CLINICAL VIGNETTE

An Under Recognized Cause of Chronic Diarrhea

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Case

A 70-year-old man with type II diabetes, hypertension, and chronic kidney disease presented with diarrhea and associated loss of appetite for the past six weeks. He initially had some associated aches and presumed he had flu. He also reported having six to eight loose bowel movements daily often triggered by meals with unintentional weight loss of twenty pounds. His primary care physician sent bacterial/parasite enteric panels, C.diff, fecal leukocytes, O&P and all returned normal. He was given Lomotil (Atropine/Diphenoxylate) which he was taking four times daily without significant improvement and referred to GI for further evaluation and management.

At his initial GI office visit he reported no abdominal pain, melena, or blood per rectum but did note occasional nausea with defecation. Medications included insulin glargine, amlodipine, olmesartan, hydrochlorothiazide, simvastatin and tamsulosin. Labs were notable for a WBC of 12.05 $x10^9$/dL, hemoglobin 15.5 g/dL, platelets 319, albumin 3.0 g/dL, sodium 134 mmol/L, BUN 24 mg/dL and creatinine 1.58 mg/dL. Celiac panel was normal. Cholestyramine was prescribed and an EGD and colonoscopy scheduled.

On his EGD ulcers were seen in the duodenum and biopsied given olmesartan use. Colonoscopy was unremarkable with random biopsies to evaluate for microscopic colitis. Duodenal biopsies returned showing nearly complete villous atrophy with increased intraepithelial lymphocytes, scattered neutrophils, focal sub epithelial collagen deposits and increased lamina propria eosinophils. Colon biopsies showed patchy sub epithelial collagen deposits, pithy surface epithelial injury and increased lamina propria eosinophils. Findings were consistent with medication induced injury favoring olmesartan induced injury.

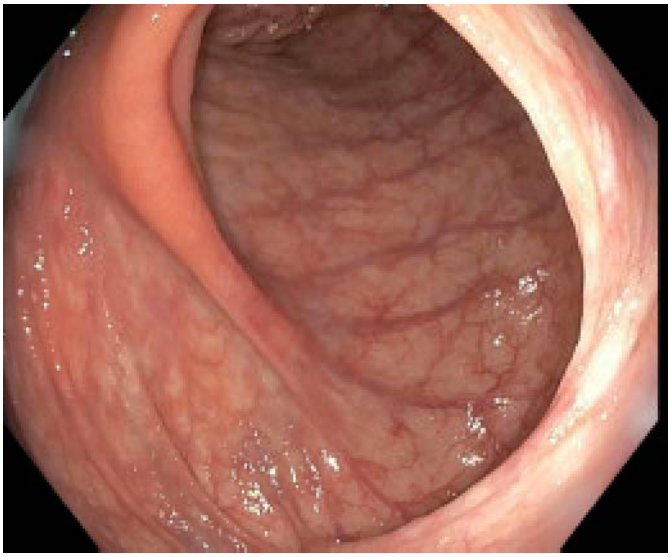
Olmesartan was stopped and budesonide 9mg daily prescribed for a thirty-day course. Upon follow up six weeks later he had complete resolution of his symptoms. He reported one to two formed stools daily and albumin improved to 4.0 g/dL.

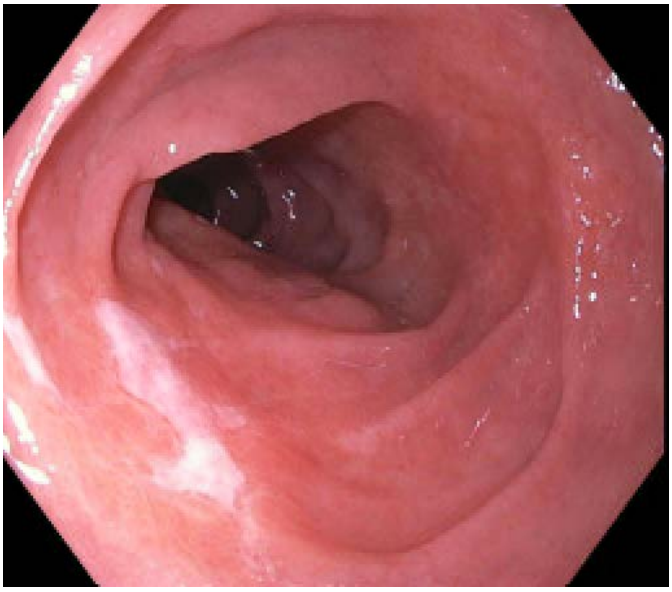
Discussion

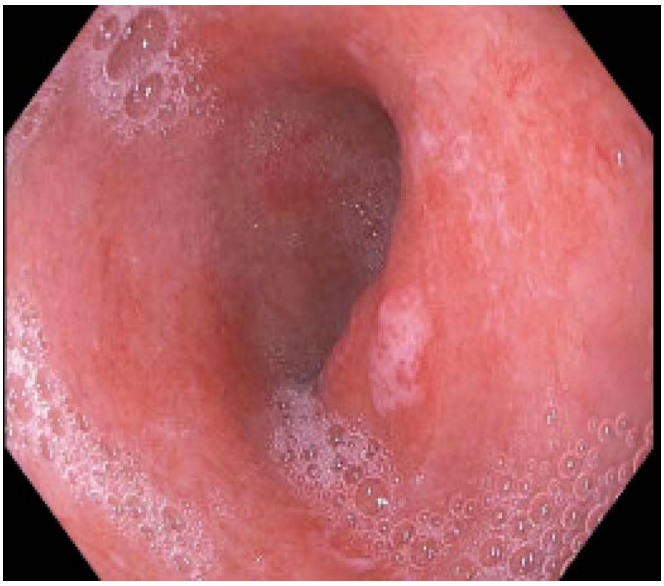
Patients with spruelike enteropathy can exhibit diarrhea, weight loss, nausea, vomiting, abdominal pain, bloating and fatigue. Endoscopically villous atrophy and mosaicism can be seen. Histologically villous atrophy, inflammation with increased intraepithelial lymphocytes (IELs) and collagen deposition can be present. Celiac disease is the most common cause of villous atrophy and increased IELs but can be caused by other conditions such as Crohn's disease, autoimmune enteropathy, CVID, giardia, tropical sprue and effects from medications such as azathioprine, methotrexate, and mycophenolate.[1] Olmesartan is an angiotensin II receptor blocker (ARB) used to treat hypertension and first approved in 2002.[2] A series of 22 patients evaluated at the Mayo clinic with unexplained diarrhea and enteropathy attributed to olmesartan use was reported in 2012. In 2013 the FDA issued a warning regarding risk for enteropathy with olmesartan use.[3,4] The initial study's findings have been supported in subsequent studies. A systematic review of 11 publications reported patients had been on therapy a mean of 3.3 years before onset of symptoms (range 6 months to 7 years).[1,2] Our patient had been on olmesartan for at least 7 years before his presentation. The most common presenting symptoms are diarrhea (95%) and weight loss (89%) with nausea/vomiting (56%), abdominal pain (37%) and bloating (29%) also common.[1,4] Celiac antibodies were normal in all patients, but 72% had DQ2/DQ8 haplotypes (present in the majority of patients with celiac disease) exceeding the general prevalence of 30-40%.[1,3] The most common laboratory abnormalities were normocytic normochromic anemia (45%) and hypoalbuminemia (39%).[1] Endoscopically the duodenum can appear normal or may exhibit villous blunting or ulceration.[1] Duodenal villous flattening was the most common histologic finding (98%). Increased IELs were seen in 65% of patients and increased sub epithelial collagen in 33%.[1] All studies reported discontinuation of olmesartan led to 100% resolution of diarrhea and weight gain in 78%. Improvement in symptoms were reported as soon as one week after stopping Olmesartan, with an average time of 8 months for complete resolution of symptoms.[1,4] Collagenous and lymphocytic change were also described in the stomach and colon in patients with olmesartan induced enteropathy.[1,4,5] A case study from Japan described a 73-year-old man on olmesartan for 5 years who presented with diarrhea and weight loss and was found to have duodenal villous atrophy, increased IELs with collagen deposition and collagenous colitis (all were also present in our patient).[4] With cessation of Olmesartan, his symptoms improved after 3 weeks with normal duodenum on repeat EGD. Colonoscopy after 3 months still showed collagenous colitis with normal colonic mucosa on 6 month repeat colonoscopy.[4] This patient did not have positive HLA DQ2/DQ8 but the report of increased incidence of the haplotypes in other studies suggests a possible genetic pre-

disposition. The long duration from the start of therapy until the onset of symptoms suggests a cell mediated component rather than a type 1 hypersensitivity.[3,4] Given the delay between initiation of ARB therapy and the development of symptoms, providers should be aware of this under recognized condition and have a high index of suspicion if evaluation for other causes of diarrhea is normal.

Figures







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