Sprue-Like Enteropathy and Liver Injury: A Rare Emerging Association with Olmesartan

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Abstract
Olmesartan-induced enteropathy is an underreported phenomenon, first described in 2012. While olmesartan’s antihypertensive properties were confirmed early on, its association with a sprue-like enteropathy was subsequently noted. Although this association has been reported with olmesartan, there have been few reports of this association with other angiotensin-receptor blockers. We present a case of a 79-year-old male who presented with diarrhea, weight loss, jaundice, and transaminitis. Further history revealed that he had been taking olmesartan 40 mg daily for hypertension. Workup of his diarrhea and jaundice included duodenal and liver biopsies revealed findings consistent with a sprue-like enteropathy and an autoimmune hepatitis-like pattern. On discontinuation of olmesartan, his 1-month follow-up revealed significant improvement in his clinical status as well as his liver function tests. Olmesartan is an effective antihypertensive medication; however, physicians must be mindful of its side effect of causing a sprue-like enteropathy and liver injury. Patients should be counseled on discontinuing olmesartan, and they should be started on an alternative therapy for hypertension.

Keywords
olmesartan, sprue-like enteropathy, olmesartan-induced enteropathy, transaminitis, liver injury

Introduction
Olmesartan is an angiotensin receptor blocker (ARB) that was first approved on April 25, 2002, for the management of hypertension, either as a single medication or in combination with other antihypertensive drugs.1 Several side effects were noticed including headache, upper respiratory tract infections, rhabdomyolysis, angioedema, and more recently and less common, sprue-like enteropathy, and transaminitis. Further history revealed that he had been taking olmesartan 40 mg daily for hypertension. Workup of his diarrhea and jaundice included duodenal and liver biopsies revealed findings consistent with a sprue-like enteropathy and an autoimmune hepatitis-like pattern. On discontinuation of olmesartan, his 1-month follow-up revealed significant improvement in his clinical status as well as his liver function tests. Olmesartan is an effective antihypertensive medication; however, physicians must be mindful of its side effect of causing a sprue-like enteropathy and liver injury. Patients should be counseled on discontinuing olmesartan, and they should be started on an alternative therapy for hypertension.

In addition, there have been a few reports of hepatic injury linked to olmesartan.9,10 Barge et al suggested that the mechanism for hepatic injury could be autoimmune related in the case report he published in 2017, and this was reiterated by de la Torre-Aláez et al in January 2020.9,10

In this article, we report a rare case of SE along with liver injury associated with olmesartan use in a 79-year-old male who presented with nonbloody diarrhea, dehydration, weight...
loss jaundice, and new-onset transaminitis that resolved after olmesartan discontinuation.

Case Presentation

A 79-year-old African American male was sent to the emergency department (ED) from his gastroenterologist’s office due to dehydration and orthostatic hypotension. The patient reported chronic nonbloody diarrhea for more than 4 weeks associated with gradual onset of jaundice. He stated having about 4 loose watery greenish foul-smell bowel movements per day, sometimes happening after meals, but it can also occur regardless of food intake. The patient described nonradiating intermittent epigastric pain, achy in nature, with no alleviating or worsening factors. He also reported nausea, few episodes of nonbloody nonbilious vomiting, generalized weakness, appetite loss, and about 30 pounds weight loss over the last 3 to 4 weeks. He denied fever, chills, dysphagia, odynophagia, rash, oral ulcers, joint pain, and swelling. No history of recent sick contacts, travel, or change in diet.

Medical history was significant for prostate cancer more than 6 years ago status postradiation, hypertension, nonischemic cardiomyopathy, vitiligo, benign prostatic hypertrophy, depression, chronic obstructive pulmonary disease, and insomnia. Drug history includes olmesartan 40 mg daily, metoprolol 100 mg daily, escitalopram 20 mg daily, trazodone 50 mg nightly as needed, finasteride 5 mg daily, aspirin 81 mg daily, isosorbide mononitrate 30 mg daily, furosemide 40 mg daily, and doxazosin 8 mg daily. Family history was significant for heart disease in the father, with dementia and hypertension in the mother. He is a nonsmoker, but drinks alcohol socially, no drug abuse.

In the ED, vital signs were a temperature of 97.5 °F, blood pressure of 69/37 mm Hg, heart rate of 71 beats per minute, and oxygen saturation of 98% on room air. His body mass index was 19.8 kg/m². Physical examination revealed a cachectic appearance with dry mucous membranes and scleral icterus. The abdomen was flat, soft, and nontender with no rebound tenderness and negative Murphy sign. The rest of the examination was unremarkable.

Laboratory testing revealed a white blood cell count of 4 × 10³/µL (normal value: 4.5-11 × 10³/µL), hemoglobin 10.7 g/dL (normal value: 12-16 g/dL), blood urea nitrogen 22 mg/dL (normal value: 5-25 mg/dL), creatinine 1.36 mg/dL (0.61-1.24 mg/dL), aspartate transaminase 191 U/L (normal value: 10-42 U/L), alkaline phosphate 98 U/L (normal value: 38-126 U/L), total bilirubin 9.6 mg/dL (normal value: 0.2-1.3 mg/dL), direct bilirubin 4.3 mg/dL (normal value: ≤1.1 mg/dL), total cholesterol 122 mg/dL (normal value: <200 mg/dL), LDL 70 mg/dL (normal value: <100 mg/dL), triglycerides 44 mg/dL (normal value: 0-149 mg/dL), and TSH 1.5 µIU/mL (normal value: 0.30-5.0 µIU/mL).

### Table 1. Summary of Main Laboratory Investigations at Admission and Follow-up.

| Laboratory findings       | Admission | One-month follow-up | Reference value |
|---------------------------|-----------|---------------------|-----------------|
| Hemoglobin                | 10.7      | —                   | 12-16 g/dL      |
| WBC                       | 4.0       | —                   | 4.5-11.0 K/µL   |
| Platelets                 | 195       | —                   | 140-450 K/µL    |
| INR                       | 15.1      | —                   | 0.88-1.15       |
| BUN                       | 22        | 12                  | 5-25 mg/dL      |
| Creatinine                | 1.36      | 0.92                | 0.61-1.24 mg/dL |
| Glomerular filtration rate| >60       | >60                 | >60             |
| Total protein             | 5.8       | 6.2                 | 6-8 g/dL        |
| Albumin                   | 2.9       | 3.3                 | 3.5-5 g/dL      |
| ALT                       | 331       | 34                  | 10-60 U/L       |
| AST                       | 191       | 28                  | 10-42 U/L       |
| Alkaline phosphate        | 98        | 105                 | 38-126 U/L      |
| Total bilirubin           | 9.6       | 1.7                 | 0.2-1.3 mg/dL   |
| Direct bilirubin          | 5.1       | —                   | 0.0-0.2 mg/dL   |
| Indirect bilirubin        | 4.3       | —                   | ≤1.1 mg/dL      |
| Total cholesterol         | 122       | —                   | <200 mg/dL      |
| LDL                       | 70        | —                   | <100 mg/dL      |
| Triglycerides             | 44        | —                   | 0-149 mg/dL     |
| TSH                       | 1.5       | —                   | 0.30-4.50 µIU/mL|

Abbreviations: WBC, white blood cell count; INR, international normalized ratio; BUN, blood urea nitrogen; ALT, alanine transaminase; AST, aspartate transaminase; LDL, low-density lipoprotein; TSH, thyroid stimulating hormone.
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Dilatation. Magnetic resonance cholangiopancreatography report stated moderately distended gallbladder that contains a large amount of layering sludge without evidence of discrete gallstones, wall edema, or significant pericholecystic fluid with no evidence of biliary dilatation or cholelithiasis. A hepatobiliary scintigraphy scan showed no evidence of cholecystitis or obstruction. Endoscopic retrograde cholangiopancreatography revealed the same findings of magnetic resonance cholangiopancreatography. The patient was managed conservatively with intravenous fluid, and electrolyte repletion while completing the rest of the workup.

Further investigations including fecal neutral fat and celiac serology were negative. Ceruloplasmin, iron, and ferritin level were within the normal range. Urine 5-hydroxyindoleacetic acid and blood serotonin were unremarkable. Alpha-1 antitrypsin level was within normal. Autoimmune workup showed normal esophagus, duodenum, and minimal chronic gastritis. Colonoscopy revealed nodular, congested colonic mucosa involving ascending colon and rectum, with no evidence of gross colitis, inflammatory bowel disease, or radiation proctitis.

Duodenal and gastric biopsy showed moderate to marked chronic duodenitis with the absence of villous architecture (intraepithelial lymphocytosis and villous atrophy) along with moderate chronic lymphocytic gastritis (intraepithelial lymphocytosis), with no *Helicobacter pylori* or amyloid identified, raising the possibility of malabsorption pattern such as celiac/SE (Figure 1A and B). Colon biopsy revealed mild nonspecific chronic inflammation in ascending colon and hepatic flexure with no amyloid deposits identified or signs of microscopic colitis. Liver biopsy stated evidence of lymphocytic-predominant portal chronic inflammatory infiltrate, with cholestasis, and mild steatosis suggesting an autoimmune hepatitis-like pattern. No cirrhosis or iron deposition was identified. No florid duct lesion or granuloma suggesting primary biliary cirrhosis (Figure 1C and D).

OIE and liver injury were considered in the setting of duodenal and liver biopsy results along with negative celiac and autoimmune markers and lack of response to a gluten-free diet. The patient’s diarrhea improved gradually on discontinuation of olmesartan, which he has been taking for more than a year. At the 1-month follow-up, the patient showed a significant clinical improvement clinically along with a remarkable decline in his liver function tests (Table 1).
was counseled to avoid olmesartan and to consider alternative antihypertensive agents.

Discussion

Historically, there have been several cases and studies describing OIE. This phenomenon was first described in 2012 by a study of 22 patients by Rubio-Tapia et al who suggested an association between olmesartan and SE. The study found that discontinuation of olmesartan in these patients resulted in clinical improvement of their unexplained chronic SE along with histologic recovery on follow-up biopsy in 18 patients. Since then, a significant increase in reporting of OIE has been recorded. A retrospective cohort study performed by Lagana et al revealed 10 of 20 patients taking olmesartan had sprue-like features on duodenal biopsy compared with 4 of 20 controls not taking ARBs. Patients taking other ARBs showed similar results to controls. In a larger study in 2013 by DeGaetani et al who studied 72 patients with villous atrophy and negative celiac serology, 19 (26%) had medication-induced enteropathy. Sixteen of 19 patients were olmesartan-related.

OIE commonly manifests with diarrhea and weight loss and less frequently with nausea, vomiting, abdominal pain, and bloating. More severe manifestations such as dehydration, acute renal failure, and perforation were also reported. Previous studies and reports showed variable timing between olmesartan initiation and OIE development ranging from months to years.

OIE is a diagnostic challenge considering a wide range of differential diagnoses. Therefore, other possible causes should be excluded before considering OIE such as CD, GI infections, inflammatory bowel disease, tropical sprue, malignancy, immunodeficiency diseases, or microscopic colitis. Enteropathy associated with other agents should also be considered including azathioprine, mycophenolate, methotrexate, neomycin, and colchicine.

The histopathological picture in OIE revealed a spectrum of findings in the duodenum such as total or partial villous atrophy, accumulation of intraepithelial lymphocytes, crypt apoptosis, and thickened subepithelial collagen layer. Aggregation of lymphocytes has also been noted in the stomach and colon in some studies. While the exact mechanism of OIE remains unknown, it is suggested to be cell-mediated immune damage. Several theories regarding the pathophysiology have been suggested including the inhibitory role of olmesartan on transforming growth factor-β, which has been shown by Matt et al to be central in maintaining homeostatic condition in the GI tract. It has also been suggested that angiotensin II receptor activation by angiotensin II has a proapoptotic effect on intestinal tissue as olmesartan is blocking angiotensin I receptors in the gut. The role of olmesartan in overexpression of CD8+ cells and interleukin (IL) 15 and disrupting the tight junction protein between the intestinal epithelial cells has also been proposed as another pathogenic mechanism of OIE. Currently, guideline-directed diagnosis and management are not well established. However, the first step should be to exclude alternative etiologies to OIE in the diagnostic workup. As per Rubio-Tapia et al, diagnostic features of OIE include GI symptoms such as chronic diarrhea, steatorrhea, weight loss, negative serology for CD, histological evidence of villous blunting, lack of improvement on a gluten-free diet, exclusion of other etiologies, and clinical and histologic improvement off of the offending agent. While our case has met all criteria of OIE, a follow-up biopsy was declined by the patient due to the resolution of his symptoms and the invasive nature of the testing.

ARBS other than olmesartan have rarely been implicated in SE. Few case reports and studies have reported similar enteropathy associated with valsartan, irbesartan, and telmisartan. The main step in the management of OIE involves discontinuing the use of olmesartan like in our case. Corticosteroids have shown a benefit in alleviating symptoms in a study by Marthey et al.

Liver injury in association with OIE has been underreported in the literature. The presence of acute liver injury and jaundice in our patient supports the uniqueness of our case. Barge et al and de la Torre-Aláez et al suggested a reversible autoimmune process causing liver injury with olmesartan. However, both cases presented with an isolated liver injury without GI symptoms compatible with SE. A case by Eusebio et al manifested with SE associated with transaminitis suggesting a different possible mechanism. It is proposed that increased gut permeability in GI syndromes may play a role in the development of liver injury. With damaged epithelium and bowel mucosa, toxins, and microbial components may be translocated from the bowel lumen to the liver via the portal circulation resulting in inflammation triggered by Kupfer cells and inflammatory cytokines including TNF (tumor necrosis factor)-α, IL-1β, and IL-6 explaining the development of hepatic injury in patients with OIE. Nevertheless, our patient’s liver biopsy supported the former theory rather than the latter.

Our patient was diagnosed with OIE associated with symptomatic liver injury after being exposed to olmesartan for approximately 18 months with a clinical improvement and a remarkable decline of liver enzymes after olmesartan discontinuation. Olmesartan was not reintroduced for rechallenge due to the severity of illness related to this medication. Upper endoscopy and follow-up biopsy were offered; however, the patient preferred to avoid any further invasive procedure in the setting of symptoms resolution.

Conclusion

Clinicians should consider olmesartan as one of the possible causes for SE. Moreover, liver injury is an underrecognized phenomenon that has been reported rarely with olmesartan and requires further studies.
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Ethics Approval
Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent
Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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