

Olmesartan-associated enteropathy: heterogeneity of involvement along gastrointestinal tract

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To the Editor

Olmesartan is an antihypertensive agent belonging to angiotensin II receptor blocker class of drugs that has recently been described as a possible cause of severe sprue-like enteropathy.¹ Olmesartan-associated enteropathy (OAE) is a rare condition that should be considered in patients with chronic unexplained diarrhea who are taking olmesartan-containing medications. This condition may be difficult to recognize because of clinical and histological similarities to other clinical diseases including celiac disease or autoimmune enteropathy and therefore a high index of suspicion is required.

OAE may be limited to small intestine or involve other segments of the gastrointestinal tract. We report 2 cases with extensive involvement of gastrointestinal tract, where small bowel involvement does not predominate, illustrating the heterogeneity of involvement along gastrointestinal tract.

Case 1

A 60-year-old man with diabetes mellitus, hypertension, dyslipidemia, and chronic kidney disease presented to emergency department with profuse watery diarrhea and acute kidney injury (AKI). Usual medications included insulin, olmesartan, and atorvastatin. He was admitted and started intravenous fluid therapy. Olmesartan was not administered during admission. Microbiologic stool examinations were negative for bacteria, parasites, and fungus. After a week, the patient was clinically improved and was discharged home, resuming his medications. However, 2 weeks later, he was readmitted with watery diarrhea (5–10 bowel movements per day) without blood or mucus and AKI. Intravenous fluid therapy was started. Diarrhea improved and creatinine returned to normal. Microbiologic stool exami-

nations, stool fat, thyroid function tests, and celiac serology were all negative. Esophagogastroduodenoscopy and colonoscopy showed no macroscopic abnormalities; however, biopsies taken from stomach, duodenum, and colon (but not terminal ileum) revealed abnormal histological findings including lymphocytic gastritis (Fig. 1A), marked villous atrophy, and increased intraepithelial lymphocytes at duodenum (Fig. 1B) and lymphocytic colitis (Fig. 1C), establishing the diagnosis of OAE. Olmesartan was replaced with lisinopril. Three weeks later, diarrhea had not relapsed and histological improvement in gastric (Fig. 1D) and duodenal (Fig. 1E) biopsies was seen.

Case 2

An 87-year-old man with diabetes mellitus, hypertension, dyslipidemia, and glaucoma presented a 2-month history of watery diarrhea characterized by approximately 10 bowel movements per day and weight loss of approximately 10 kg. Usual medications included insulin and olmesartan. Laboratory investigations revealed AKI and hypokalemia. Intravenous fluid therapy was started, with progressive normalization of creatinine and potassium levels. Stool culture for bacteria, parasites, and fungus and *Clostridium difficile* toxin were negative. Stool fat examination, thyroid function tests, and celiac serology were also normal. Esophagogastroduodenoscopy and colonoscopy showed no mucosal abnormalities. After a few days, diarrhea had improved significantly with 2 to 3 bowel movements per day and soft stools. Gastric and duodenal biopsies revealed mild chronic gastritis. Ileal biopsies had not been made. Colon biopsies displayed architectural preservation with lymphoplasmacytic infiltrate in corion and intraepithelial lymphocytosis, suggestive of lymphocytic colitis (Fig. 2). A literature search for causes of lymphocytic colitis was performed and an association with olmesartan was noted, consistent with rapid improvement after its cessation. The patient had started taking olmesartan approximately 1 year before. A diagnosis of OAE was therefore established. Olmesartan was replaced with amlodipine. After 4 months, the patient was asymptomatic.

Discussion

OAE is a rare condition that should be considered in patients with chronic unexplained diarrhea taking olmesartan. It is most common in seventh to eighth decades of life, with no gender predilection. Symptoms usually consist of chronic nonbloody diarrhea often associated with weight loss, fatigue, nausea, vomiting, abdominal pain, and bloating, typically after months to years of exposure.²

OAE can follow a severe course complicated by dehydration, AKI or electrolyte disturbances.³ Both our patients required

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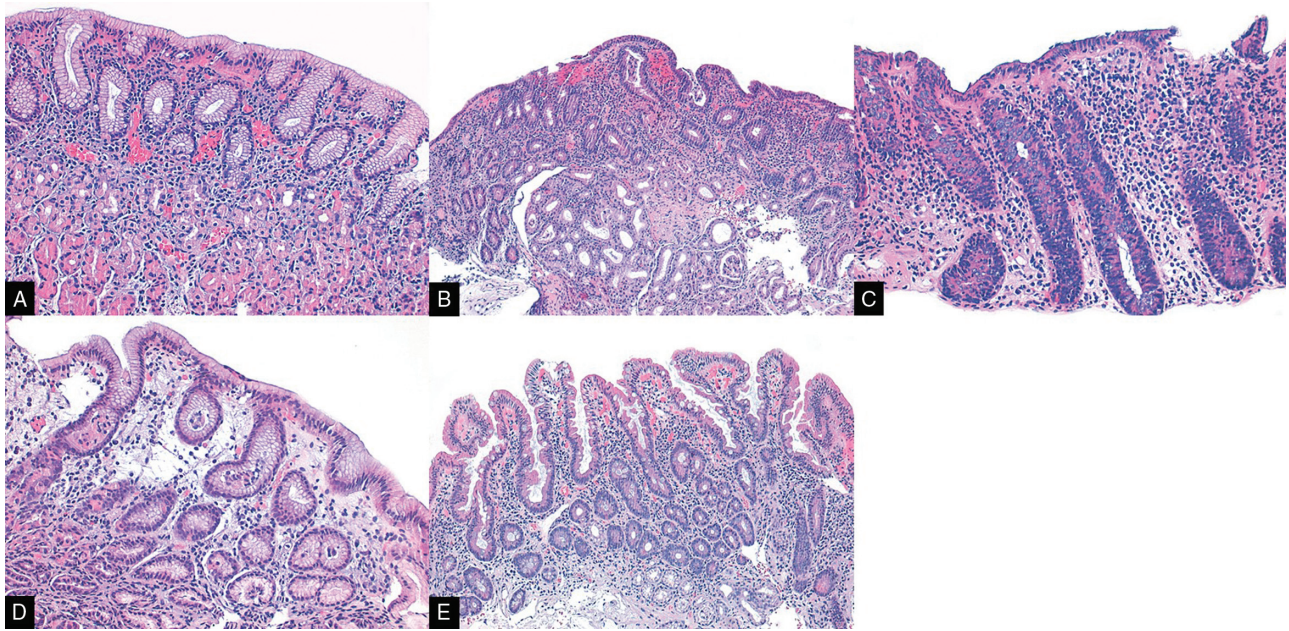


Figure 1. Olmesartan-associated enteropathy histological changes involving different segments along the gastrointestinal tract. A, Gastric biopsy showing lymphocytic infiltration of gastric pit and overlying epithelium characteristic of lymphocytic gastritis. B, Duodenal biopsy demonstrating villous flattening and increased lymphocytes in the mucosa. C, Colon biopsy demonstrating mucosal glands with many small lymphocytes infiltrating the glandular epithelium, features of lymphocytic colitis. D, Gastric biopsy obtained 3 weeks later demonstrates significant improvement with a reduction in the number of lymphocytes observed. E, Duodenal biopsy obtained at the same time also reveals significant improvement with restoration of normal villous architecture and less lymphocytes.

hospitalization in context of AKI and electrolyte disorders, illustrating this potential severity. The first patient has even had relapse of diarrhea and AKI requiring rehospitalization within a short period of time related to reintroduction of olmesartan. Symptomatic recurrence has been previously reported following reintroduction of olmesartan,⁴ supporting the concept that olmesartan must be replaced for an antihypertensive agent belonging to a different class.

Imaging and endoscopic studies usually reveal no macroscopic abnormalities. Histological abnormalities may be limited to small bowel, where villous architectural distortion, increased intra-epithelial lymphocytes, and subepithelial collagen thickening may be found in duodenum (usually the most prominently affected segment), jejunum, or ileum or extend to other segments of gastrointestinal tract, with gastric biopsies possibly revealing

lymphocytic or collagenous gastritis and colon biopsies often demonstrating lymphocytic or collagenous colitis.

Diagnostic criteria include symptom development while taking olmesartan, supportive histological findings on gastrointestinal biopsies and exclusion of other causes of diarrhea and weight loss.⁵ The mainstay of treatment is discontinuation of olmesartan, which is usually associated with resolution of diarrhea in a few days and histological improvement in less than 2 months.⁶ The cases described fulfill these diagnostic criteria and, notably, demonstrate this rapid clinical and histological recovery following discontinuation of the causal agent.

These cases demonstrate that OAE may have heterogeneous patterns of involvement along gastrointestinal tract. Although the first patient had extensive involvement with evidence of lymphocytic gastritis, duodenitis, and colitis, the second patient had predominantly lymphocytic colitis, with only mild changes in upper gastrointestinal tract. The association with lymphocytic colitis is well known,⁷ and, therefore, OAE must be considered in the differential diagnosis of lymphocytic colitis.

One limitation is that terminal ileum was not biopsied in either case. It is, however, important to note that when normal mucosa is observed in a colonoscopy performed during diagnostic work-up for diarrhea, it is recommended to perform 2 or more biopsies from ascending, transverse, descending, and sigmoid colon each to exclude microscopic colitis, but not from terminal ileum.⁸ With increased awareness for OAE, perhaps ileal biopsies would be more often considered in patients taking olmesartan.

The long period of exposure before symptoms and the heterogeneity of involvement along gastrointestinal tract here demonstrated may complicate diagnosis. Notably, these cases also reflect the potential severity of this disease, albeit with rapid recovery following discontinuation of the causal agent. Therefore, the importance of an early diagnosis cannot be over-emphasized and OAE should be promptly considered in every

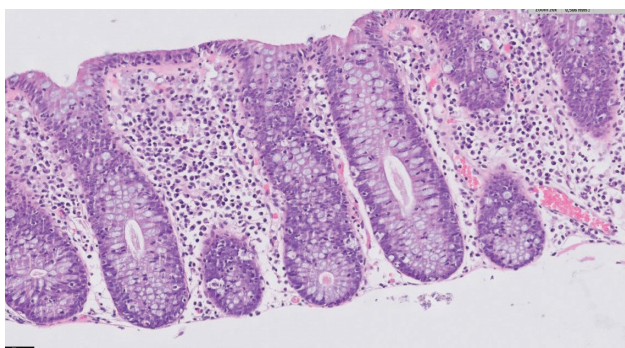


Figure 2. Colon biopsies demonstrating architectural preservation with lymphoplasmacytic infiltrate in lamina propria and intraepithelial lymphocytosis, features characteristic of lymphocytic colitis.

patient with chronic diarrhea taking olmesartan, which can significantly improve patient outcome and avoid many unnecessary investigations.

Acknowledgments

None.

Conflicts of interest

The authors declare no conflict of interest.

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