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CASE PRESENTATION

Collagenous sprue: a rare cause of watery diarrhea and villous atrophy – case report

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ABSTRACT

Collagenous sprue is a rare and unrecognized cause of diarrhea and weight loss, mainly affecting the duodenum and small bowel. The clinical picture often resembles that of coeliac sprue, the main differential diagnosis, albeit, being refractory to a gluten-free diet. The histological features are fundamentally characterized by the deposition of collagen beneath the basement membrane of gut mucosa. Treatment should be initiated as soon as the diagnosis is established, so as to prevent the progression of fibrosis. We will describe the case of a 76-year-old woman with collagenous sprue, her diagnostic workup, histopathological examination, and response to treatment.

Keywords: Watery diarrhea, Malabsorption, Weight loss, Collagenous sprue, Case report.

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Introduction

Collagenous sprue (CS) is a poorly recognized cause of watery diarrhea, severe malabsorption, and progressive weight loss (1). Its clinical presentation is all but similar to coeliac sprue, which is the main differential diagnosis; however, they do differ on one key aspect, in that CS is less or even not responsive to gluten-free diet (2, 3). Data is scarce; only a few more than 60 patients have been reported to suffer from this rare illness.

CS was first reported in 1970 by Weinstein et al. (4), who described the case of a 51-year-old woman with malabsorption and histological findings of subepithelial collagen deposition and intestinal villi atrophy compatible with celiac disease but with poor response to a gluten-free diet. However, similar cases can be found in the literature, dating as far back as 1947, described by Schein (5).

Endoscopic and histopathological examination

The endoscopic findings of patients with CS are mainly nonspecific with different degrees of mucosal scalloping and patchy loss of the normal vascular pattern, mainly in the proximal small intestine (1).

Histological examination shows flattening villous height, detachment of the epithelium, intraepithelial lymphocytosis, and its hallmark feature, the deposition of collagen beneath the basement membrane, often presenting with focal distribution and thickness variation (2, 6, 7). Lesions in the duodenum are pathognomonic of CS (8).

Apart from the flattening villous height, similar features may be observed among patients with the more well-known condition collagenous colitis (3). Indeed, collagen deposition in the small bowel is predictive of similar findings in the colonic mucosa (i.e., collagenous colitis). More rarely, these findings may also be present in gastric mucosa (i.e., collagenous gastritis).

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Intraepithelial lymphocytosis is also common in these organs (9). Despite the similarity of histopathological lesions between the two diseases, CS seems to be associated with a more severe clinical presentation than collagenous colitis (8).

Risk factors and associated conditions

Notably, CS is apparently associated with certain autoimmune and immune-mediated disorders (10-12). Additionally, certain drugs, such as non-steroidal anti-inflammatory drugs, angiotensin-converting-enzyme inhibitors, and angiotensin receptor antagonists, have been linked to CS (8, 13). The latter drug family, specifically olmesartan (14), has been associated with sprue-like biopsy findings. Nevertheless, a recent systematic review yielded inconsistent findings (15). It is speculated that the pathogenesis of olmesartan-associated enteropathy is the inhibition of transforming growth factor β, which plays a vital role in gut immune homeostasis (14).

Prognosis

The first published cases in the literature had grim prognoses, with progressive worsening malabsorption, diarrhea, and ultimately, a fatal outcome (16). Nevertheless, more recent reports with extensive biopsy data have documented complete resolution of the collagen deposits, suggesting a potential reversion of lesions for extended periods after corticosteroid treatment (17, 18), heralding an overall good prognosis with proper treatment (8).

Case presentation

We present the case of a 76-year-old black woman with a history of arterial hypertension and depressive syndrome and regular intake of furosemide 20 mg qd, olmesartan 20 mg in association with hydrochlorothiazide 12.5 mg qd, and mirtazapine 30 mg qd.

For two years, the patient had bouts of watery diarrhea and weight loss with a hiatus of normal bowel transit and stool consistency and baseline weight restoration. One episode led to the admission of the patient in a medicine ward for severe hypoalbuminemia (1.7 g/dL) and associated anasarca. Computerized tomography of the thorax, abdomen, and pelvis yielded irrelevant findings. Upper and lower endoscopy were also described as normal, albeit no biopsies were taken. Viral serologies for HIV, HBV, and HCV were negative. Thyrotropin receptor (TRAb) antibodies were positive, but the patient remained euthyroid. The remaining autoimmune assessment was negative, including the coeliac disease panel (negative anti-transglutaminase, anti-gliadin, and anti-endomysium, normal IgA levels) and anti-Saccharomyces cerevisiae. Fecal elastase was normal, and the stools had no undigested fats or fibers, compatible with normal pancreatic function. Bacteriologic and parasitological stool cultures were inconclusive, and the Clostridioides difficile toxin was negative. Fecal calprotectin had a very high value (1805 mg/Kg; normal < 50 mg/kg). Renal protein wasting was also excluded.

The patient began a tailored nutritional (no gluten-free) plan with positive clinical response: good oral feeding tolerance and stool normalization. She was discharged to the medicine outpatient clinic.

She remained clinically stable for 7 months, but then she had a clinical recidive, profuse watery diarrhea, abdominal pain and emesis, with no fever. At admission, she was markedly dehydrated with acute kidney insufficiency (creatinine 7.5 mg/dL), severe metabolic acidemia (pH 7.10; bicarbonate 6.3 mEqs/L), and hypokalemia (potassium 2.5 mEqs/L). In the intensive care unit, fluid load and parenteric nutritional support were given. There was no need for vasopressor support, ventilatory assistance, or kidney function replacement therapy. No immunomodulatory or immunosuppressor therapy (such as corticosteroids) was administered. After 3 days, the patient was transferred to the intermediate care unit and then to the general ward, with positive, albeit slow, clinical evolution over time. Despite poor oral feeding tolerance, even with a customized meal plan, gradual hardening of stool consistency and decreased bowel transit frequency were observed.

Endoscopic monitoring with upper endoscopy and gastric and duodenal (D2 segment) biopsy samples was performed.

The gastric mucosa was atrophic with diffuse edema and loss of the large curvature folding. A similar appearance with remarkable loss of the normal folds was observed in the duodenum (Figure 1, upper row). On the other hand, ileocolonoscopy findings (few colon

diverticula) were irrelevant (Figure 1, lower row). Colon and ileum biopsies were taken.

Anatomopathological examination

Upon microscopic examination, the antral gastric mucosa biopsy showed severe lymphoplasmacytic inflammatory infiltration with increased intraepithelial lymphocytes. Helicobacter pylori microorganisms and collagen deposits were not identified (Figure 2). Duodenal mucosa biopsies disclosed moderate villous atrophy without crypt hyperplasia, superficial epithelium detachment, increased lymphoplasmacytic inflammatory infiltration, and mild to moderate collagen subepithelial deposits with a thickness of 6–7 µ (Figure 3). Terminal ileum mucosa biopsies showed

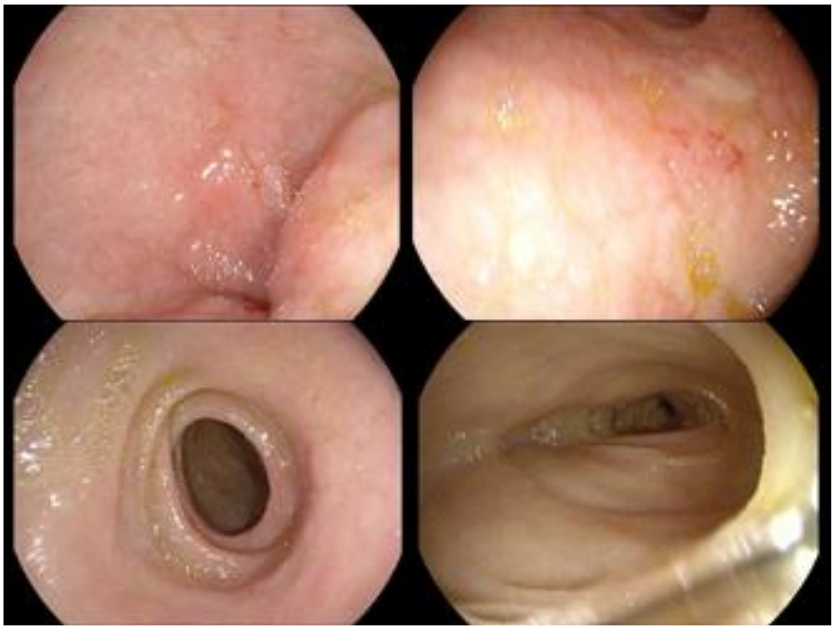

Figure 1. Endoscopic aspects of duodenum (upper row) and colon (lower row). The duodenum displays diffuse edema and loss of normal folding.

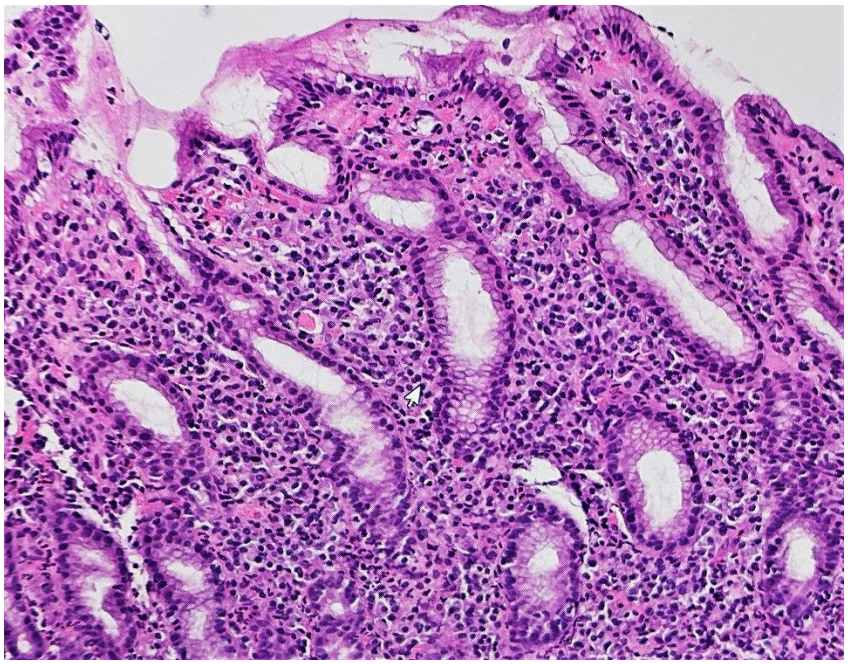

Figure 2. Gastric antral mucosa with heavy lymphoplasmacytic infiltration and intraepithelial lymphocytosis. Collagen deposits are lacking (HE; 100x).

morphological alterations similar to the ones described in the duodenum (Figure 4). Masson trichrome stain confirmed collagen subepithelial deposits (Figure 5). Epithelioid granulomas were not identified. Colon mucosa biopsies revealed a mild cryptic architectural distortion, normal superficial and glandular mucus activity, and heavy lymphoplasmacytic inflammatory infiltration of the lamina propria with eosinophilia and subepithelial collagen deposits. No intraepithelial lymphocytosis was observed (Figure 6).

Outcome and follow-up

After the CS diagnosis, the patient was prescribed

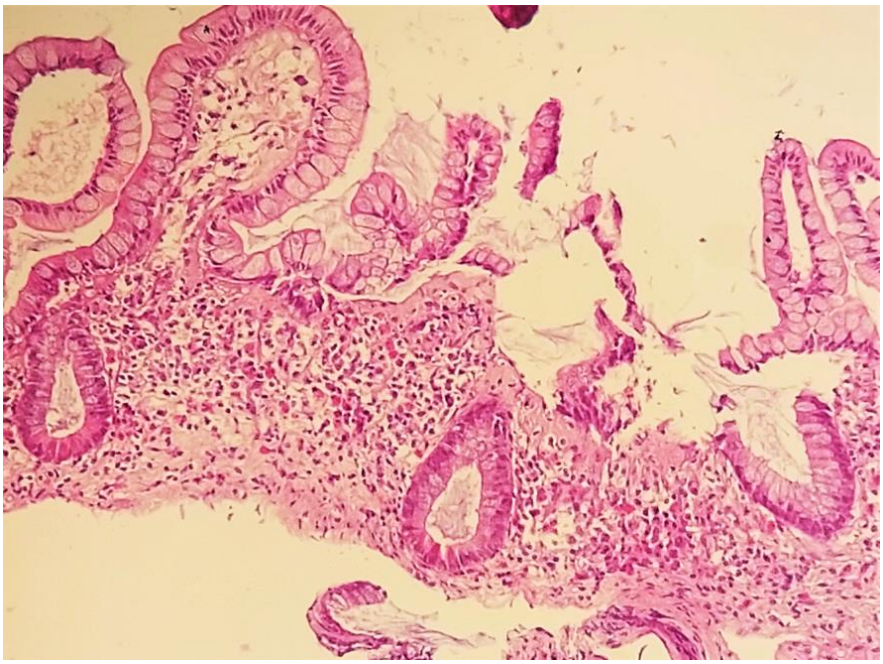

Figure 3. Duodenal mucosa with severe villous atrophy, subepithelial collagen deposits, and superficial epithelial detachment (HE; 100 x).

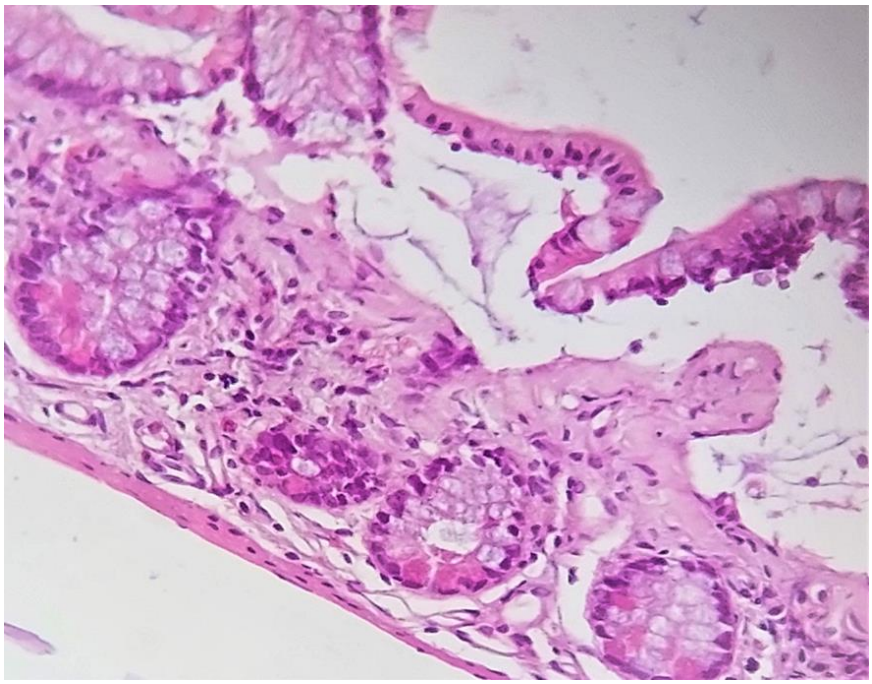

Figure 4. Ileum mucosa with severe villous atrophy, subepithelial collagen deposits, and superficial epithelial detachment (HE; 400x).

budesonide 9 mg daily for 8 weeks, which was then slowly tapered over the next weeks, and oral supplementation of calcium and vitamin D.

Subsequently, as the diarrhea completely subsided, the patient recovered the lost weight and her former general health status in about 4 months with no dietary restrictions. The patient is regularly (biannual) followed at the gastroenterology outpatient clinic.

Laboratory blood tests indicated a low hemoglobin level (6.4 g/L), tomography was performed, demonstrating a borderline hepatitis B and C infection, and the alpha-fetoprotein level was 4.66 IU/mL. An

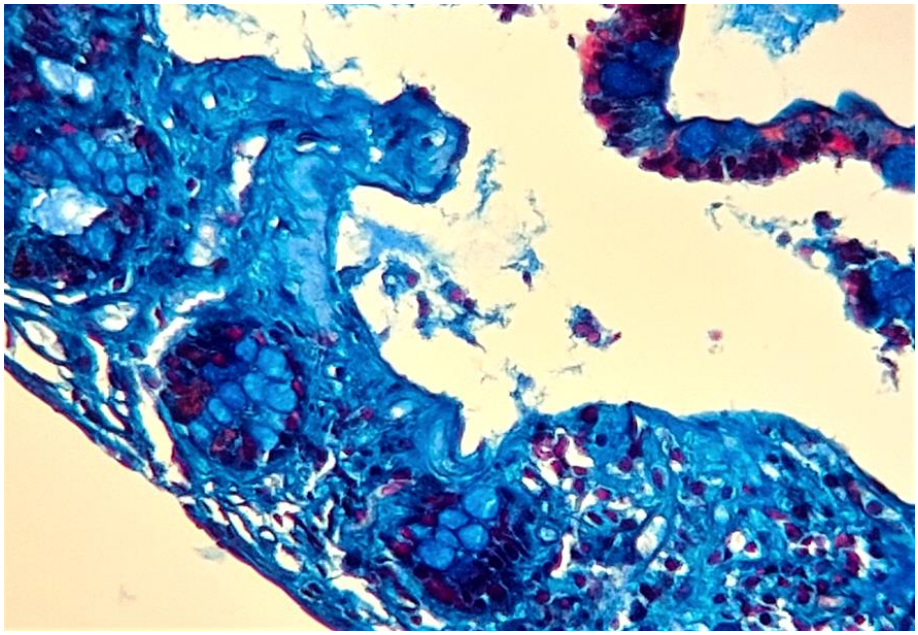

Figure 5. Ileum mucosa. Trichrome stain disclosed the key histological finding of collagen in the subepithelial region (400x).

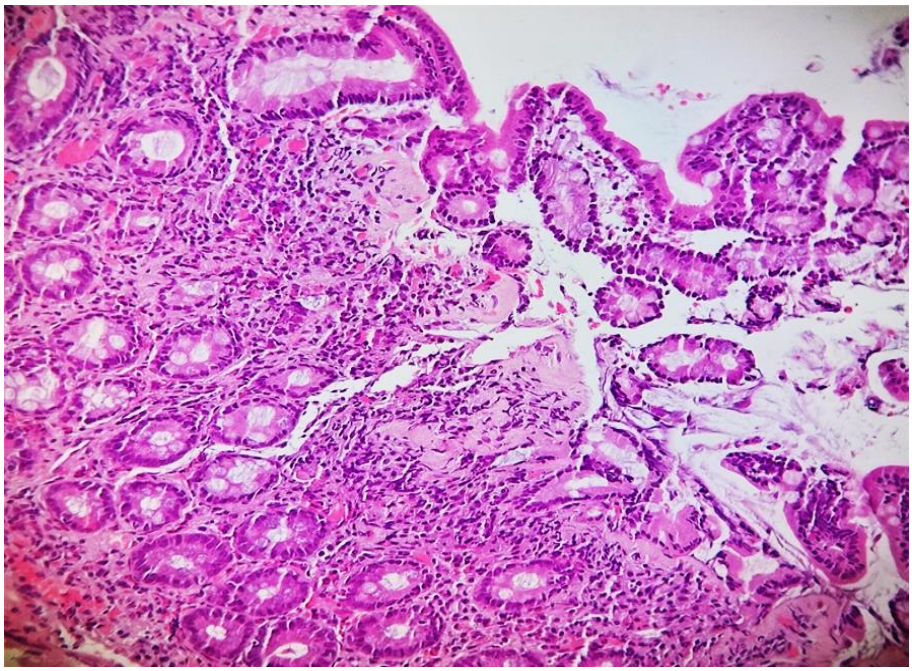

Figure 2. Pathological examination of the hepatic lesion. (a) revealed brownish pigment in hepatocytes (hematoxylin and eosin staining, bar = 100 μm). At higher power, the granular brown pigment was present within hepatocytes, and Kupffer cells (b), and hematopoietic tissue proliferated in the sinusoids, comprising erythroid and myeloid precursors (c) (bar = 50 μm).

iron workup indicated a serum ferritin level of 1, 057 mg/dL and transferrin saturation of 86%. Hemoglobin typing results revealed AE CS Bart's (Hb A, 86.6%; Hb E, 11.9%; Hb CS, 1.2%; Hb Bart's, 0.3%).

Discussion

Despite the diagnostic challenge this case represented, which was reflected in the long duration of the disease, a full recovery after proper treatment was observed. Although subsequent biopsies were not undertaken, it is reasonable to assume, as described in the literature, an at least partial regression of collagen deposition mirroring the clinical improvement.

The patient was formerly medicated with olmesartan, which has been associated throughout the literature with sprue-like enteropathy/collagenous sprue and collagenous colitis (14, 19-22). Even though she had no ambulatory full adherence to therapy because of vomiting and decreased oral tolerance, upon admission, due to patient instability, all antihypertension drugs were suspended during the 1-month hospital stay. Marked improvement occurred only after gut-selective corticosteroid treatment, making it hard to establish a causal nexus with olmesartan suspension. Regardless, at discharge, the patient was prescribed a perindopril and amlodipine association.

The clinical picture of CS is similar to that of coeliac disease, and so are its histopathological features. A distinctive feature is the absence of the typical celiac serology in CS. For this reason, when a supposed celiac seronegative patient is gluten-free diet refractory, it is of utmost importance to check for the diagnostic CS collagenous band in the gut mucosa (3).

Conclusion

In conclusion, in a malabsorption clinical setting and mucosal paleness and scalloping findings in upper endoscopy with no serological criteria for celiac disease diagnosis, gut biopsies are key to the diagnosis. Increasing awareness of this largely unknown entity will broaden the differential diagnosis of seronegative villous atrophy, leading to earlier disease detection and therapeutic management that may reverse clinical deterioration and, at least partially, intestinal collagenous fibrosis.

Conflict of interests

Authors have no conflicts of interest or financial ties to disclose.

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