Drug-Induced Spruelike Enteropathy: What Clinicians Need to Know About Olmesartan

Wesley Prichard, DO; Fantley C. Smither, MD; Laurel Fick, MD; Evan West, MD; Kapil Mehta, MD; and Anthony Martin, DO

ABSTRACT: The constellation of chronic diarrhea, abdominal pain, weight loss, and malnutrition accompanied with biopsy-proven villous atrophy and/or an elevated tissue transglutaminase antibody level usually leads to a diagnosis of celiac disease. However, when symptoms do not improve with gluten avoidance, other etiologies of spruelike enteropathy must be considered. Since 2012, there have been several case reports of the use of the commonly used antihypertensive agent olmesartan mimicking a celiac-like enteropathy. We present 4 cases of drug-induced sprue to increase clinical awareness of this adverse drug reaction.

KEYWORDS: Olmesartan, sprue, enteropathy, celiac disease, medication adverse effects

The workup to determine the etiology of chronic diarrhea in the elderly population is frequently prolonged, expensive, risky, and frustrating for both patient and clinician.[1] The constellation of chronic diarrhea, abdominal pain, weight loss, and malnutrition accompanied with biopsy-proven villous atrophy and/or a classically elevated tissue transglutaminase antibody (TTGa) serology usually leads to a diagnosis of celiac disease. However, when symptoms do not improve with gluten avoidance, other etiologies of spruelike enteropathy must be considered. Since 2012, there have been several case reports of the use of olmesartan, a commonly used antihypertensive, mimicking a celiac-like enteropathy, yet clinician awareness is lacking. We present 4 cases of drug-induced sprue to increase clinical awareness of this adverse drug reaction.

CASE 1

An 80-year-old woman presented with severe chronic diarrhea, an unintentional 15-lb weight loss, and abdominal pain for several months.

Her past medical history was significant for hypertension, which was being controlled with olmesartan. Initial esophagogastroduodenoscopy (EGD) and colonoscopy results revealed blunting of the villi with increased lymphocytosis, lymphocytic gastritis, and lymphocytic colitis, findings that were felt to be consistent with celiac disease. However, results of TTGa and endomysial antibody tests were negative.

Despite 2 months of adherence to gluten avoidance, the woman continued to lose weight and have significant diarrhea, requiring admission to the hospital for total parenteral nutrition (TPN) and treatment with glucocorticoids. After a brief period of improvement, her diarrhea and abdominal pain returned.

Biliary colic was thought to be contributing to her refractory pain, so she underwent a cholecystectomy. Following 6 more months of gluten avoidance, she again required hospitalization for diarrhea and weight loss. EGD and biopsy again demonstrated blunted villous architecture, but this time without intraepithelial lymphocytosis. Biopsy results were negative for parasites. Despite that stool studies were negative for pathogenic bacteria, she was empirically given antibiotics without improvement.

A computerized tomography (CT) angiogram was negative for mesenteric ischemia or other structural etiology to explain her symptoms.

The next month, she was hospitalized a fourth time for nausea, weight loss, and orthostatic hypotension despite her extensive workup. Duodenal findings were consistent with celiac disease, but her celiac studies were negative, and she had not responded to a gluten-free diet over the previous 10 months.

After a thorough literature review of her medications, attention was turned toward her consistent use of olmesartan. After discontinuing the medication, her symptoms slowly resolved, and she regained weight over the next 6 months.

CASE 2

A 75-year-old woman with a history of hypertension treated with olmesartan for several years presented with abdominal pain, nausea, diarrhea, and an unintentional 40-lb weight loss over the past year. Three prior admissions for similar symptoms had resulted in a diagnosis of

Table. Characteristics of Reported Cases of Olmesartan-Induced Enteropathy

Authors	Total Cases	Number of Women	Median Age (y)	Number of Non-Hispanic Whites
Rubio-Tapia et al[3]	22	13	69.5	21
DeGaetani et al[6]	16	8	66.5	Not reported
Scialom et al[9]	7	4	72	Not reported
Prichard et al	4	4	77.5	4
Nielsen et al[4]	1	1	62	Not reported
Fiorucci et al[5]	1	0	68	Not reported
Stanich et al[10]	1	1	57	Not reported

sphincter of Oddi dysfunction, and 2 subsequent sphincterotomies had failed to improve her symptoms.

Colonoscopy with biopsy demonstrated collagenous sprue, but a trial of rectal budesonide foam failed. Results of EGD showed villous atrophy of the duodenum with prominent subepithelial collagen-layer thickening, and increased lamina propria plasma cells consistent with collagenous sprue. Biopsy findings were thought to be secondary to refractory sprue from untreated celiac disease, so a gluten-free diet was initiated for short duration without symptom improvement. Results of TTGa serology tests were negative twice.

Due to intractable nausea, emesis, and chronic diarrhea, she was hospitalized and placed on TPN for severe malnutrition. Her medication list was thoroughly reviewed, and olmesartan was stopped at the time of admission. After several days of supportive care and antiemetics, her symptoms improved, and she was able to tolerate enteral nutrition.

A month after discharge, she had gained 5 lb, and her symptoms had completely resolved. A follow-up EGD with duodenal biopsy showed near-normal villous architecture and mild inflammation.

CASE 3

A 61-year-old woman presented for an EGD secondary to her unintentional 50-lb weight loss over the past year, along with nausea, and vomiting. Results of a colonoscopy 1 month prior were normal. Her only past medical history was for hypertension, which had been controlled with olmesartan for 2 years.

Results of EGD with biopsies demonstrated changes consistent with chronic gastritis, as well as severe villous atrophy and increased lymphoplasmacytic infiltrates in the lamina propria, suggestive of spruelike enteropathy. Adherence to a gluten-free diet did not improve her symptoms.

Two months later, an abdominal CT was ordered to further investigate her weight loss. An incidental pancreatic pseudocyst was discovered, and she was referred for endoscopic ultrasound (EUS). Upon EUS probe insertion into the patient's stomach, blood was discovered with very friable tissue, along with scarring of the antrum. The EUS probe was replaced with an esophagogastroduodenoscope, which was passed into the duodenum, where severe villous atrophy was noted; biopsies on repeat EGD were significant for chronic duodenitis with continued severe villous atrophy and crypt hyperplasia.

After detailed research regarding the possible effects of her chronic medications, she was suspected to have olmesartan-induced sprue. A TTGa test was ordered but never performed, because her symptoms completely resolved after discontinuation of olmesartan.

CASE 4

An 81-year-old woman with a past medical history significant only for hypertension presented to the emergency department with a 4- to 5-month history of diarrhea, an unintentional weight loss of 40 lb, and profound weakness. Her weakness had progressed to the point that she was unable to perform her activities of daily living.

The patient denied blood in her stools, fever, or abdominal pain. Her family history was significant for colon cancer in her mother, but she had had a normal colonoscopy 3 years prior. Her medications were metoprolol, amlodipine, hydrochlorothiazide, and olmesartan, the latter of which she had been taking for more than a year.

Her admission laboratory test results were significant for severe hypokalemia (2.6 mg/dL), slightly elevated transaminases, and prerenal azotemia. Her complete blood cell count and *Clostridium difficile* test results were normal. The patient was hospitalized and placed on TPN. An EGD and flexible sigmoidoscopy with biopsies were performed.

Duodenal biopsies showed marked villus atrophy and intraepithelial lymphocytosis, consistent with a spruelike injury. Colon biopsies showed mild focal colitis, while the rectal biopsies showed acute proctitis with pseudomembrane-like inflammatory exudates. TTGa test results were negative. The biopsy findings and

negative celiac serology results were attributed to olmesartan use, and the medication was discontinued.

As her clinical course improved, she was transitioned to oral nutrition and discharged to a rehabilitation facility. On follow-up by phone, the patient reported having gained weight and that the symptoms had completely resolved after discontinuation of olmesartan.

DISCUSSION

We present a series of 4 patients in 3 years who developed classic spruelike symptomatology and pathology that did not improve with gluten avoidance. These patients had each taken olmesartan (40 mg daily) for greater than 9 months before symptom onset. Intestinal biopsies confirmed spruelike enteropathy, but celiac serology results (TTGa, >95% sensitivity and specificity[2]) were negative in all cases in which it was tested. After a delayed diagnosis was made, discontinuation of olmesartan resolved the symptoms and biopsy findings, supporting the diagnosis of olmesartan-induced enteropathy.

This clinical association was first published in 2012 by authors at the Mayo Clinic, who reported 22 cases of olmesartan-induced sprue,[3] which have since been followed by more reported cases.[4-6] Given the overall low number of reported cases, we believe that the incidence likely is higher due to lack of clinician awareness and a delay of symptom onset after initiating the medication.

The US Food and Drug Administration reported an olmesartan warning of intestinal effects in 2013,[7] but approximately 1.9 million patients were prescribed the drug in 2012. We found 52 reported cases. The accompanying **Table** shows the characteristics of these cases—olmesartan-associated spruelike enteropathy appears to have a female predominance, a median age of approximately 67.5 years, and a white predominance. Our case series comprised 4 white women, the median age (77.5 years) of whom was older than the mean age of all reported cases; the Mayo Clinic study[3] had a similar white representation, while the other cases did not report patients' race.

We present a series of 4 patients in 3 years who developed classic spruelike symptomatology and pathology that did not improve with gluten avoidance. Each had taken olmesartan for more than 9 months.

The injury mechanism is hypothesized to be a cell-mediated immune response rather than a type I hypersensitivity reaction. Angiotensin II receptor blockers (ARBs) such as olmesartan increase levels of angiotension II, subsequently promoting gene expression of transformation growth factor β, which generates inflammation and apoptosis instead of preserving immune gut homeostasis.[8] Olmesartan is converted into an active form by intestinal breakdown and has a longer half-life compared with other ARBs, possibly contributing to the unique association of this specific ARB instead of a class effect.[8-10]

Primary care providers and gastroenterology specialists should be aware of this delayed adverse effect of olmesartan, despite a well-tolerated profile in the beginning of its use. ■

Wesley Prichard, DO, *is a resident in the Internal Medicine Residency Program at St. Vincent Hospital in Indianapolis, Indiana.*

Fantley C. Smither, MD, *is a transitional intern at St. Vincent Hospital.*

Laurel Fick, MD, *is associate director of the Internal Medicine Residency Program at St. Vincent Hospital.*

Evan West, MD, *is chief resident in the Internal Medicine Residency Program at St. Vincent Hospital.*

Kapil Mehta, MD, *is on faculty at the Internal Medicine Residency Program at St. Vincent Hospital.*

Anthony Martin, DO, *is associate director of the Internal Medicine Residency Program at St. Vincent Hospital.*

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