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Trientine-induced enteritis in Wilson's disease treatment

To the Editor:

We read with great interest the updated EASL-ERN Clinical Practice Guidelines on Wilson's disease (WD). WD is a rare genetic disorder of copper metabolism, in which impaired biliary copper excretion leads to hepatic and neurologic accumulation, risking significant morbidity and mortality without treatment.[1] As highlighted in the practice guidelines, the cornerstone of WD treatment is lifelong copper chelation to prevent progressive organ damage.[2]

D-Penicillamine (DPA) was the first oral chelator used and was long considered first-line therapy.[3] However, DPA is associated with a lengthy list of potential side effects, including sensitivity reactions, nephrotoxicity, bone marrow suppression, dermatologic reactions, lupus-like syndrome, and hepatotoxicity, and paradoxical worsening of neurologic symptoms.[4] Trientine (TETA) has emerged as a non-inferior alternative and is generally better tolerated than DPA.[5] TETA has the more favorable side effect profile, however, reports of gastritis, colitis, neurologic worsening and anemia have been reported.[6,7] Multiple formulations of TETA exist, including trientine dihydrochloride (TETA 2HCl) and trientine tetrahydrochloride (TETA 4HCl) which differ in pharmacokinetic profiles, bioavailability, and temperature stability.[8] Zinc may be used as adjunctive therapy but typically is inadequate as monotherapy for initial symptomatic treatment because it does not chelate copper directly. Instead, zinc blocks intestinal copper absorption and sequesters it in epithelial cells.[9] WD requires lifelong treatment to prevent further consequences of impaired copper metabolism.

We report a rare case of trientine-induced enteritis ultimately necessitating a change in chelation therapy. A 37-year-old woman with anxiety and history of renal cell carcinoma previously treated with nephrectomy presented with acute liver injury. Laboratory studies revealed total bilirubin 5.5 mg/dl, alkaline phosphatase 57 IU/L, aspartate aminotransferase 93 IU/L, alanine aminotransferase 33 IU/L, albumin 3.5 g/dl, international normalized ratio 2.4. Work-up for causes of acute liver injury was notable for ceruloplasmin 5.3 mg/dl and 24-hour urinary copper excretion 1,690 μg/24 h. Kayser-Fleischer rings were present on slit lamp examination. Liver biopsy confirmed WD diagnosis with hepatic copper quantification 533 μg/g dry weight. Treatment was initiated with TETA 2HCl. She was on no other medications at that time.

Three months later, the patient required hospitalization with profuse watery diarrhea (5-10 bowel movements daily including nocturnal episodes), anasarca, and unintentional weight loss. Laboratory evaluation suggested malabsorption including low albumin (1.7 g/dl), electrolyte derangements (*i.e.* magnesium 1.2 mg/dl), iron deficiency (iron 41 μg/dl, total iron binding capacity 529 μg/dl, transferrin saturation 8%, ferritin 12 ng/ml), and vitamin deficiencies (vitamin A 20 mcg/dl, vitamin D 18.4 ng/ml). Additional laboratory values included total bilirubin 1.5 mg/dl, alkaline phosphatase 88 IU/L, aspartate aminotransferase 59 IU/L, alanine aminotransferase 60 IU/L, and international normalized ratio 1.6. Fecal calprotectin was markedly elevated >2,000 μg/g (normal range ≤80 μg/g). CT scan of the abdomen showed mildly dilated fluid-filled small bowel loops without evidence of obstruction, and stable hepatomegaly (20.0 cm) and splenomegaly (14.9 cm).

Upper endoscopy revealed small esophageal varices but otherwise normal appearing mucosa in the esophagus, stomach, and duodenum. The colonic mucosa appeared normal on colonoscopy, while the terminal ileum appeared edematous with scattered superficial erosions. Histopathologic examination of the duodenum and terminal ileum showed villous blunting and crypt hyperplasia as well as active duodenitis and ileitis, respectively (Fig. 1A). No chronic inflammation, architectural destruction, or granulomas were found to support a diagnosis of inflammatory bowel disease. Serologic testing for celiac disease was negative, no infections were identified, no other potential medications were possible culprits, and no malignancy or infiltrative etiologies were found. Upon discontinuation of the TETA 2HCl, the patient's symptoms and laboratory abnormalities improved without requiring corticosteroids or other additional interventions that are often needed in inflammatory bowel disease or microscopic colitis. Thus, medication-induced enteritis was suspected.

The patient ultimately required additional chelator therapy given the large degree of excess copper stores. She was reluctant to take DPA because of concerns of neuropsychiatric worsening, and TETA was cautiously reintroduced using the TETA 4HCL formulation. Unfortunately, within 1 month, she developed recurrent severe diarrhea with fecal calprotectin once again rising to >2,000 μg/g. Liver chemistries and synthetic function remained stable. TETA was discontinued indefinitely. She experienced complete resolution of diarrhea within 1 month of stopping. She was temporarily managed on zinc monotherapy and later transitioned to DPA, which she has tolerated well without new neurologic or psychiatric symptoms (Fig. 1B).

This case highlights trientine-induced enteritis as a rare, but important adverse side effect. The patient had a clear association between TETA and clinical symptoms. The recurrence of symptoms upon rechallenge with a different TETA formulation and resolution of symptoms following cessation strongly implicate TETA as the causative agent. While there have been a few prior reports of TETA-induced colitis with and without duodenitis or ileitis, we are not aware of any prior reports that demonstrate isolated enteritis due to trientine.[7,10] Clinicians should remain vigilant for gastrointestinal toxicity in patients

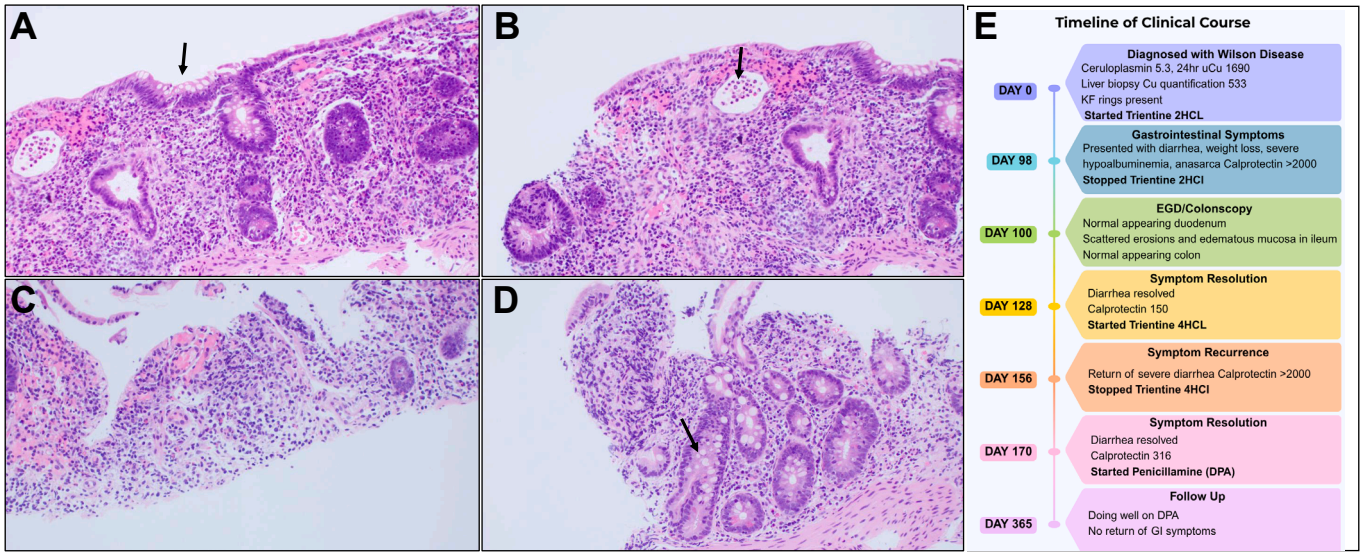

Fig. 1. Endoscopic histopathology and clinical timeline. Histopathology from small intestinal biopsies showing features of active enteritis including villous blunting (A), acute inflammatory infiltration with a neutrophilic abscess (B), erosions (C), and crypt hyperplasia (D); Timeline of clinical course beginning with Wilson's disease diagnosis and subsequent symptomatic response to treatment implicating trientine as the causative agent of drug-induced enteritis (E).

treated with trientine. Early recognition is essential to guide timely therapeutic adjustments.

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Supplementary data

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