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Single Case

Coexisting Collagenous Sprue and Celiac Disease: A Case Report

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Abstract
Introduction: Collagenous sprue (CS) is an extremely rare enteropathy of unknown etiology and if untreated, can lead to substantial morbidity and mortality. CS often copresents with celiac disease. The presence of a subepithelial collagen band on histology differentiates CS from celiac disease, as both have villous blunting. The management of the two diseases is different, and thus it is critical that the proper diagnosis of CS is made promptly to prevent complications. ***Case Presentation:*** We present a case report of CS in an elderly male who was initially diagnosed with celiac disease alone before returning to care years later with unresolved gastrointestinal symptoms. ***Conclusion:*** Clinicians must verify that CS has been ruled out following a celiac disease diagnosis. In regard to CS's mechanism, CS's high frequency of comorbid autoimmune conditions and its robust response to corticosteroids support an immune-mediated process. Future research should continue to aim to elucidate the mechanism as it would allow for a more targeted approach to treatment, such as anti-fibrotic or specific immunomodulator therapy.

Introduction

Collagenous sprue (CS) is a very rare small bowel enteropathy discovered in 1947 with only a few hundred cases noted [1]. CS primarily involves the duodenum and proximal jejunum and is most commonly found in middle-aged to elderly females. It presents similarly to celiac disease, most commonly with chronic diarrhea and abdominal pain [2]. CS also

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frequently manifests with malnutrition, weight loss, microcytic anemia, and vitamin deficiencies. Untreated CS can have catastrophic sequelae, with death most often attributed to severe malnutrition [3].

The diagnosis of CS is based on the clinical presentation and presence of partial or total villous atrophy and a subepithelial collagen band on esophagogastroduodenoscopy biopsy of the proximal duodenum. The subepithelial collagen band (generally at least 10 μm in thickness) differentiates CS from celiac disease, as both have villous atrophy [4]. The collagen band also differentiates CS from other sprue-like conditions with villous atrophy, including tropical sprue, autoimmune enteropathy, and eosinophilic gastroenteritis [5]. Gross endoscopic findings seen in both CS and celiac disease include scalloping and notching of duodenal folds, although these findings may be occasionally absent [6]. Laboratory studies are vital, especially a complete blood count and celiac serologies. Up to 70% of CS cases occur with a comorbid autoimmune disease [7, 8]. Furthermore, as many as half of CS patients have comorbid celiac disease, especially in those unresponsive to a gluten-free diet (GFD) [4]. CS can also be triggered by specific medications, including angiotensin receptor blockers (ARBs) and NSAIDs [9].

The etiology of CS remains unknown with a spectrum of evolutive possibilities to its development [10]. This includes the hypothesis that the disease is triggered by food hypersensitivity (such as gluten hypersensitivity as seen in celiac disease), medication hypersensitivity, immune system hypersensitivity (as seen in autoimmune diseases), gene sensitivity, or as a complication of paraneoplastic disorders [11]. Currently, the literature best supports a primary immune-mediated pathogenesis due to CS's robust autoimmune disease associations and responsiveness to corticosteroids. Given the high degree of overlap, CS was once thought to be a refractory variant of celiac disease [12]. However, distinguishing the two diseases is crucial as the management is different. While both require adherence to a GFD, CS also generally requires immunosuppressive therapy for optimal outcomes [8]. Here, we present a case of an elderly male diagnosed with celiac disease who later received an additional diagnosis of CS.

Case Report

A 75-year-old male with a past medical history of coronary artery disease and hypertension presented to a gastroenterology clinic with intermittent nonbloody diarrhea, abdominal bloating, 20 lbs weight loss, and generalized weakness for 6 months. He had no relevant family history. Social history was significant for active tobacco use and occasional alcohol use. His medications were aspirin, losartan, simvastatin, and metoprolol succinate. Vital signs were within normal limits. Physical exam was notable for a thin male (BMI 23.3) with generalized muscle wasting and a benign abdomen. Laboratories were significant for hemoglobin 13.8 g/dL, albumin 3.8 g/dL, anti-tissue transglutaminase (TTG) IgA 158 U (normal: 0–20 U), gliadin IgA 201 U (normal: 0–20 U), and endomysial antibody 1:40 (normal: <1:5). Human leukocyte antigen (HLA) testing was not performed. An upper endoscopy revealed partial villous atrophy of the first and second portions of the duodenum along with marked intraepithelial lymphocytosis (IEL) consistent with celiac disease (shown in Fig. 1, 2). A colonoscopy showed multiple small adenomatous and hyperplastic polyps. He was started on a GFD and referred to nutrition. The patient chose not to follow-up with gastroenterology.

One year following his celiac disease diagnosis, the patient was diagnosed with Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, and Skin changes (POEMS) syndrome after referral to hematology/oncology for peripheral neuropathy complicated by bilateral foot drop, as well as an elevated IgM kappa monoclonal protein and VEGF. Remission of POEMS syndrome was achieved with 6 cycles of cyclophosphamide, rituximab, and dexamethasone followed by 5 cycles of melphalan and dexamethasone.

Four years after the initial celiac disease diagnosis, weight loss (12 lbs since last visit) continued, and the patient was referred back for GI evaluation. He admitted nonadherence to a GFD. Repeat labs showed a hemoglobin 13.2 g/dL (normal: 13.4–16.0 g/dL) and tissue transglutaminase IgA >250 U (normal: 0–20 U) and gliadin IgA ≥250 U (normal: 0–20 U). Other notable laboratory findings included 25-hydroxyvitamin D 16 ng/mL (normal: 30–100 ng/mL) and vitamin B12 258 pg/mL (normal: 211–911 pg/mL). A repeat upper endoscopy with proximal duodenal biopsies showed a subepithelial collagen band of 32.2 μm along with previous villous atrophy, consistent with CS (shown in Fig. 3). This finding prompted reevaluation of the initial duodenal biopsy which also revealed a subepithelial collagen band but to a lesser degree (28.6 μm) (shown in Fig. 2). Gastric biopsy was unremarkable without evidence of collagenous gastritis. A repeat colonoscopy with biopsies was negative for collagenous colitis. Given the CS diagnosis, the patient plans to adhere to a strict GFD and will consider budesonide initiation if he has an inadequate clinical response to diet alone.

Discussion

CS and Celiac Disease

CS is typically seen in patients with an autoimmune disorder, as in our patient. There is a large degree of overlap between CS and celiac disease. In fact, it was once thought that CS was a refractory version of celiac disease. Evidence no longer supports this link as there are ample cases of CS in patients without celiac disease and cases attributed to medications and other diseases processes. Additionally, while approximately 70% of CS patients carry either celiac disease-associated HLA DQ-2 or DQ-8, these alleles are not exclusive to celiac disease and can be present in other autoimmune diseases [3, 12]. Moreover, this group of CS patients typically lacks positive celiac serologies, unless they have biopsy-proven celiac disease as well. Therefore, while it is possible that there is more than one pathway to CS development, it is more likely that a nonspecific autoimmune environment is the key ingredient rather than specifically requiring a celiac disease background.

CS and celiac disease present with similar enteropathy symptoms, although CS tends to be more severe [13]. In addition, both may present with microcytic anemia and vitamin deficiencies. Celiac serologies may be elevated in both conditions if CS is presenting in a patient with comorbid celiac disease. Thus, it is on histologic evaluation where the difference will be evident. In celiac disease, biopsies of the duodenal bulb and distal duodenum reveal villous atrophy or blunting and significant IEL [14]. Conversely, while CS will also demonstrate villous abnormalities, it will typically lack an IEL (unless it presents concurrently with celiac disease) but have a subepithelial collagen band [2].

It is crucial to rule out CS in all patients with celiac disease because CS commonly mimics celiac disease and can present together. Delay in diagnosis can be deadly due to the differences in management. In our patient, the subepithelial collagenous band was not mentioned in the initial pathology report, resulting in a delay of appropriate treatment. Of note, although the patient did receive appropriate steroid therapy for POEMS syndrome, the duration was inadequate for CS which generally requires months of uninterrupted therapy to induce remission [8].

CS and Other Collagenous Gastrointestinal Diseases

CS can also present concurrently with collagenous gastritis and/or colitis. Among 155 patients with CS in one systematic review, 6.5% of the patients also had collagenous gastritis, 18.7% had collagenous colitis, 10.9% had both conditions, and 63.9% had neither condition [3]. While our patient did not have collagenous involvement in other areas of the GI tract, ample cases of CS's co-presentation supports our current understanding of CS's fibroblastic, immune-mediated pathogenesis [13].

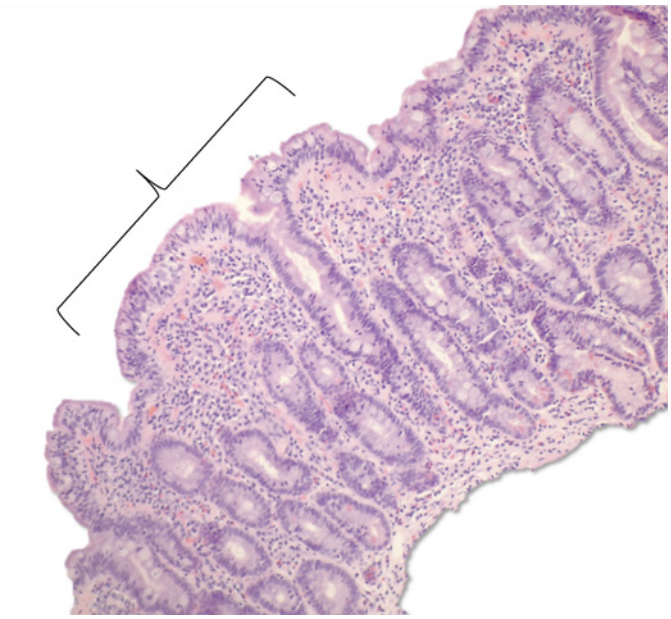

Fig. 1. Initial proximal duodenal biopsy with hematoxylin and eosin (H&E) stain under 10× view demonstrating villous atrophy (bracket).

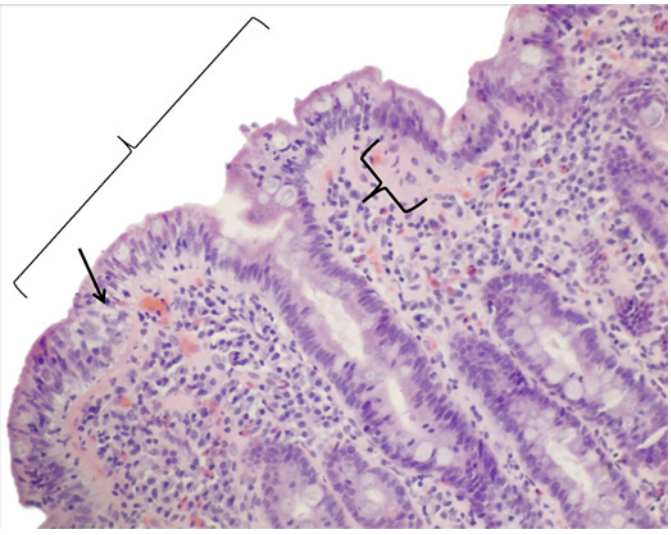

Fig. 2. Initial proximal duodenal biopsy with H&E stain under 20× view demonstrating villous atrophy (large outer bracket), intraepithelial lymphocytosis (arrow), and 28.6 μm subepithelial collagen band (small inner bracket).

CS and Medication Associations

Certain medications have been implicated in CS's development. ARBs, especially olmesartan, are the medication class most closely linked to CS. While olmesartan more commonly causes a nonspecific enteropathy, there have been cases of the drug resulting in CS as well. Studies have shown that about one-third of patients with CS were taking olmesartan at time of CS diagnosis [9, 13]. In patients with presumed olmesartan-induced CS, discontinuation of the medication has resulted in disease resolution [15, 16]. Although less frequently reported

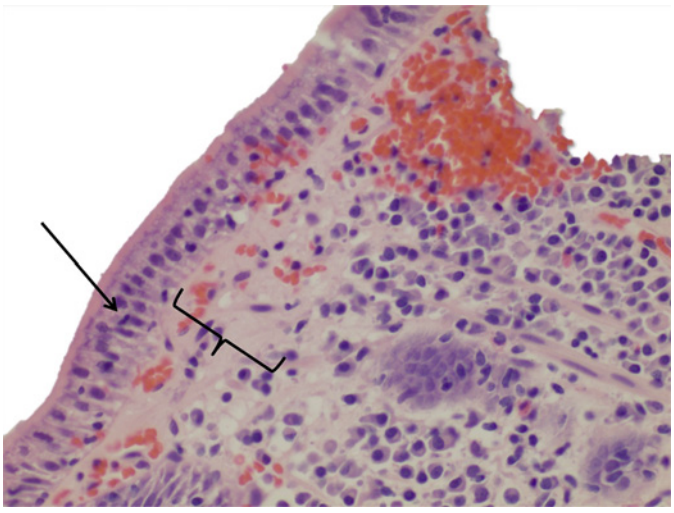

Fig. 3. Repeat proximal duodenal biopsy with H&E stain under 40× view demonstrating intraepithelial lymphocytosis (arrow) and 32.2 μm subepithelial collagen band (bracket).

compared to olmesartan, losartan has also been linked to a sprue-like enteropathy [17]. Since the patient had been taking losartan for several years prior to his CS diagnosis and remains on the medication, we are unable to definitively conclude that losartan is not a factor in the patient's CS development. Nevertheless, given his concurrent celiac disease, it is much more likely that celiac disease primarily contributed to CS's development as opposed to medication effect. At present, the exact mechanism of ARB-induced enteropathy is unknown.

Therapeutic Modalities for CS

Initial management for CS requires instituting a strict GFD. However, in the majority of cases, combination therapy with steroids (typically budesonide due to less systemic absorption) will be necessary to attain symptomatic improvement. In steroid-refractory cases, the addition of thiopurine therapy (6-thioguanine or azathioprine) is recommended [18]. In patients with contraindications to these primary modalities or in refractory cases, tumor necrosis factor inhibitors (anti-TNFs) such as infliximab can be considered [19]. In severe cases of malabsorption, patients may also require coadministration of total parenteral nutrition. Finally, in patients who are unresponsive to immunomodulatory agents and total parenteral nutrition, they should be referred for small bowel transplant evaluation [10]. Fortunately, in CS patients treated with a combination of a GFD and an immunosuppressive agent, approximately 80% of them will achieve symptomatic remission after 12–24 months, although only 30% will demonstrate histologic response [8].

Conclusion

CS often copresents with celiac disease. As a result, clinicians must verify that CS has been ruled out following a celiac disease diagnosis because each condition is managed differently. To minimize the risk of a CS diagnosis being overlooked during pathology review for celiac disease, we recommend that endoscopists explicitly write "rule out collagenous sprue" for small bowel biopsy specimens. A limitation of this report is that it is based on a single patient; however, prior literature supports this presentation and discussion. In regard to CS's

mechanism, although it remains unclear, CS's high frequency of comorbid autoimmune conditions and its robust response to corticosteroids support an immune-mediated process. Thus, future research should continue to aim to elucidate it as understanding the mechanism would allow for a more targeted approach to treatment, such as anti-fibrotic or specific immunomodulator therapy. The CARE Checklist has been completed by the authors for this case report, attached as supplementary material (for all online suppl. material, see https://doi.org/10.1159/000543939).

Statement of Ethics

This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines. Written informed consent was obtained from patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

T.M.S. performed background research and drafted the article; A.S. reviewed pathology slides and captured the images; A.S., J.L.R., E.R.F., and S.A.S. proofread and critically revised the article for important intellectual content; E.R.F. and S.A.S. provided final approval of the article.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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