SHORT REPORT

Concomitant presentation of collagenous sprue and HFE hemochromatosis

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Abstract
Collagenous sprue (CS) is a progressive malabsorptive disorder characterized by collagen deposition beneath the basement membrane of small bowel epithelium in refractory celiac sprue.1 CS is a pathologically distinct entity from celiac disease, despite a similar clinical presentation. The etiology of CS is unclear, although there are speculations that CS and celiac disease may share similar pathogenetic pathways.2 On the other hand, HFE hemochromatosis (HH) is a distinct disease entity. Celiac disease and HH are common HLA-associated genetic disorders in Northern European populations. There are a few case reports linking celiac disease and HH. We present a patient diagnosed with concurrent CS and HH.

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1. Case presentation

A 40-year-old man of Irish and German descent with a history of acute myocardial infarction 2 months prior, presented with watery, malodorous, large volume liquid stool 15 times daily for 5 months, and a 60-pound weight loss. The patient was initially evaluated at a local hospital with a negative work-up including stool microbiological studies, CT abdomen and pelvis, colonoscopy, and EGD without biopsies. He had no response to loperamide and a gluten-free diet for 2 weeks. He presented to our hospital for further evaluation. Physical examination revealed a cachectic man with a soft abdomen, increased bowel sounds, no hepatosplenomegaly and without tenderness to palpation. A review of systems was significant for alopecia, nausea, vomiting, bloating, and chest discomfort. Medications included aspirin, prasugrel, omeprazole, potassium chloride, carvedilol, and simvastatin.

The patient was admitted to the hospital, where he was found to have hypokalemia, hypomagnesemia, hypocalcemia and a serum albumin level of 1.8 g/dL. He underwent a CT enterography that showed no signs of active small bowel disease or malignancy. He then had EGD showing diffuse

Abbreviations: CS, Collagenous sprue; HH, HFE Hemochromatosis.
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scalloping, blunting of the duodenal villi, and sloughing of mucosa with biopsy forceps (Fig. 1). Duodenal histology shows abnormal villous architecture with markedly thickened and irregular subepithelial collagen table that incorporates capillaries and lamina propria cells. A trichrome stained section highlights the abnormal collagen table in blue (100×, Fig. 2). A flexible sigmoidoscopy revealed normal appearing mucosa of the sigmoid colon and rectum; however, histopathology demonstrated collagenous colitis and proctitis (Fig. 3). The patient was started on oral budesonide and total parenteral nutrition (TPN), with improvement in diarrhea and nutritional status. He continued to have approximately 8 bowel movements daily and was transitioned to oral prednisone after trials of ciprofloxacin and tinidazole for possible concurrent small bowel bacterial overgrowth. The patient was then cycled off TPN as he had sufficient oral intake and clinical improvement in diarrhea after a 15-day hospital stay. He was discharged to home on oral prednisone with outpatient follow up.

At admission, serum iron was 224 μg/dL, serum ferritin was 2200 ng/mL, and AST and ALT were elevated >3 times the upper reference limit. Further work up demonstrated a homozygous C282Y mutation in the HFE gene. A liver biopsy showed mild to moderate hemosiderosis with preserved liver architecture without significant hepatocellular necrosis, cholestasis or steatosis (Fig. 4). The duodenal biopsy did not reveal stainable iron. After 12 once-weekly phlebotomy sessions, serum ferritin and liver enzymes returned to normal. Subsequent EGD and flexible sigmoidoscopy with duodenum, colon, and rectal biopsies showed normal villous architecture and resolution of the abnormal subepithelial collagen table (H&E, 100×, Fig. 5). At follow-up 9 months later and off prednisone therapy, EGD and flexible sigmoidoscopy with biopsies remain normal. The patient was treated

Figure 1  EGD showing diffuse scalloping, blunting of the duodenal villi, and sloughing of mucosa with biopsy forceps.

Figure 2  Trichrome stain highlights the abnormal collagen table in blue (100×).

Figure 3  Sigmoid biopsy, H&E shows thickened subepithelial collagen table that also incorporates lamina propria cells and capillaries. The lamina propria is expanded by mononuclear inflammatory cells, and the surface epithelium is injured. Occasional intraepithelial lymphocytes are also identified.

Figure 4  Liver biopsy shows increased periportal hepatocellular-predominant iron deposition, characteristic of hereditary hemochromatosis. The portal tracts are demarcated by the arrows, and the iron granules stain blue in this Perl's iron stain.
with prednisone for 6 months. Treatment response while off prednisone demonstrates that phlebotomy contributed to disease remission.

A second case of an 84-year-old man with a history of hypertension, hyperlipidemia, atrial tachycardia, hypothyroidism, prostate cancer status post radiation therapy, chronic renal insufficiency, gout, and hemochromatosis maintained with once monthly phlebotomy presented with watery diarrhea and incontinence over the course of one month. In 2004, he underwent gene testing that was negative for C282Y and H63D mutations of the HFE gene. A liver biopsy at that time showed severe hepatocellular iron deposition suggestive of HH and an iron index of 5, however there was no significant fibrosis. He had no history of blood transfusion or iron infusion. A flexible sigmoidoscopy at the time of diarrhea showed collagenous colitis. The patient responded to treatment with bismuth subsalicylate and continued monthly phlebotomy.

2. Discussion of diagnosis

Diagnostic criteria of CS and HH have been well defined in the literature. A combined evaluation with endoscopy, laboratory tests, and histopathology yield a specific diagnosis. However, the challenging part is the identification of etiology and pathogenesis of CS and HH and their relationship. Both CS and collagenous colitis have been linked to immune-mediated disorders. There are reported associations between collagenous colitis and Crohn’s disease, ulcerative colitis, lupus, primary biliary cirrhosis, polymyalgia rheumatica, diabetes, thyroid disease, celiac disease, pancreatitis, and pernicious anemia. There was an increased prevalence of Crohn’s disease, diabetes mellitus, and Sjogren’s syndrome in patients with celiac disease. Collagenous sprue or collagenous colitis has also been reported to be a part of autoimmune disorders.

Environmental factors may contribute to the onset of many autoimmune disorders. Rubio-Tapia et al. proposed that autoimmune disease in association with environmental factors (drugs, infection, and food antigens) may lead to gut inflammation and CS. Vesoulis et al. reported a case of synchronous occurrence of collagenous colitis and Clostridium difficile-associated pseudomembranous colitis. While dysbiosis and viruses such as rotavirus may contribute to the pathogenesis of collagenous colitis and celiac disease, their role in CS has not been studied.

The relation of celiac disease and hemochromatosis has been shown in case reports. The diagnosis of HH after the successful treatment of celiac disease has been described. Butterworth et al. concluded that HFE gene mutations are more common in patients with celiac disease and may offer a survival advantage. In another study, Leyden et al. failed to show an increased frequency of HFE mutations in patients with celiac disease. Thus the association of celiac disease and HH remains uncertain. Interestingly, collagenous sprue, a distinct disease entity from celiac disease with different pathogenetic pathways, diagnostic criteria, and prognosis, has not been reported to concomitantly occur with hemochromatosis in the literature.

Our patient did not have celiac disease but rather CS and collagenous colitis. A relationship between CS and HH remains speculative. There are several possibilities that the two disease entities have causality relationship; or the two share common etiopathogenetic pathways; or the concurrent presentation of two conditions was coincidental. Mechanistically, it is hard to imagine that CS with characteristic poor iron absorption would lead to the phenotypic features of HH; rather CS might conceivably protect against or obscure such features. Our patient restored a normal serum ferritin with only 12 one-unit phlebotomies. This constitutes about 3 g of storage iron, roughly three times the normal for an adult male, that while indicative of phenotypic iron overload in HH has been reported to be associated with chronic inflammation. Gut mucosal injury is known to occur in response to reactive oxygen species involved in the inflammatory cascade. Iron-derived oxidant activity may exacerbate inflammation of intestinal mucosa in inflammatory bowel disease and conceivably iron overload of relatively modest amounts may contribute to intestinal mucosal damage. A prospective study shows that iron chelators significantly reduce reactive oxygen species in patients with ulcerative colitis. The data support the speculation that HH with iron overload may be associated with intestinal mucosal injury and resultant CS. Resolution of submucosal collagen bands and associated inflammation in the small and large bowels after phlebotomy, with and without steroid use in our patient, might further support the hypothesis.

CS and HH may share similar pathogenetic pathways. HH has been reported to be associated with ulcerative colitis and primary sclerosing cholangitis. CS is a rare disease entity, with unknown genetic association. In contrast, the HLA-D locus has been shown to be associated with celiac disease, which is in close proximity to the HFE locus on chromosome 6, leading to speculation that there might be a genetic linkage of the two diseases. It may be further hypothesized that the genetic predisposition for either disease lessens manifestations of the other and may serve as a mutual protective mechanism. Injury to iron transporters in the apical membrane of enterocytes in celiac disease can lead to iron deficiency, reducing iron overload in HH. Our first patient with HH had relatively low iron stores.
and did not have advanced liver disease, which may be due to a protective effect from underlying CS.

3. Treatment and management

CS is often associated with poor prognosis and even mortality. Recent literature has shown treatment success with a combination of corticosteroids and other immunosuppressants. There was reported clinical response of 80% in patients with CS treated with immunosuppressive drugs (mainly steroids) and gluten free diet for 6 or more months. However, complete histopathological response and resolution is uncommon. Most reported cases of CS demonstrate a poor response to gluten free diet alone. Other reported treatment options included parenteral nutrition, low carbohydrate and low fat diets, probiotics, fiber supplementation, and vitamin supplementation. Schmidt et al. present a case report of clinical improvement with infliximab (5 mg/kg body weight) after failure of high dose steroids in a patient with CS. For the treatment of HH with iron overload, periodic phlebotomy to maintain normal body iron stores is the standard of care.

The main treatment regimen in our patient was oral corticosteroids (prednisone and budesonide) along with phlebotomy. After 6 months of therapy, we observed both clinical and histopathological remission for CS as well as normalized serum ferritin and ALT/AST level for HH. One year later and after corticosteroid taper, histopathology of the small bowel and colon remain normal with intermittent phlebotomy. In the second case, our patient responded to therapy with bismuth subsalicylate and monthly phlebotomy. After 6 months of therapy, we observed both clinical and histopathological remission for CS as well as normalized serum ferritin and ALT/AST level for HH. In the second case, our patient responded to therapy with bismuth subsalicylate and monthly phlebotomy. In summary, it is plausible that iron overload caused collagen deposition in the small bowel and resultant CS.

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