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【 CASE REPORT 】

Olmesartan-associated Gastritis Observed Over Time

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Abstract:
A 61-year-old woman who had been taking olmesartan for 7 years complained of epigastric pain, diarrhea, loss of appetite, and weight loss. Esophagogastroduodenoscopy revealed roughened mucosa and erosions in the stomach and duodenum. An endoscopic biopsy failed to identify the cause of the mucosal disorder. Small-bowel capsule endoscopy revealed villous atrophy in the small bowel, which led to suspicion of olmesartan-associated sprue-like enteropathy and gastritis. After the discontinuation of olmesartan, the symptoms and gastric mucosal findings improved. A final diagnosis of olmesartan-associated gastritis was confirmed. Olmesartan-associated gastritis should be considered in patients taking olmesartan for upper gastrointestinal symptoms.

Key words: olmesartan, gastritis, enteropathy, loss of appetite, esophagogastroduodenoscopy

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Introduction

Advances in medical science have led to the development of drugs with diverse mechanisms of action that offer therapeutic benefits across various diseases. However, these drugs can cause organ damage as side effects. Notable drug-induced gastrointestinal disorders include antibiotic-associated diarrhea (1), nonsteroidal anti-inflammatory drug (NSAID)-related gastric injury (2), proton pump inhibitor (PPI)-induced collagenous colitis (3), and immune-related adverse event (irAE) gastrointestinal disorders caused by immune checkpoint inhibitors (4).

Recently, rare cases of olmesartan-induced gastrointestinal disorder have been reported. This condition presents with symptoms such as diarrhea and abdominal pain, as well as sprue-like findings, including villous atrophy of the small intestine, similar to celiac disease, which is termed olmesartan-associated sprue-like enteropathy (5-8). In previous studies, gastrointestinal disorders caused by olmesartan have mainly been reported in the small bowel, with only a few reports of gastritis.

We herein report the course of progressive inflammatory findings in the stomach of a patient with olmesartan-associated gastritis complicated by enteropathy that occurred seven years after the initiation of oral olmesartan.

Case Report

A 61-year-old woman presented to the outpatient clinic with complaints of epigastric pain and appetite loss. Her social history was unremarkable, with no history of smoking or occasional alcohol consumption. The patient had a history of hypertension and non-alcoholic fatty liver, for which another clinic prescribed olmesartan (10 mg/day) and ursodeoxycholic acid (300 mg/day), which she had been taking for 7 years. Esophagogastroduodenoscopy revealed roughened mucosa and erosions extending from the middle of the gastric body to the duodenal bulb (Fig. 1). She was administered oral vonoprazan; however, her symptoms did not im-

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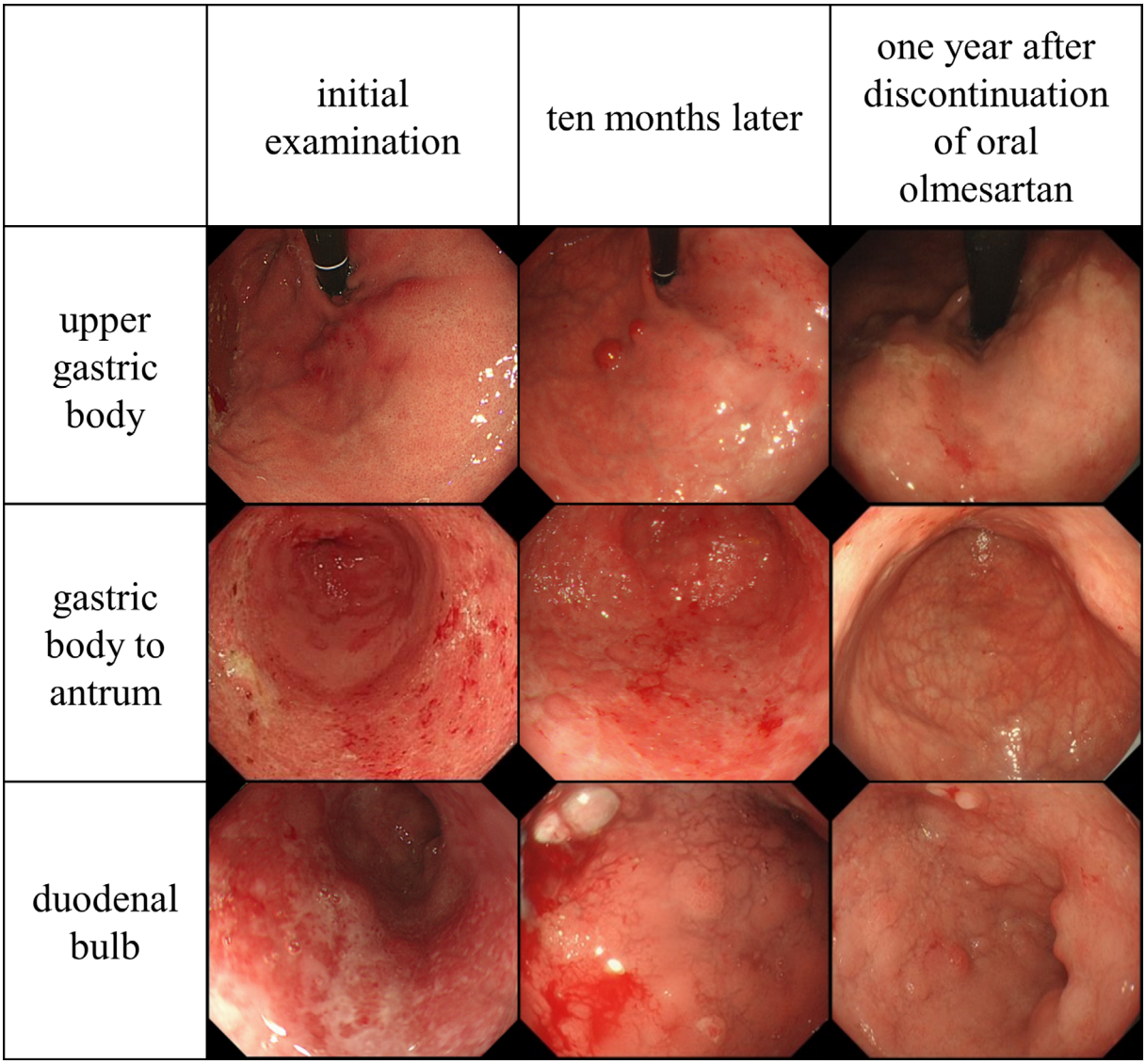

Figure 1. **Esophagogastroduodenoscopy findings. No remarkable changes were observed in the upper part of the gastric body, but roughened mucosa and erosions in the gastric antrum and duodenal bulb were observed. Ten months later, gastritis extended to the upper gastric body, mucosal nodules became apparent, and gastritis worsened in the gastric antrum. One year after discontinuation of olmesartan, the mucosal findings improved; however, the atrophic mucosa remained.**

prove. Nine months after the initial examination, the patient developed diarrhea, which occurred up to 9 times a day, as well as significant weight loss (from 56 kg to 36 kg) over the course of a year. Consequently, she was referred to our hospital for a further evaluation and management.

A physical examination revealed no signs of abdominal tenderness, rebound tenderness, or guarding. Blood tests revealed no abnormalities. Albumin was low at 3.0 g/dL, but there were no other biochemical abnormalities. The serum gastrin level was slightly elevated at 53 pmol/L, but negative for anti-parietal cell antibodies and anti-intrinsic factor antibodies. Thyroid-stimulating hormone (2.16 mU/L) and free T4 (1.05 ng/mL) levels were both within the normal range (Table 1). The *Treponema pallidum* antibody test was negative, and the rapid plasma reagin test was <1.0 U/m. Stool culture test results were negative. Abdominal computed tomography showed no wall thickening or surrounding inflammatory findings in the stomach or intestinal tract. Esophagogastroduodenoscopy revealed redness of the mucosa of the gastric antrum and body with edematous changes and excessive mucus production. The gastritis worsened and extended into the upper gastric body. Erythematous nodularities (approximately 10 mm in size) were observed extending from the fornix to the upper portion of the gastric body (Fig. 1). The duodenal bulb has multiple superficial elevations and erosions. Serum anti-*Helicobacter pylori* antibodies and histology (Giemsa stain) of the gastric biopsy specimens were negative.

A gastric biopsy of the body and antrum revealed mucosa with foveolar hyperplasia. A gastric body, antrum, and duodenal biopsy revealed inflammatory cell infiltration, predominantly neutrophils, within the mucosa, suggesting in-

flammatory changes. There was no evidence of gland atrophy or presence of a collagen band (Fig. 2). Immunostaining revealed no evidence of malignant lymphoma, amyloidosis, or eosinophilic gastroenteritis. Colonoscopy and a biopsy revealed no discernible changes in inflammation. Small-bowel capsule endoscopy revealed scattered red mucosa from the duodenal bulb to the small bowel and villous atrophy in the small bowel (Fig. 3).

H. pylori infection was ruled out based on negative findings for serum anti-*H. pylori* antibodies and the histology of the biopsy specimens. Autoimmune gastritis was ruled out based on the absence of anti-parietal cell and anti-intrinsic factor antibodies. Gastric syphilis was ruled out based on negative results for *T. pallidum* antibody and rapid plasma reagin tests. An endoscopic biopsy excluded inflammatory bowel disease (IBD), malignant lymphoma, gastrointestinal amyloidosis, collagenous gastritis/colitis, and eosinophilic gastroenteritis. Blood tests, esophagogastroduodenoscopy, colonoscopy, and a biopsy revealed no apparent cause for the mucosal disorder.

Table 1. **Blood Test Results.**

Test	Result	Unit
WBC	5,100	/μL
RBC	455	$\times 10^4$/μL
HGB	12.7	g/dL
PLT	32.7	$\times 10^4$/μL
CRP	0.07	mg/dL
BUN	10	mg/dL
Cre	0.74	mg/dL
eGFR	61.3	mL/min/1.73 m^2
Na	141	mEq/L
K	3.7	mEq/L
Cl	108	mEq/L
TP	5.3	g/dL
Alb	3.0	g/dL
CK	32	U/L
TSH*	2.16	μIU/mL
Free T4	1.05	ng/dL

*thyroid stimulating hormone

Drug-induced gastroenteropathy was considered as a differential diagnosis. The patient was administered olmesartan, ursodeoxycholic acid, vonoprazan, probiotics, and polycarbophil calcium at the time of our hospital visit. She had not taken any oral or topical NSAIDs during the clinic visit. Given the patient's long-term use of olmesartan, other medications were initially suspected; however, one month after discontinuation of drugs other than olmesartan, no improvement in symptoms was observed.

Small-bowel capsule endoscopy revealed partial villous atrophy of the small bowel, which led to suspicion of olmesartan-associated sprue-like enteropathy and gastritis. After the discontinuation of olmesartan, her symptoms improved within one month. One year later, her weight had increased to 51 kg and her albumin level to 3.8 g/dL. After discontinuation of olmesartan, her blood pressure was within the normal range; therefore, no alternative antihypertensive medication was administered. Esophagogastroduodenoscopy was repeated one year after the discontinuation of olmesartan. The mucosal findings showed improvement; however, the mucosa had transitioned to an atrophic state in the gastric antrum and body (Fig. 1). A gastric biopsy was again performed, revealing persistent inflammatory cell infiltration into the mucosa and inflammation. Epithelial regenerative changes and intestinal epithelialization were also observed.

Discussion

Olmesartan-associated sprue-like enteropathy has been reported as a side effect of olmesartan, an angiotensin II (AII) receptor blocker (ARB) (5, 6). This side effect has been described in previous studies, with reported incidences ranging from 0.24 to 29.2 per 1,000 individuals (9, 10). However, there are few reports on olmesartan-associated gastritis (5, 7, 8, 11-13). Some patients present with both enteropathy and gastritis, whereas others exhibit gastritis and enteropathy independently (5-8). Symptoms include abdominal pain, diarrhea, weight loss, nausea and/or vomiting, and gastroesophageal reflux, similar to ordinary gastroenteropathy.

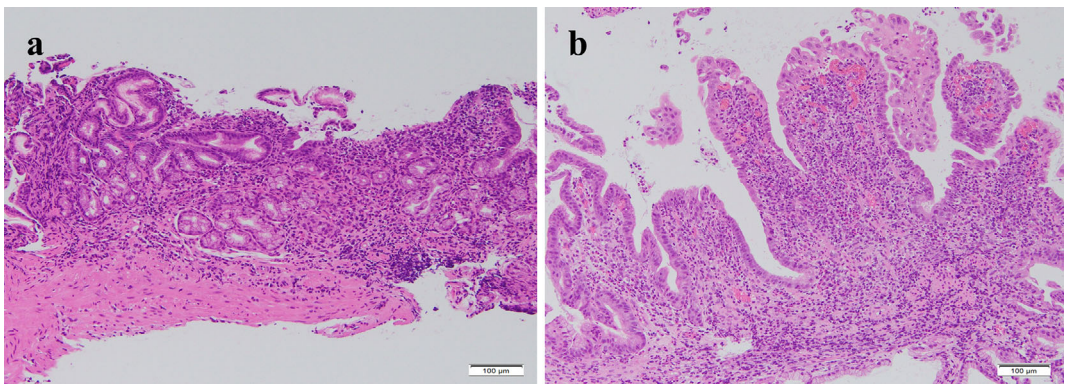

Figure 2. **a: Gastric biopsy [Hematoxylin and Eosin (H&E) staining ×100], b: duodenal biopsy (H&E staining ×100). Inflammatory cell infiltration, predominantly neutrophils, within the mucosa without apparent gland atrophy or collagen bands.**

Endoscopic findings of ARB-induced gastritis include erythema, nodularity, friability, erosion/ulceration, polyps, hyperemia, and atrophy (7, 8, 13). However, specific endoscopic changes in the stomach have not been identified (Table 2). Histologically, glandular atrophy, increased intraepithelial lymphocytes, subepithelial collagen thickening, and corkscrew glands have been reported (7, 13). However, specific findings are lacking (Table 2). Therefore, excluding other causes of gastritis and observing improvements in gastritis following discontinuation of olmesartan are important for diagnosing olmesartan-associated gastritis. In the present case, esophagogastroduodenoscopy revealed progressive worsening and extension of gastritis. Later, gastric nodularity and polyps emerged, confirming the worsening of gastritis. Gastric erythema, friability, and erosion improved one year after discontinuation of olmesartan; however, the mucosa had transitioned to an atrophic state in the gastric antrum and body. These findings suggest that the healing process in severe gastritis leads to mucosal atrophy. Gastric and duodenal biopsies demonstrated inflammatory cell infiltration, predominantly neutrophils, within the mucosa, indicative of inflammatory changes without specific findings of malignant lymphoma, gastrointestinal amyloidosis, or eosinophilic gastroenteropathy. Although the present case was complicated by enteropathy and inflammation in the duodenum, biopsy revealed no villous atrophy. Despite the nonspecific and atypical nature of the endoscopic findings and biopsy results, the patient exhibited improvement following the discontinuation of olmesartan, leading to the diagnosis of olmesartan-related gastritis.

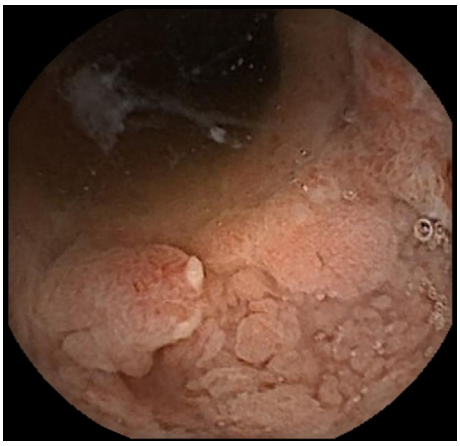

Figure 3. Small-bowel capsule endoscopy findings. Red mucosa scattered from the duodenal bulb to the small bowel and villous atrophy in the small bowel.

The case was complicated by olmesartan-associated enteropathy, which aided in the diagnosis. The differential diseases associated with diarrhea include infectious enteropathy, drug-induced enteropathy, IBD, thyroid dysfunction, and

Table 2. Clinical Features of Patients with ARB-induced Gastritis.

Case (reference)	Drug	Symptom	Endoscopic findings	Histologic features
14 cases (5)	Olmesartan	Diarrhea Weight loss Nausea Vomiting Abdominal pain Bloating Fatigue	None noted	Lymphocytic gastritis Collagenous gastritis Chronic gastritis
5 cases (11)	Olmesartan	None noted	None noted	Collagenous gastritis
1 case (8)	Olmesartan	Epigastric pain Weight loss nausea	Erosions	Ulceration Intraepithelial lymphocytes
1 case (12)	Olmesartan	Diarrhea Weight loss	Erosive gastritis	Eosinophilic micro abscesses Lymphoplasmacytic infiltrates
15 cases (7)	Olmesartan Telmisartan	Gastroesophageal Reflux weight loss Abdominal pain Diarrhea Nausea Omiting	Erythema Mucosal nodularity Friability Erosion/ulceration polyps Atrophy	Surface epithelial injury Intraepithelial lymphocytosis Lymphoplasmacytic lamina propria Infiltrate Glandular atrophy Patchy subepithelial collagen deposition Subepithelial collagen thickening
1 case (13)	Olmesartan	Vomiting Bloating Watery diarrhea	Hyperemia	Inflammation and corkscrew glands
Our case	Olmesartan	Epigastric pain Diarrhea Loss of appetite Weight loss	Roughened mucosa Erosions Redness with edema Excessive mucus Production Erythematous nodularities	Mucosa with foveolar hyperplasia Inflammatory cell infiltration in mucosa

ARB: angiotensin II receptor blocker

celiac disease. Stool culture, a biopsy, and blood tests were negative for infectious enteropathy, IBD, and thyroid dysfunction. Anti-tissue transglutaminase IgA and anti-endomysial IgA antibodies are useful in the diagnosis of celiac disease; however, they were not investigated in the present case. As the endoscopic biopsy was negative for collagenous colitis and her symptoms improved only after discontinuation of olmesartan, the diagnosis of olmesartan-associated sprue-like enteropathy was confirmed.

The onset of drug-induced gastrointestinal disorders varies. The most common onset of drug-induced gastrointestinal disorders is within 4 weeks for antibiotic-related diarrhea (1), within 3 months for NSAID-related gastric injury (2), within 1-9 months for PPI-induced collagenous colitis (3), and within 11 weeks for irAE gastrointestinal disorders (4). The development of gastrointestinal problems several years after drug administration is uncommon. Previous studies have reported that ARB-associated gastritis develops 6 months to 6 years (median 24 months) after administration (7), which is longer than with other drugs. Because the present patient had a history of taking olmesartan for seven years, we initially did not consider it the causative drug, which delayed the diagnosis. If a patient receiving long-term oral olmesartan develops gastrointestinal disorders, the side effects related to olmesartan should be considered.

The mechanism of the pathophysiology of olmesartan-associated sprue-like enteropathy is unknown; however, two theories have been proposed: [1] angiotensin type I (AT1) inhibition induces enteritis by suppressing transforming growth factor-β, an anti-inflammatory cytokine (5, 14); and [2] olmesartan acts selectively on the AT1 receptor and competitively inhibits AII binding, allowing AII to bind to the angiotensin type II (AT2) receptor, which promotes apoptosis in the small intestine (6). Both AT1 and AT2 receptors are present in the small intestine and stomach, where they regulate various physiological processes, including glucose and amino acid absorption, fluid and electrolyte absorption and secretion, gastrointestinal motility, inflammation, and blood flow (15). A similar mechanism may be involved in the development of ARB-induced gastritis in the stomach.

Treatment of olmesartan-related gastrointestinal disorders involves the discontinuation of olmesartan. Following discontinuation, most patients show improvement in symptoms and endoscopic findings (6, 7). However, in severe cases of olmesartan-associated sprue-like enteropathy, steroids or enteric-coated budesonide are used for treatment (16, 17). In the present case, stomach discomfort resolved, diarrhea ceased 20 days after discontinuation of olmesartan, and there was marked endoscopic improvement of gastritis after 1 year. However, the mucosa transitioned to an atrophic state in the gastric antrum and body endoscopically after treatment. Although *H. pylori*-associated atrophic gastritis is a cancer risk factor, the prognosis of ARB-induced gastritis is unclear, as there are no reports on its long-term course. Therefore, careful follow-up for ARB-induced gastritis is necessary even after the gastritis has improved.

In conclusion, when symptomatic nonspecific gastritis is observed in patients receiving olmesartan therapy, olmesartan-associated gastritis should be considered a potential differential diagnosis, even in patients with long-term use.

The authors state that they have no Conflict of Interest (COI).

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