CASE REPORT

Severe spruelike enteropathy and collagenous colitis caused by olmesartan

Shiho Kaneko¹, Kana Matsuda¹*, Yasuko Mizuta¹, Shoya Shiratori¹, Kazuma Kishi¹, Akihisa Nakamura¹, Masataka Yagisawa¹, Nobuyuki Ehira¹, Minoru Uebayashi¹ and Hiroya Kobayashi²

Abstract

Background: Olmesartan, which is an angiotensin II receptor blocker, reportedly causes spruelike enteropathy, with intestinal villous atrophy as its typical histopathological finding. Interestingly, collagenous and/or lymphocytic gastritis and colitis occur in some patients. We report the case of a 73-year-old Japanese man with a 2-month clinical history of severe diarrhea and weight loss. There were few reports in which spruelike enteropathy and collagenous colitis were both observed and could be followed up.

Case presentation: We report a case of a 73-year-old man with a 2-month clinical history of severe diarrhea and weight loss. He had taken olmesartan for hypertension treatment for 5 years. Endoscopic examination with biopsies revealed intestinal villous atrophy and collagenous colitis. Suspecting enteropathy caused by olmesartan, which was discontinued on admission because of hypotension, we continued to stop the drug. Within 3 weeks after olmesartan discontinuation, his clinical symptoms improved. After 3 months, follow-up endoscopy showed improvement of villous atrophy but not of the thickened collagen band of the colon. However, the mucosa normalized after 6 months, histologically confirming that the preexistent pathology was finally resolved.

Conclusions: This report presents a case in which spruelike enteropathy and collagenous colitis were both observed and could be followed up. In unexplained cases of diarrhea, medication history should be reconfirmed and this disease should be considered a differential diagnosis.

Keywords: Villous atrophy, Collagenous colitis, Spruelike enteropathy, Intestinal diseases, Case report

Background

Angiotensin II receptor blockers (ARBs) are widely used antihypertensive agents. One of the ARBs is olmesartan, which has been available since 2002. In 2012, Rubio–Tapia et al. first described olmesartan-associated spruelike enteropathy [1]. Thus, the United States Food and Drug Administration issued a warning for the risk of enteropathy in 2013. Spruelike enteropathy is characterized by severe diarrhea, weight loss, nausea, vomiting, abdominal pain, bloating, and fatigue. Additionally, villous atrophy, mucosal inflammation, and subepithelial collagen deposition are observed in small intestinal biopsy [1]. Other gastrointestinal tract parts also manifest various alterations. Furthermore, enteropathy reportedly exhibits collagenous and/or lymphocytic gastritis and colitis [1, 2]. Pathological evidence of the stomach and colon suggests that olmesartan may affect the entire gastrointestinal tract. There were few reports in which sprue-like enteropathy and collagenous colitis were both observed and could be followed up.

Herein, we report a case of severe enteropathy and collagenous colitis associated with olmesartan use.

*Correspondence: kana.matsuda@true.ocn.ne.jp
¹ Department of Gastroenterology, Kitami Red Cross Hospital, Higashi-2, Kita-6, Kitami 090-0026, Japan

Full list of author information is available at the end of the article
Fig. 1  Esophagogastroduodenoscopy at the initial visit.  

a White-light imaging shows villous atrophy and a mosaic pattern of the duodenal mucosa.  
b Magnification endoscopy with narrow-band imaging shows villous atrophy of the duodenal mucosa.

Fig. 2  

a Duodenal biopsy (hematoxylin–eosin, 0924; top: –743; width: 5205; height: 3719; visibility: visible; mso-wrap-style: square).  
b Duodenal biopsy (Masson trichrome, ichromeichrome eosin, 0924; top).  
c Colonic biopsy (hematoxylin–eosin, 0924; top: – 743; width: 5205; height: 3719; visibility: visible).  
d Colonic biopsy (Masson trichrome, ichromeichrome eosin, 0924; top).
Case presentation

A 73-year-old Japanese man with a history of olmesartan intake (20 mg daily for 5 years) for hypertension treatment was admitted to a local hospital complaining of watery, nonbloody diarrhea approximately 10 times daily since 2 months. In 2 months, he lost 10 kg of his weight. Blood tests, CT, and endoscopy were performed, but the cause of his diarrhea remained unknown. Hence, he was referred to our hospital for further examination. His physical examination results were unremarkable. However, laboratory results (Additional file 1) indicated anemia (hemoglobin, 10.5 g/dL) and hypoalbuminemia (3.4 g/dL). We searched DQA1 and DQB1. HLA DQ4 and DQ6 were positive. Meanwhile, stool culture, Clostridium difficile toxin, HLA-DQ2/DQ8, and IgA antibodies to tissue transglutaminase and endomysial, were all negative. Abdominal computer tomography was unremarkable. Esophagogastroduodenoscopy (EGD) revealed villous atrophy and a mosaic pattern of the duodenal mucosa (Fig. 1), while colonoscopy (CS) detected villous atrophy of the terminal ileum and diffuse slight edema of the colon (Additional file 2). The stomach, duodenum, terminal ileum, and colon were randomly biopsied. Pathological findings of the duodenum and ileum showed villous atrophy, intraepithelial lymphocyte infiltration, and collagen band, and those of the colon showed a 14 μm collagen band (Fig. 2). Moreover, capsule endoscopy displayed villous atrophy of the entire small intestine. Taken together, we suspected that the patient had olmesartan-associated sprue-like enteropathy. Hence, olmesartan, which was stopped on admission because of hypotension, remained withdrawn, and was switched to amlodipine.

Within 3 weeks after olmesartan discontinuation, his clinical symptoms improved. Three months later, diarrhea resolved, and the duodenum, terminal ileum, and colon showed a normal appearance on EGD/CS (Fig. 3). As shown in the biopsies of the duodenum and terminal ileum, the villous architecture of the duodenal and ileal mucosa almost completely recovered (Fig. 4), but in colonic biopsies, the collagen band only slightly improved (Additional file 3). Six months after discontinuing olmesartan, follow-up endoscopy showed a histologically normal colonic mucosa.
**Discussion and conclusion**

Olmesartan-associated sprue-like enteropathy is a type of enteropathy induced by olmesartan administration. It is characterized by severe diarrhea and weight loss. The duration of olmesartan exposure before the onset of diarrhea varies from months to years [1, 3]. Diagnosis of olmesartan-induced sprue-like enteropathy requires the following: gastrointestinal symptoms, negative IgA tissue transglutaminase antibodies, evidence of enteropathy with or without collagen deposition or intraepithelial lymphocytosis, lack of clinical response to a gluten-free diet, exclusion of other causes of enteropathy, and evidence of clinical and histologic improvement after olmesartan discontinuation [1]. However, the mechanisms responsible for this enteropathy remain unknown. The long period between the start of olmesartan therapy and the onset of diarrhea suggests cell-mediated immunity rather than type 1 hypersensitivity [1]. ARBs inhibit the transforming growth factor, which is responsible for gut immune homeostasis [1, 4]. HLA-DQ2 or DQ8 haplotypes were present in 71% of patients with olmesartan-associated sprue-like enteropathy [3]. The prevalence of HLA DQ2/DQ8 in these patients is higher than in the general population, suggesting some genetic component [1]. However, neither DQ2 nor DQ8 was present in our patient’s case. Previous reports have shown that improvement of symptoms begins in approximately 1 week [5, 6], and that the average time to complete improvement of symptoms is 8 months [2]. Our patient’s symptoms improved in approximately 3 months, with no results contradictory to the past reports.

The endoscopic findings of this disease are generally nonspecific. Mosaic mucosa, ulceration, and villous atrophy in the duodenum may be shown in EGD [2]. CS or capsule endoscopy may reveal villous atrophy and ulceration in the jejunum and ileum [2]. In our case, the duodenal mucosa appeared to have a mosaic pattern. Capsule endoscopy also showed villous atrophy of the entire small intestine.

Celiac disease is well known to cause villous atrophy similar to this pathology, and magnification endoscopy is useful for evaluating villous atrophy [7]. In the present case, villous atrophy could not be observed using a nonmagnification endoscope during the first CS but was clearly visualized using a magnification endoscope during EGD. Therefore, in the endoscopy of patients with diarrhea of unknown cause, including this disease, magnification endoscopy of the duodenum and terminal ileum should be employed. In addition, capsule endoscopy is useful for observing the entire small intestine in celiac disease and this disease [8, 9]. In the present case, duodenal biopsy results already revealed the characteristic findings of sprue-like enteropathy; hence, we observed the small intestine by capsule endoscopy instead of balloon endoscopy. In cases when mucosal biopsy is not required, such as this case, capsule endoscopy is preferred because it is less invasive and more useful than enteroscopy.

Pathological examination of sprue-like enteropathy shows total or partial intestinal villous atrophy, increased intraepithelial lymphocytes, and a thick band of subepithelial collagen deposition [1], which were all present in our patient. When olmesartan was discontinued, clinical and pathological abnormalities improved. It is important to distinguish olmesartan-associated sprue-like enteropathy from celiac disease. Celiac disease is extremely rare in Japan [10]. In this case, IgA tissue transglutaminase antibodies and HLA DQ2/8 were negative, and celiac disease was excluded. In addition, collagenous sprue, which is a typical non-celiac villous atrophy disease, has been rarely reported in Japan [11]. Other diseases that may cause villous atrophy include autoimmune enteropathy, amyloidosis, eosinophilic enteritis, human immunodeficiency virus, tropical sprue, giardiasis, and common variable immune deficiency [12]. Through medical history, blood tests, histopathological examination, and stool culture, we ruled out these diseases.

To date, several cases of olmesartan-related sprue-like enteropathy combined with collagenous colitis have been reported. There are some Japanese cases of olmesartan-related sprue-like enteropathy [13, 14], but there are almost no cases combined with collagenous colitis. Globally, the course of collagenous colitis after improvement of symptoms has not yet been fully reported. Rubio-Tapia et al. reported that 13 patients with olmesartan-associated sprue-like enteropathy underwent random colon biopsy, and 3 of them had collagenous colitis [1]. However, no follow-up colon biopsy was performed in all three cases. Bashari DR et al. also reported a case of olmesartan-associated sprue-like enteropathy complicated with collagenous colitis, but they did not report a follow-up CS [15]. Ebrahim VS et al. reported that collagenous colitis was observed in 2 of 3 cases, and in 1 case, a reexamination was performed 4 months after the withdrawal of olmesartan, and it is mentioned that histopathological improvement was observed [16]. Recently, Costetti M et al. reported a histopathological follow-up of the stomach and duodenum [17]. However, they did not evaluate the histopathological findings at colonic level. In our case, clinical improvement of collagenous colitis occurred within a month after olmesartan was discontinued, but the pathological improvement of the small intestine mucosa occurred within 3 months, and that of the colonic mucosa occurred after six months. This outcome supported a previous report that showed that histologic recovery was not observed for several months but the patient’s symptoms clinically were relieved by
olmesartan discontinuation [15]. Some patients with collagenous colitis showed a typical histology but had no symptoms [18]. Possibly, villous atrophy of the small intestine affected diarrhea in this case more strongly than collagenous colitis. However, this is a single case report. Therefore, further studies and discussion are needed in this regard.

Hence, this report presents a rare case in which sprue-like enteropathy and collagenous colitis were both observed and could be followed up. Villous atrophy of the small intestine may have a greater effect on diarrhea caused by olmesartan even in cases with collagenous colitis.

In conclusion, both the large and small intestines should be assessed for villous atrophy and other abnormalities.

Abbreviations
ARBs: Angiotensin II receptor blockers; CS: Colonoscopy; EGD: Esophagogastroduodenoscopy.

Supplementary Information
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Additional file 1. Initial Laboratory Studies.
Additional file 2. Colonoscopy showed a diffuse slight edema of the colon.
Additional file 3. Biopsy showed slight improvement of the collagen band in the colon 3 months after olmesartan discontinuation (Masson trichrome).

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Authors’ contributions
SK contributed to conceptualization, data curation, resource collection, and writing of the original manuscript. KM contributed to conceptualization, data curation, resources, original draft writing, and review and editing. YM, SS, KK, AN, MY, NE, and MU contributed to conceptualization, data curation, and resource collection. HK contributed to data curation and resources. All authors have read and approved the manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations
Ethics approval and consent to participate
Ethics approval by committee was not required for this case report. It was conducted in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent for study participation was obtained from the patient.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Competing interests
The authors declare that they have no competing interests.

Author details
1Department of Gastroenterology, Kitami Red Cross Hospital, Higashi-2, Kita-6, Kitami 090-0026, Japan. 2Department of Pathology, Asahikawa Medical University, 1-1 Midorigaoka Higashi-2 Hokkaido, Asahikawa, Japan.

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