Case Report

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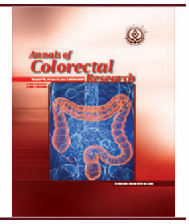

Collagenous Enteritis - An Alternative Cause of Malabsorptive Enteropathy

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Abstract

Introduction: Collagenous Enteritis (CE) is a recently described and rare pathological diagnosis characterized by intestinal villus blunting, intraepithelial lymphocytic infiltrate, and expanded subepithelial collagenous bands.
Case Presentation: We discuss the case of a 40-year-old woman with prior history of cervical cancer who presented to our center with a two-year history of progressive unintentional weight loss (32 kg), chronic diarrhea, and severe malnutrition. During this time, she was labeled as having celiac disease but despite documented adherence to a prolonged gluten-free diet, she continued to experience diarrhea, fatigue, and weight loss. After extensive workup, pathology from a follow-up push enteroscopy revealed the presence of intestinal intraepithelial lymphocytosis and severe villus blunting in addition to a patchy enlarged subepithelial collagen layer characteristic of CE extending from the duodenum to the terminal ileum.
Conclusion: With a better understanding of CE and its response to various treatment modalities, a more favorable outlook has replaced its once grim prognosis. Discontinuation of offending medications and initiation of corticosteroids remain the mainstay of therapy, often with favorable outcomes. In our case, treatment with corticosteroids and maintenance on a strict gluten-free diet resulted in significantly reduced stool output and gradual weight gain.

Keywords: Collagenous sprue, Malabsorption, Diarrhea

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Introduction

Collagenous Enteritis (CE) is a recently described and rare pathological diagnosis characterized by intestinal villus blunting, intraepithelial lymphocytic infiltrate, and expanded subepithelial collagenous bands. Its rarity, clinical resemblance to more commonly encountered causes of enteropathy, and need for pathology make it an elusive diagnostic challenge.

Case Presentation

A 40-year-old woman with prior history of cervical cancer (treated with chemotherapy and radiotherapy) presented to our academic medical center with a two-

year history of progressive unintentional weight loss (32 kg), chronic diarrhea, and severe malnutrition.

Esophagogastroduodenoscopy (EGD) and colonoscopy three months prior to admission had revealed duodenal villous blunting with intraepithelial lymphocytes on biopsy; the patient was diagnosed with celiac disease. Despite documented adherence to a prolonged gluten-free diet, she continued to experience diarrhea, fatigue, and weight loss prior to presenting to our center.

Exam revealed an ill-appearing cachectic woman, weighing 36.2 kg (body mass index 12.9 kg/m^2), with temporal and proximal muscle wasting and a moderately distended abdomen without tenderness. Initial laboratory workup revealed normocytic anemia (hemoglobin 8.7 g/dL), hypokalemia (potassium 3.1 mmol/L), hypoalbuminemia (albumin 2.0 g/dL), and elevated erythrocyte sedimentation rate (ESR; 19 mm). The total bilirubin was 0.6 g/dL and mild elevations in liver enzyme levels were also noted (aspartate transaminase 103 U/L; alanine aminotransferase 45 U/L; alkaline phosphatase 110 U/L). Infectious workup for enteric pathogens, parasites, *Clostridium difficile*, *Tropheryma whipplei*, HIV, CMV, and Vibrio was negative. Inflammatory and secretory diarrhea workup including stool calprotectin, VIP, somatostatin, urine 5-hydroxyindoleacetic acid, and gastrin levels were all within normal limits. Autoimmune assays for immunoglobulins and anti-nuclear antibodies were unremarkable. In the malabsorptive workup, pancreatic elastase and fecal fat were within normal limits. HLA analysis confirmed positive HLA-DQ2 and negative DQ8. Follow-up celiac serologies were negative, although the patient was noted to be on a prolonged gluten-free diet. CT demonstrated enlarged fatty liver, large volume ascites, and terminal ileum wall thickening. A liver biopsy demonstrated severe steatosis and minimal steatohepatitis in line with the patient's history of malnutrition.

Despite the initiation of an elemental diet and scheduled antidiarrheals, the patient continued to have refractory diarrhea. She subsequently underwent capsule endoscopy notable for diffuse villous blunting along the entire length of the small bowel, scalloping of mucosal folds, mucosal erythema, and granularity. Pathology from a follow-up push enteroscopy revealed the presence of intestinal intraepithelial lymphocytosis and severe villus blunting in addition to a patchy enlarged subepithelial collagen layer characteristic of collagenous enteritis extending from the duodenum to the terminal ileum (Figures 1 and 2). Treatment with high-dose methylprednisolone and maintenance on a strict gluten-free diet resulted in significantly reduced stool output and gradual weight gain. She was subsequently switched to maintenance oral prednisone.

Discussion

Collagenous Enteritis (CE) was initially described in 1947 as an idiopathic malabsorptive syndrome characterized by deposition of subepithelial eosinophilic hyaline material (1). The term collagenous sprue was formally introduced in 1970 in

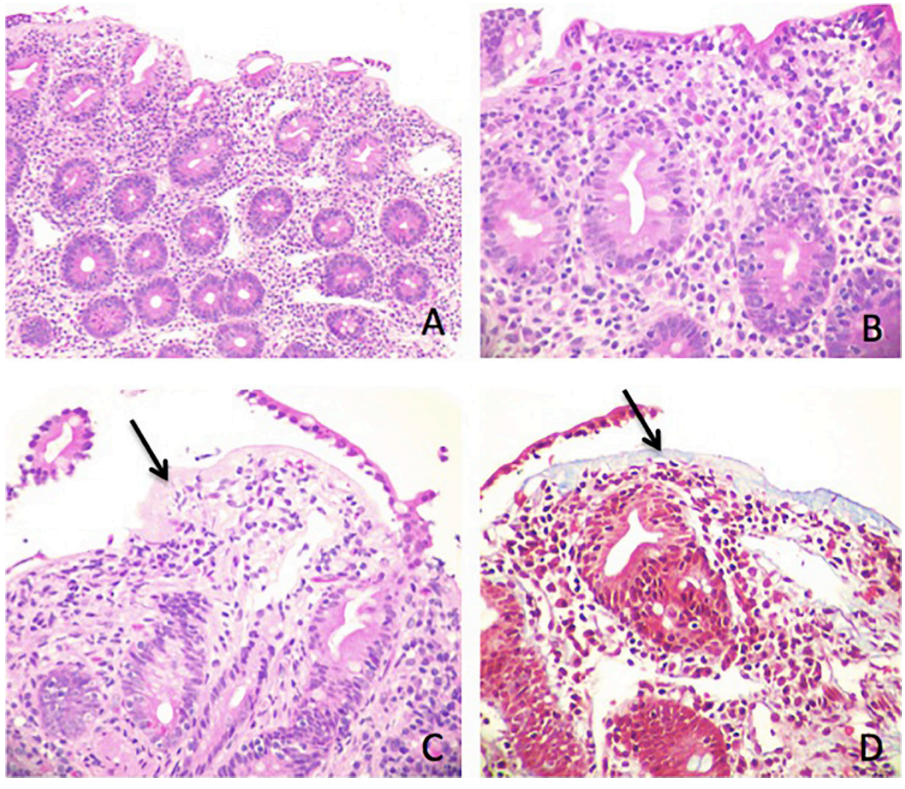

Figure 1: Duodenal biopsy: (A) Severe villous blunting with sloughing of the surface epithelium. (B) High-power view with expanded lamina propria and lymphoplasmacytic infiltrates. (C) Thick subepithelial collagen layer. (D) Trichrome stain.

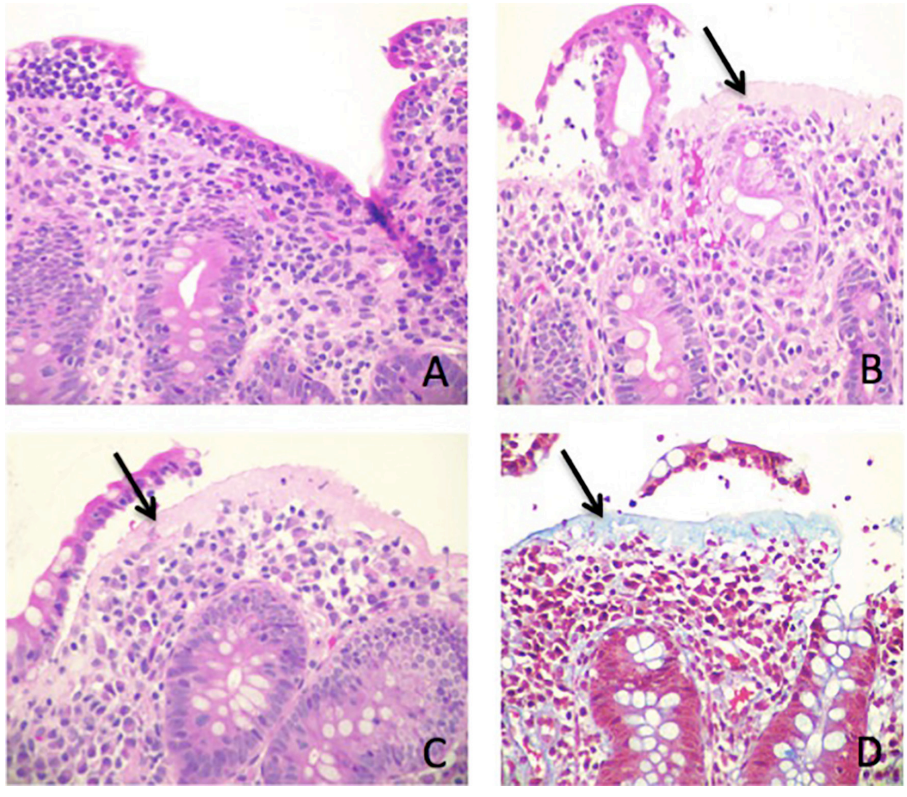

Figure 2: Jejunum/ileum biopsy: (A) Increased intraepithelial lymphocytes. (B) Thickened subepithelial collagen layer. (C) Ileum showing lymphocytosis. (D) Trichome stain for subepithelial collagen.

recognition of a celiac-like condition unresponsive to a gluten-free diet with the histopathologic hallmark of subepithelial collagen deposition (2). In cases reported thus far, CE shows a 2:1 female-to-male ratio and can affect individuals of any age (3, 4). Reported ages have ranged from 2 to 85 years, with the overwhelming majority occurring in the fifth decade of life (3-6).

Patients with CE often present with a nonspecific clinical picture with symptoms of nausea, bloating, watery diarrhea, and weight loss, with associated laboratory evidence of anemia and hypoalbuminemia (2, 4, 7). Due to clinical overlap with other enteropathies, diagnosis requires endoscopy with biopsy. Endoscopic findings suggestive of CE include diffuse mucosal edema, erythema, and granularity with flattening of villi and scalloping of mucosal folds (4, 6). Clinical severity is directly proportional to the extent of small bowel (especially duodenum and jejunum) involvement and not the severity of mucosal abnormality on biopsy (8).

From a prognostic standpoint, whereas historically CE has been associated with an intractable clinical course characterized by severe malnutrition necessitating parenteral support and ultimately leading to death, newer evidence suggests a heterogenous clinical course with more favorable outcomes (2, 5). In many studies, CE has also been associated with lymphocytic gastritis, collagenous gastritis, microscopic colitis, paraneoplastic syndromes, common variable immunodeficiency, T-cell lymphomas, and a host of other autoimmune conditions (6, 9-13).

The pathophysiology of CE remains largely unknown. Owing to their similar clinical presentation and shared susceptibility alleles (i.e. HLA DQ2 and DQ8), CE was previously thought to represent a refractory form of celiac spectrum disorders (3, 4, 14, 15). However, newer studies have demonstrated HLA DQ6/DQ9 positivity in those with CE in the absence of HLA DQ2/DQ8 (16). Various case series implicate angiotensin II receptor blockers (ARBs; most notably olmesartan), non-steroidal anti-inflammatory drugs (NSAIDs), and proton pump inhibitors (PPIs) as potential triggers of CE (11, 17-19). Taken together, this differentiates CE as a distinct entity arising from the interaction between genes and environmental exposures, with a possible HLA-mediated immune mechanism (4, 16). Furthermore, the absence of celiac-associated antibodies (i.e., anti-TTG, anti-gliadin, and anti-endomysial antibodies) in most cases of CE and lack of response to a gluten-free diet lends additional support to this notion. Interestingly, no associated triggers of CE were identified in this case and our patient continued to have refractory diarrhea despite adherence to a gluten-free diet.

With a better understanding of CE and its response to various treatment modalities, a more favorable outlook has replaced its once grim prognosis. Discontinuation of offending agents (ARBs, NSAIDs, PPIs) and initiation of corticosteroids remain the mainstay of therapy, often with favorable outcomes (4, 6, 7, 12, 19). When CE manifests secondary to a paraneoplastic syndrome, treatment of underlying malignancy

leads to clinical improvement (10). Refractory cases treated with azathioprine, thioguanine, or tumor necrosis factor-α inhibitors have also yielded notable treatment responses (14, 20).

Conflicts of interests: None declared.

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