human Services, 2013. cited 15 Mar 2018. https://www.fda.gov/Drugs/DrugSafety/ucm359477.htm.
4 Silva BMD, Neves SJ, Martinez AG, et al. Enteropathy Associated with Olmesartan. *GE Port J Gastroenterol* 2016;23:96–100.
5 Dong YH, Jin Y, Tsacogianis TN, et al. Use of olmesartan and enteropathy outcomes: a multi-database study. *Aliment Pharmacol Ther* 2018;47:792–800.
6 Marco-Marqués A, Sanahuja-Martinez A, Bosca-Watts MM, et al. Could HLA-DQ suggest why some patients have olmesartan-related diarrhea and others don’t? *Am J Gastroenterol* 2015;110:1507–8.
7 Scialom S, Malamut G, Meresse B, et al. Gastrointestinal disorder associated with olmesartan mimics autoimmune enteropathy. *PloS One* 2015;10:e0125024.
8 Esteve M, Temírio R, Cansascio A, et al. Potential coeliac disease markers and autoimmunity in olmesartan induced enteropathy: A population-based study. *Dig Liver Dis* 2016;48:154–61.
9 Choi EY, McKenna BJ. Olmesartan-associated enteropathy: A review of clinical and histologic findings. *Arch Pathol Lab Med* 2015;139:1242–7.
10 Marietta EV, Cartee A, Rishi A, et al. Drug-Induced Enteropathy. *Dig Dis* 2015;33:215–20.
11 Rostom A, Dubé C, Cranney A, et al. Celiac disease: Summary. *Agency for Healthcare Research and Quality* 2004.
12 Naiyer AJ, Hernandez L, Ciaccio EJ, et al. Comparison of commercially available serologic kits for the detection of celiac disease. *J Clin Gastroenterol* 2009;43:225–32.
13 Maglio M, Ziberna F, Aitoro R, et al. Intestinal production of anti-tissue transglutaminase 2 antibodies in patients with diagnosis other than celiac disease. *Nutrients* 2017;9:1050.