Olmesartan-Associated Enteropathy
A Review of Clinical and Histologic Findings
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Olmesartan is an antihypertensive medication belonging to the angiotensin II receptor blocker class of drugs that has recently been associated with severe enteropathy. Olmesartan-associated enteropathy is uncommon and may be difficult to recognize because of its clinical and histologic similarities to other clinical entities, including celiac sprue and autoimmune enteropathy. The purpose of this article is to review the clinical and histologic findings of olmesartan-associated enteropathy that have been reported in the literature and to discuss clinical entities to consider in the differential diagnosis of olmesartan-associated enteropathy.

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Olmesartan medoxomil (trade name Benicar), the prodrug of olmesartan, is an angiotensin II receptor blocker (ARB) that was approved for use in the United States as an antihypertensive medication in 2002. Other drugs containing olmesartan include Benicar HCT (olmesartan medoxomil/hydrochlorothiazide), Azor (olmesartan/amldopine), and Tribenzor (olmesartan/amldopine/hydrochlorothiazide).

Rubio-Tapia et al were the first to report an association between olmesartan use and the development of unexplained severe enteropathy in 2012. In July 2013, the Food and Drug Administration approved changes to drug labels containing olmesartan to include a warning that olmesartan could cause "sprue-like enteropathy." There are approximately 100 cases currently reported in the English-language literature that support olmesartan-associated enteropathy (OAE) as a distinct clinical entity.

The aim of this article is to provide a review of clinicopathologic findings of OAE with a focus on microscopic features of gastrointestinal tract biopsies described in the literature as well as to provide a brief discussion of other entities to consider in the differential diagnosis of OAE.

CLINICAL AND LABORATORY FINDINGS

Based on cases reported to date, OAE affects both men and women equally, and it most frequently affects patients in the seventh to eighth decades of life (mean age, 68 years; range, 46–91 years). Most patients with OAE present with chronic nonbloody diarrhea and weight loss. Other commonly reported symptoms are fatigue, nausea, vomiting, abdominal pain, and bloating. Patients typically develop symptoms months to years after initiation of olmesartan therapy. In the series by Rubio-Tapia et al., the average duration of exposure to olmesartan was 3.1 years (range, 0.5–7 years). Hospitalization and possibly admission to the intensive care unit may be required for severe symptoms, including severe dehydration, acute renal failure, electrolyte imbalance, and the need for parenteral nutrition.

The most frequently reported laboratory abnormalities are normocytic normochromic anemia and hypoalbuminemia. Celiac serology results have been negative in all reported patients tested for anti-transglutaminase, anti-gliadin, or anti-endomysial antibodies. Detection of anti-enterocyte antibodies and anti-nuclear antibodies has been reported in a few cases. Either HLA-DQ2 or HLA-DQ8 was identified in 45 of 65 individuals (69%) with OAE, most of whom showed HLA-DQ2.

Workup for infectious causes of chronic diarrhea is negative in nearly all reported cases of OAE. One patient was reported to have Clostridium difficile in a stool sample and Helicobacter pylori gastritis was reported in another patient. These patients’ symptoms, however, completely resolved only after discontinuation of olmesartan. Small-bowel bacterial overgrowth was detected in at least 13 patients with OAE, but resolution of symptoms did not occur with antibiotic treatment.

IMAGING AND ENDOSCOPIC FINDINGS

Imaging and endoscopic findings in the gastrointestinal tract may reveal no significant abnormalities. Reported

* References 3, 6, 7, 9, 10, 13, 15, 18–20.
imaging abnormalities include diffuse edema and bowel wall thickening of the small intestine, and enlarged abdominal lymph nodes. Reported abnormal endoscopic features of the small bowel include mucosal nodularity, villous atrophy, and ulceration.  

**MICROSCOPIC FINDINGS**

The most frequently reported microscopic finding in duodenal biopsies from patients with OAE is villous architectural distortion. Of the cases we identified in the literature with duodenal biopsies, 92 of 100 individuals (92%) had total or partial villous blunting (Figures 1 and 2). A total of 5 biopsies (5%) had normal duodenal villous architecture, 2 of which had increased intraepithelial lymphocytes. Villous architecture was not specified in 3 biopsies.

Increased intraepithelial lymphocytes (IELs) and subepithelial collagen thickening are also commonly reported findings in duodenal biopsies. Increased IELs were reported in 61 of 100 biopsies (61%), ranging from 25 to more than 100 lymphocytes per 100 enterocytes (Figure 3). Subepithelial collagen thickening was reported in 22 of 100 biopsies (22%; Figures 4 and 5). Variable degrees of lamina propria chronic inflammation, acute inflammation, and increased eosinophils may be present. No aberrant or clonal lymphocytes have been detected by immunohistochemical stains or T-cell receptor gene rearrangement polymerase chain reaction assay.

Microscopic involvement of other gastrointestinal tract sites may also be seen in OAE. Ulcers or microscopic features of lymphocytic and/or collagenous gastritis have been reported in stomach biopsies (Figure 6). Described findings in the jejunum and terminal ileum include villous blunting, subepithelial collagen thickening, increased IELs, crypt apoptosis, crypt hyperplasia, and lamina propria chronic inflammation with increased eosinophils. Colon biopsies may show increased IELs, subepithelial collagen thickening (Figure 7), and lamina propria chronic inflammation that can resemble lymphocytic or collagenous colitis. Colonic crypt apoptoses have also been described.

It is unknown whether microscopic changes can be seen in the biopsies of patients with OAE prior to the development of severe diarrhea. Lagana et al. published a retrospective cohort study to investigate whether any histopathologic changes could be identified in duodenal biopsies of patients who experienced abdominal pain without diarrhea while taking olmesartan (n = 20) or other ARBs (n = 20). No single histopathologic finding was statistically more frequent in patients taking olmesartan compared with age- and sex-matched controls. The authors, however, noted a trend toward significance in the finding of at least one spruelike microscopic feature in the patients taking olmesartan but not in those taking other ARBs, and they raised the possibility that there may be a spectrum of changes with olmesartan use. This study, however, was limited by small sample size and lack of follow-up information regarding patient outcomes.

**DIAGNOSIS, TREATMENT, AND OUTCOME**

Patients often receive a diagnosis and are treated for other causes of enteropathy before a diagnosis of OAE is given; these other causes are most commonly celiac sprue or autoimmune enteropathy. A presumptive diagnosis of OAE is made in patients who develop symptoms while taking olmesartan, who have supportive histologic findings on gastrointestinal biopsies, and for whom other causes of diarrhea and weight loss have been excluded.

Discontinuation of olmesartan has been the mainstay of treatment. Clinical resolution of diarrhea often occurs within a week of stopping olmesartan. Patients with OAE are typically unresponsive to a gluten-free diet and do not experience symptomatic recurrence after restarting a gluten-containing diet. Symptomatic improvement is reported in some patients treated with steroids or other immunosuppressant therapy prior to receiving a diagnosis of OAE. No fatalities have been reported.

Histologic improvement was reported in all 46 patients with follow-up biopsies. Normal villous architecture was reported in 41 of 46 follow-up biopsies (89%) that were obtained 2 months or more after cessation of olmesartan therapy in patients who previously had complete or partial villous blunting. Two patients with previous biopsies demonstrating complete villous blunting had partial villous blunting at 2-month follow-up. The degree of improvement in villous architecture was not specified in the remaining 3 cases. Increased IELs were noted in the follow-up biopsy in one of the patients with normal villous architecture. The presence of increased IELs or thickened subepithelial collagen was not reported in any of the 21 follow-up biopsies obtained from patients who had either of these features on prior biopsies.

**COMMENT**

Establishing a causal relationship in drug-induced enteropathy is difficult. Although deliberate rechallenge with olmesartan to prove causality following withdrawal and symptomatic improvement is not usually attempted given the severity of symptoms, symptomatic recurrence following reintroduction of olmesartan has been documented. Gallivan and Brown reported a case of a patient with severe diarrhea whose clinical symptoms resolved upon discontinuation of both olmesartan and atorvastatin. Upon selectively reintroducing olmesartan to determine which drug was causing the patient’s symptoms, the patient had a recurrence of diarrhea. DeGaetani et al. also reported on a patient with symptomatic improvement off olmesartan who had recurrence of symptoms upon rechallenge with the medication. Furthermore, there are several reports of olmesartan interruptions done prior to knowledge or diagnosis of OAE (usually motivated by hypotension) that resulted in resolution of diarrhea while off olmesartan and subsequent relapse after restarting olmesartan therapy.

DeGaetani et al. studied 72 patients with “seronegative villous atrophy” at a tertiary care center; the condition was defined by villous blunting on duodenal biopsy and negative celiac serology results. Interestingly, the two most common diagnoses in these patients were seronegative celiac disease (28%) and medication-related villous blunting (26%), the latter of which was attributed to olmesartan in 16 of 19 cases, and mycophenolate mofetil and methotrexate in the remaining 3 cases.

Current data suggest OAE is likely a rare event in patients taking olmesartan. Menne and Haller analyzed data collected in the ROADMAP study in which diabetic patients had received either 40 mg/d olmesartan (n = 2232) or placebo (n = 2215), and they found no differences in the occurrence of diarrhea or abdominal discomfort between olmesartan and placebo (n = 20) or other ARBs (n = 20).
Figure 1. Olmesartan-associated enteropathy. Duodenum biopsy showing complete villous blunting (hematoxylin-eosin, original magnification ×100). Photo courtesy of Joel Greenson, MD.

Figure 2. Olmesartan-associated enteropathy. Duodenum biopsy showing partial villous blunting, lamina propria inflammation extending down to the base of mucosa, and increased intraepithelial lymphocytes (hematoxylin-eosin, original magnification ×100).

Figure 3. Olmesartan-associated enteropathy. Higher-power view of Figure 2 duodenum biopsy showing increased intraepithelial lymphocytes and mixed chronic lamina propria inflammation composed of lymphocytes, plasma cells, and eosinophils (hematoxylin-eosin, original magnification ×200).

Figure 4. Olmesartan-associated enteropathy. Duodenum biopsy showing complete villous blunting and subsurface collagen deposition with detachment of overlying surface epithelium (hematoxylin-eosin, original magnification ×100).
these two groups. In the retrospective case-control study by Greywoode et al, analysis of clinical data from patients 50 years and older who had undergone esophagogastroduodenoscopy (n = 2088) or colonoscopy (n = 12 428) procedures found no significant association between olmesartan use and diarrhea. They also found no significant association between olmesartan use and histologic diagnosis of celiac disease or microscopic colitis. The study was limited, however, by the small number of patients taking olmesartan: 22 patients (1%) in the esophagogastroduodenoscopy group and 83 patients (0.7%) in the colonoscopy group.

The mechanism of OAE is currently unknown. The long latency period between initiation of olmesartan and development of symptoms is suggestive of cell-mediated immune damage, and inhibitory effects of ARBs on transforming growth factor β, an important mediator of gut homeostasis, may play a role. Rubio-Tapia et al also propose the possibility that HLA-DQ2 may predispose a person to immune-mediated damage, given that a higher prevalence of HLA-DQ2 is observed in patients with OAE compared with the general population.

Rare cases of enteropathy associated with ARBs other than olmesartan have been reported, suggesting the possibility of ARB class effect. We are aware of only 5 case reports in which patients developed severe enteropathy while taking irbesartan (2 cases), valsartan, telmisartan, or eprosartan (only abstract available for review in English). The reported clinicopathologic findings in these patients were similar to those of OAE.

**Differential Diagnosis**

**Autoimmune Enteropathy.—**Autoimmune enteropathy (AIE) is a rare cause of intractable diarrhea, malabsorption, and marked weight loss that has histologic features closely resembling those seen in OAE. Akram et al proposed the following 5 criteria to diagnose adult AIE, of which the first 4 are required for diagnosis: (1) adult-onset diarrhea longer than 6 weeks, (2) malabsorption, (3) specific small-bowel histology (partial/complete villous blunting, deep crypt lymphocytosis, crypt apoptotic bodies, minimal surface lymphocytosis), (4) exclusion of other causes of villous atrophy, and (5) presence of anti-enterocyte and/or anti-goblet cell antibodies. Histologic findings of AIE include flattened small-bowel mucosa, prominent crypt epithelial injury, and inflammation composed of lymphocytes, plasma cells, and neutrophils (Figure 8). There may be a loss of Paneth cells and/or goblet cells, and there may be apoptoses, neutrophilic cryptitis, and few surface lymphocytes. The process may be restricted to the small bowel or involve the entire gastrointestinal tract. Patients with OAE may present with clinical findings similar to those with AIE; they may also have histologic features similar to patients with AIE. In fact, the two entities may be indistinguishable histologically, unless the subsurface collagen that is a feature of some cases of OAE is present. Thus, before suggesting a diagnosis of AIE, it is prudent to investigate the patient’s clinical history and medication list. If the patient has been taking an olmesartan medoxomil-containing preparation, it would make sense to discontinue the medication and observe for clinical improvement before undertaking immunosuppressive therapy that may be indicated for AIE.

**Celiac Sprue.—**In fully developed sprue, the small-bowel mucosa is completely flat, with a very cellular lamina propria and regenerative epithelium, all features that are also found in OAE. There is prominent surface epithelial lymphocytosis, more striking than in most cases of OAE, and cytoplasmic lipid droplets are often present in the surface epithelium (Figure 9). Celiac sprue lacks the apoptotic bodies that are sometimes found in OAE and has less deep mucosal active inflammation and epithelial injury. Most cases also lack the subsurface collagen that may be present in OAE, although this may be present in the related entity, collagenous sprue. Again, clinical features are extremely helpful in arriving at the appropriate diagnosis, specifically the serologic tests associated with gluten sensitivity that have positive results in patients with celiac disease and negative results in those with OAE, and the lack of history of olmesartan use. The findings of celiac disease are generally restricted to the small bowel, although lymphocytic or collagenous gastritis and/or lymphocytic or collagenous colitis may be present in some patients.

**Graft-Versus-Host Disease.—**Patients with bone marrow transplants who develop gastrointestinal graft-versus-host disease (GVHD) that affects the small bowel may have variable degrees of mucosal architectural distortion, depending on the grade and duration of the GVHD injury. Findings are often subtle, with mild villous blunting, loss of crypts, and apoptosis (Figure 10). In some cases, however,
GVHD may lead to flat small-bowel mucosa when there is significant crypt injury. The lamina propria tends to be relatively paucicellular, and a case of GVHD that has significant mucosal flattening would likely have more prominent apoptosis than OAE. Surface lymphocytosis and subsurface collagen deposition are not features of small-bowel GVHD. As with all of the entities in the differential diagnosis of OAE, clinical history is key in establishing the correct diagnosis.

**Common Variable Immune Deficiency.**—Patients with common variable immune deficiency may have abnormalities throughout the gastrointestinal tract, including flattened small-bowel mucosa, prominent lymphoid aggregates, apoptoses, increased IELs, collagenous changes, and infections (eg, cytomegalovirus, Cryptosporidium, Candida, Giardia). Some of these features, such as the villous blunting, apoptosis, and increased IELs, are also seen in OAE, resulting in somewhat similar histology. However, OAE does not generally have prominent lymphoid aggregates or frequent mucosal infections. The paucity of plasma cells in the lamina propria of patients with common variable immune deficiency (present in more than two-thirds of cases) is a key finding in making the histologic diagnosis or suggesting appropriate testing for common variable immune deficiency (Figure 11). Patients with common variable immune deficiency usually present at younger ages than those with OAE, often in the second and third decades of life, an age range in which olmesartan use would be unusual.

**Bacterial Overgrowth.**—Abnormal proliferations of enteric bacteria may occur in the small bowel for a variety of reasons, including dysmotility, hypochlorhydria, blind loops, and myopathies. Patients with bacterial overgrowth may present with malabsorption, diarrhea, anemia, and abdominal pain. Histologic features that resemble those of OAE include variable villous blunting and cellular lamina

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**Figure 8.** Autoimmune enteropathy. Small intestine biopsy with complete villous blunting, chronic inflammation, prominent crypt epithelial injury, and loss of Paneth cells and goblet cells (hematoxylin-eosin, original magnification ×100).

**Figure 9.** Celiac sprue. Small intestine biopsy showing fully developed sprue with complete flattening of villi, prominent surface epithelial lymphocytosis, and lamina propria inflammation composed of lymphocytes and plasma cells. Cytoplasmic lipid droplets are present in the surface epithelium (hematoxylin-eosin, original magnification ×100).

**Figure 10.** Graft-versus-host disease. Small intestine biopsy showing prominent apoptotic cells (hematoxylin-eosin, original magnification ×400).

**Figure 11.** Common variable immune deficiency. Small intestine biopsy with villous blunting and increased intraepithelial lymphocytes but no plasma cells in the lamina propria (hematoxylin-eosin, original magnification ×200).
propria. Surface lymphocytosis and sometimes neutrophils may be clues to consider bacterial overgrowth. Subsurface collagen deposition and apoptoses are not generally prominent features. Clinical findings, including history of diseases associated with motility disorders (eg, connective tissue diseases, diabetic neuropathy, Parkinson disease), other gastrointestinal tract diseases, or prior operations, should prompt consideration of bacterial overgrowth in the setting of an otherwise nonspecifically abnormal small-bowel biopsy, and medication history is important in ruling out OAE. It is interesting to note that concurrent small-intestinal bacterial overgrowth was observed in several patients with OAE, but symptoms only fully resolved with discontinuation of olmesartan.

**CONCLUSIONS**

Olmesartan-associated enteropathy is a rare cause of severe enteropathy that should be considered in the differential diagnosis of patients with unexplained chronic diarrhea who are taking olmesartan-containing medications. Microscopic findings may be limited to the small intestine or show diffuse involvement of the entire gastrointestinal tract. Although the microscopic findings are not specific, they can be helpful in suggesting the diagnosis of OAE in the right clinical setting.

**References**