Collagenous Sprue: A Case Report and Literature Review

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Collagenous sprue (CS) is a rare disease of the small bowel that was first described in 1947 and histologically confirmed in 1970.[1,2] This disease is characterized by complete atrophy of mucosal villi and excessive subepithelial collagen deposition that may replace the crypts. Other features that are distinctive, but not pathognomonic of CS, are the expansion of the lamina propria by subcryptal inflammation and a mucosa that appears thin.[3] Some authors who doubt the existence and clinical significance of CS as a distinctive histologic picture have confused the prominent basement membrane seen in some patients with celiac disease (CD) with CS, but the degree of subepithelial collagen deposition is distinguishable from that of CD.[3] That the subepithelial collagenous thickening can be variable and patchy along the small bowel also makes the diagnosis difficult.[2,4,5] Aiding in the distinction between CS and CD is the response to gluten-free diet. As a general rule, the collagenous deposits in CD regress under gluten-free diet, whereas those of CS usually do not.[6] This, however, is not true in all cases. Patients may or may not initially respond to a gluten-free diet.[2,4] Thus far, the etiology of CS is not clear. Patients with documented CS have a clinical course that is usually, but not uniformly, dismal.[7]

This case report describes a young woman with intractable nausea, vomiting, diarrhea, and severe weight loss of 4 months' duration who was diagnosed with CS of the small bowel and, shortly thereafter, collagenous colitis. The patient was unresponsive to a high dose of steroids and a trial of gluten-free diet and is currently on home parenteral nutrition (HPN). Our literature search revealed only 15 reported cases of collagen deposition involving the small and large intestines.

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Case Report

A 31-year-old white woman was referred to our hospital for evaluation of intractable nausea, vomiting, diarrhea, and severe weight loss (52 lbs) of 4 months' duration. The patient had been healthy until she developed nausea that was unrelated to food intake. Her symptoms progressed to nausea and emesis after 2–3 weeks. The emesis usually occurred 30 minutes after eating, 1–5 times per day, was bilious in nature, and was associated with bloating, watery diarrhea (which occurred 1–5 times per day, was not malodorous, and did not contain any mucus, melena, or fresh blood). The patient also experienced nocturnal symptoms.

The patient was initially admitted to a local hospital for evaluation of nausea, vomiting, and diarrhea. During her hospitalization, her blood work was normal, except for low albumin. Radiologic findings were unremarkable. She underwent a cholecystectomy for abnormal findings on hepatobiliary iminodiacetic acid scan, but her symptoms did not improve after surgery. Colonoscopy showed normal mucosa with minimal focal active colitis. Esophagogastroduodenoscopy (EGD) revealed normal mucosal appearance, and small bowel biopsy showed chronic active enteritis with ulceration, without granulomas or villous atrophy. The patient was suspected of having CD even with negative tissue transglutaminase and gliadin antibodies, as she was homozygous for the *HLA-DQ2* gene and was placed on a gluten-free diet for 2 weeks with no response. The patient's symptoms persisted, which led to several hospitalizations. Due to nonspecific EGD findings, she was suspected of having Crohn's disease and was treated with controlled-release mesalamine (Pentasa, Shire) and budesonide with no benefit.

The patient was then referred to our facility for further evaluation. Upon physical examination, we noted that she was a thin-built woman with swollen ankles and bilateral pitting edema of lower extremities, with stable vital signs. Repeat EGD performed after hospital admission

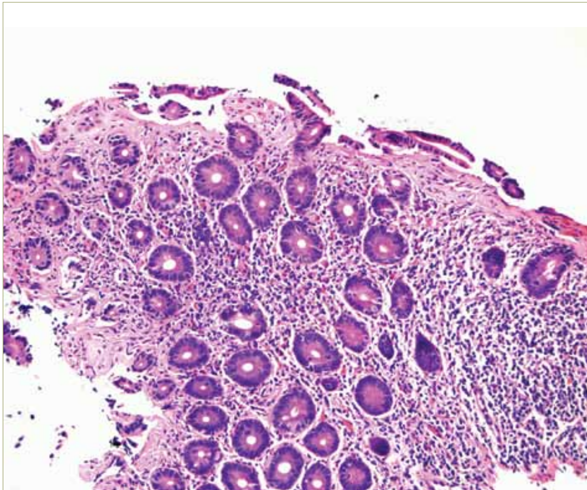

Figure 1. Jejunal biopsy demonstrating near-total villous atrophy with prominent subepithelial collagen table that is irregular and incorporates capillaries and cell nuclei. The surface epithelium shows mucin loss and is sloughed (hematoxylin and eosin stain, 200×).

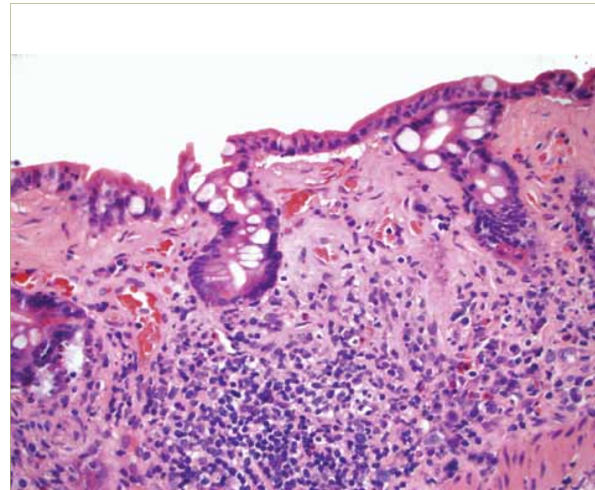

Figure 2. Subsequent jejunal biopsy reveals similar findings as found in the initial jejunal biopsy (Figure 1). At this higher power magnification, the subepithelial collagen table is remarkably thickened and has an irregular interface with the lamina propria (hematoxylin and eosin stain, 400×).

showed a normal mucosal appearance. The small bowel biopsy, however, revealed diffuse villous abnormality, with intraepithelial lymphocytosis and focal thickening of the subepithelial collagen table in the duodenum and jejunum consistent with CS (Figure 1). Immunohistochemical phenotyping revealed a mixture of B and T lymphocytes without morphologic or immunophenotypic evidence of lymphoma. Laboratory examinations revealed a total protein of 3.5 g/dL, albumin of 1.7 g/dL, pre-albumin of 7 mg/dL (normal range, 18–45 mg/dL), and otherwise normal measures.

The diagnosis of CS was based upon the patient's clinical picture and pathologic findings. She was treated with methylprednisolone sodium succinate (Solu-Medrol, Pharmacia & Upjohn) 60 mg daily intravenously and was started on parenteral nutrition. Her symptoms improved after 3 days (stool frequency decreased to 2–3 times per day). The patient tolerated soft diet and was discharged on a tapering dose of prednisone and HPN. On follow-up, the patient had gained 14 lbs in 1 month, still had 2–3 bowel movements per day, and was continuing HPN. However, her symptoms recurred with intolerance to oral intake after prednisone was tapered down to 10 mg. A high dose of prednisone (40 mg) was restarted. Her symptoms improved after reinstituting a high dose of prednisone, HPN, and clear liquid diet.

Six months later, her symptoms recurred. EGD was then repeated and again showed subepithelial collagen thickening in the duodenum and jejunum without evidence of lymphoma (Figure 2). Colonoscopy with biopsy showed new onset of collagenous colitis with involvement of the ileum (Figure 3). 5-aminosalicylic acid (5-ASA) and budesonide were added with a tapering prednisone dose. The patient developed side effects from steroids (eg, moon face, buffalo hump) and had

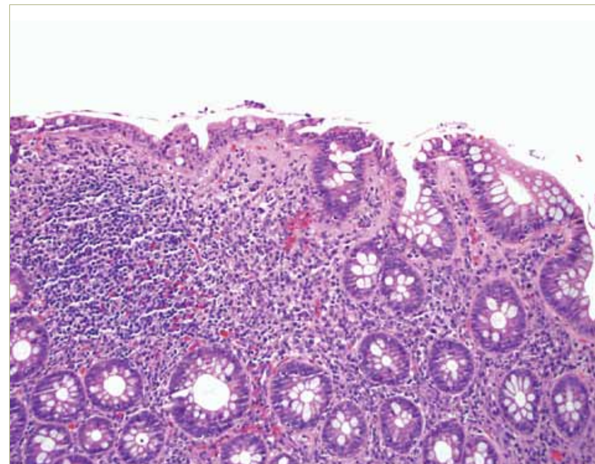

Figure 3. Multiple colon biopsies reveal collagenous colitis characterized by essentially intact crypt architecture with top-heavy lymphoplasmacytic lamina propria infiltrate and an irregular and thickened subepithelial collagen table (hematoxylin and eosin stain, 200×).

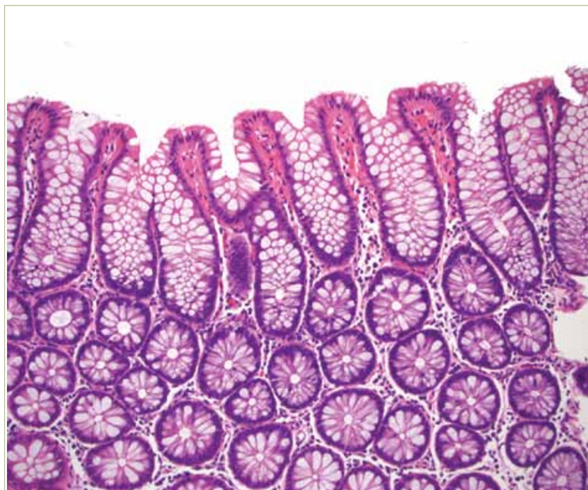

Figure 4. Most recent colon biopsies of the patient reveal normal crypt architecture, no enterocyte injury, and unremarkable subepithelial collagen table (hematoxylin and eosin stain, 200×).

two episodes of catheter-related bloodstream infections. During this period, she was evaluated by the intestinal transplant team. The patient was placed on 5-ASA and budesonide with continuation of HPN. She was started on a soft, low-residue diet.

Follow-up after 6 months revealed that she continued to experience vomiting occasionally after oral intake but also had a significant improvement in diarrhea. Repeat biopsies from the small bowel showed the same findings, but biopsies from her colon revealed resolution of collagenous deposits (Figure 4).

Discussion

CS is a rare disease of the small bowel that was first described in 1947 and histologically confirmed in 1970.[1,2] In 1970, Weinstein and associates defined CS as being refractory to a gluten-free diet, with flattened villous architecture and distinct subepithelial eosinophilic hyaline deposits of collagen.[2] Since then, additional cases of CS have been reported.[4,5,8-34] Only 14 cases of CS with collagenous colitis have been described in the literature.[3,13,24,30,35-38] Collagenous colitis is associated with inflammatory disorders of the gastric mucosa such as lymphocytic gastritis and collagenous gastritis.[39-46] CD and CS are also known to be associated with collagenous colitis. It has been suggested that CS and CD may be closely linked, though the precise relationship is not very clear.[2,16,31] There is a possibility that CS is the most serious complication of CD and the presence of pathologically significant collagenous deposits in the lamina propria is a marker of poor prognosis.[6,8] It is not known whether CS, refractory CD, non–celiac refractory sprue, and unclassified sprue share similar characteristics or even if they are the same disease.[3] The prevailing opinion, however, is that CS is a distinct clinical and pathologic entity, entirely separate from CD. CS causes severe, long-standing malabsorption, leading to diarrhea, progressive weight loss, and occasional abdominal pain, when associated with vasculitis.[2,5,20]

Patients die from severe malnutrition, small bowel lymphoma, and infection.[3,7] There are cases of CS with cessation of diarrhea and concomitant weight gain secondary to adherence to gluten-free diet.[5,13,22,24] It has been shown that complete histologic resolution of CS may occur with a gluten-free diet.[13] Some patients who have improved clinically on a gluten-free diet alone or with steroids, however, have not undergone follow-up biopsies to assess collagen. In addition, most of the reported cases of CS demonstrate a poor response to gluten-free diet at some point in their illness.[2,4,15,19,20,21,25,26] In a study by Robert and coworkers, none of the patients diagnosed with CS improved on a gluten-free diet.[3] Freeman and Berean reported a case of resolution of collagenous enterocolitis after resection of colorectal cancer.[29] The variability in outcome suggests that CS may, in fact, be a heterogeneous disease, due, in some cases, to a complication of CD (gluten sensitivity), but, in most cases, secondary to other unknown triggers or a paraneoplastic phenomenon.[3,7,29] Gene sensitivity, hypersensitivity to a special food component, medication, and environmental factors may all contribute to the disease. However, the exact etiology of the disease is unknown.

Pathophysiology

Daum and associates reported that increased collagen synthesis in the absence of adequate fibrolysis appears to be the pathophysiologic mechanism leading to the broadened subepithelial collagen band in CS.[47] This mechanism is seen in CS patients with or without underlying CD. Collagen I is the main component of the extracellular matrix (ECM) in the human gastrointestinal tract. Its synthesis is stimulated by transforming growth factor-beta, insulin-like growth factor I, platelet-derived growth factor, beta-fibroblast growth factor, interleukin-4, and interleukin-13, and it is inhibited by interleukin-1 and platelet-derived growth factor-BB.[48-51] The production of these cytokines can be affected by many factors such as diet, medication, infection, inflammation, and trauma. Matrix metalloproteinases (MMPs) are the key enzymes involved in ECM degradation.[52-55] MMP-1 (interstitial collagenase) is the primary fibrillar collagen-degrading

enzyme in the human gut. It is secreted by connective tissue cells and macrophages.[54,56] The expression and activity of MMPs are regulated at several levels: transcriptional regulation; physiologic inhibitors (alpha-macroglobulin); and tissue inhibitors of metalloproteinases (TIMPs). TIMP-1 is the central inhibitor that irreversibly inactivates most MMPs.[57] It is reported that TIMP-1 has been implicated as a key player in promoting organ fibrosis.[58] A study has shown that tissue from small bowel biopsy in such patients increased mRNA expression of collagen I (2-fold), slightly increased mRNA expression of TIMP, but did not create a parallel increase of mRNA expression of MMP. This may cause collagen overproduction and deposition.[47] Therefore, increased collagen synthesis in the absence of adequate fibrolysis appears to be the pathophysiologic mechanism leading to the broadened subepithelial band in CS. The normal width of the collagen band in the small bowel is 5–7 μm.[47] In CS, the collagenous band can be of variable thickness (7–80 μm) along the proximal small bowel. For the diagnosis of CS, the cutoff width of the collagen band is suggested to be more than 10 μm.[47] Equally important, however, is the abnormal morphology of the subepithelial collagen table. CS cases demonstrate an irregular and jagged interface with the underlying lamina propria. In addition, the collagen appears "dirty" because of the incorporation of capillaries and numerous stromal cells.

As there is no definite criterion for diagnosing CS, disease entities such as refractory or unclassified sprue and refractory CD may share similar characteristics with CS. Further research should be performed to clarify these disease entities.

The definition currently used for CS or collagenous enteritis is mainly based upon histologic findings and requires the observation of a clear-cut layer of subepithelial collagen that extends into the lamina propria, often containing entrapped lamina propria cells, is refractory to gluten-free diet, and has flattened villous architecture.[7] In addition, two other features that may accompany a poorer prognosis are subcryptal inflammation and thin atrophic-appearing mucosa.[7] We propose diagnostic criteria herein that include: clinical features such as severe malabsorption and weight loss; nonresponsiveness to gluten-free diet; laboratory findings such as negative CD antibodies; and typical histologic changes with villous atrophy, irregular and thickened subepithelial collagen deposits in the small bowel with a collagen band of significant width (ie, more than 10 μm).

Refractory sprue is defined as persistent intestinal damage and symptoms despite a well-documented gluten-free diet and exclusion of other treatable causes.[3] There are three variations in the presentation of refractory sprue: partial response to a gluten-free diet at the outset; initial good response and then relapse despite strict adherence to the diet; and no response to a gluten-free diet.[3] Refractory or unclassified sprue was first defined by Weinstein and colleagues in 1970 as a condition in which the patient has an incomplete clinical response or no response at all to a strict gluten-free diet.[2] It may be due to other foods (eg, soy protein, tuna, egg, or chicken), small bowel lymphoma, or CS.[3] Most of the cases classified as refractory sprue or unclassified sprue were actually found to be CS.[3]

Refractory CD is a form of CD that no longer responds to gluten-free diet.[9] Refractory CD is defined as malabsorption in the presence of persisting or recurring severe inflammatory infiltration of the epithelium and lamina propria, hyperplasia of crypts, and partial villous atrophy, despite strict adherence to a gluten-free diet.[59] Refractory CD can be further defined as refractory CD type I with normal intraepithelial lymphocytes, and refractory CD type II can be defined as phenotypically immature intraepithelial lymphocytes defined by a lack of characteristic T-cell markers.[59] Nonresponsive CD can be described in terms of the clinical scenario of a lack of initial response to a prescribed gluten-free diet or the recurrence of symptoms despite maintenance of gluten-free diet in a patient who initially responded to the diet.[60]

However, there are still several unsolved questions: Can all collagen deposits in the small bowel be diagnosed as CS? Is it possible that other diseases may also present as collagen deposits such as CD as the disease progresses or as the consequence of long-standing CD?[8] Does the collagen deposit cause CS, or is it a consequence of the disease? It is possible that subepithelial collagen deposition may affect the integrity of the bowel wall, but it may not be directly related to the clinical manifestations of CS.

Treatment

The management of CS is very problematic. Thus far, there are no long-term follow-up data available to compare the most effective treatment regimens. Celiac sprue must be ruled out, and dietary investigations should be considered to detect unusual allergies causing refractory sprue. Dietary gluten restriction should be the first step even though patients are often partially or totally unresponsive to gluten-free diet, as previously reported. Parenteral nutrition has been proposed as the best therapy because corticosteroid-related complications such as osteopenia are magnified in a chronic malabsorptive disorder.[3] Total parenteral nutrition allows for time to use immunosuppressives that have been used to treat refractory CD, to consider dietary investigations, and to detect unusual allergies. This offers the time and opportunity to achieve maximal intestinal rehabilitation, thus enhancing intestinal adaptation and absorption. We suggest specific

Table 1. Management Measures for Collagenous Sprue in Patients With Malabsorption Who Can Tolerate Oral Diet

1. Avoid nonsteroidal anti-inflammatory agents.
2. Complex diets are known to enhance gut adaptation more than elemental diets; however, elemental diets are recommended when intestinal inflammation is present.
3. Avoid hypertonic beverages (sodas and fruit juices).
4. Avoid high carbohydrate meals, particularly those with simple carbohydrates that result in sudden osmotic fluid losses and dehydration. All forms of carbohydrates increase bacterial proliferation. Malabsorption of large amounts of fermentable carbohydrate (mono- or disaccharides) reaching the colon leads to the production of a variety of organic acids. The rate of synthesis of organic acids and lactic acid exceeds the rate of metabolism in malabsorptive states, leading to the lowering of luminal pH that favors the growth of acid-resistant, lactate-producing bacteria, particularly d-lactate–producing bacteria such as *Lactobacillus fermenti*, *Lactobacillus acidophilus*, and *Streptococcus*. Simple sugars are rapidly metabolized to d-lactate rather than complex carbohydrates. Small, frequent meals (every 2–3 hours) are recommended, as they produce lower peak serum d-lactate levels.
5. Promote the bowel flora that do not produce d-lactate by the use of probiotics.
6. Fat malabsorption may result in increased oxalate absorption with potential renal stone formation. Fat restriction can reduce steatorrhea, decrease losses of magnesium and calcium, and decreases oxalate absorption. Medium-chain triglycerides are considered to be better absorbed in the presence of bile acid or pancreatic insufficiency.
7. High biologic value proteins are encouraged.
8. Maintain adequate hydration to prevent renal stones and increase renal clearance of d-lactate. Sipping of isotonic or hypotonic fluids between meals is recommended.
9. Control of serum oxalate by considering low-fat, low-oxalate diet, and supplementation with large amounts of calcium at each meal. Foods high in oxalates such as spinach, rhubarb, parsley, beets, cocoa, and tea should be avoided.
10. Lactose restriction may reduce stool output in those patients with a preexisting intolerance.
11. Histamine 2 receptor antagonists or proton pump inhibitors should be given to suppress gastric hypersecretion, which may be associated with deactivation of pancreatic enzymes, thus leading to an improvement in nutrient absorption and reduction of fluid losses.
12. Fiber supplementation may be helpful by enhancing adaptation via increased short-chain fatty acid production and providing an additional calorie source with enhanced sodium and water absorption. In addition, fiber supplementation may decrease the watery nature of the stools by absorbing stool water. By adding bulk to the stool, intestinal transit time is slowed.
13. Recommend supplementation of calcium, magnesium, fat-soluble vitamins, trace minerals, vitamin B12, and folate.
14. Bile-acid binding resin helps to reduce diarrhea caused by malabsorption of bile acids.
15. Antiperistaltic agents such as loperamide, diphenoxylate, codeine, or tincture of opium can be used to prolong the intestinal transit time.

measures in patients with malabsorption who can tolerate oral diet (Table 1).

The diagnosis of irreversible intestinal failure should be made after the optimal utilization of the medical and surgical therapeutic modalities currently available to enhance intestinal adoption and long-term rehabilitation. Early intestinal rehabilitation helps to eliminate parenteral nutrition dependence and more timely consideration of intestinal transplant. The current data do not support direct referral for a preemptive intestinal transplant in long-term survivors with irreversible intestinal failure without HPN failure.[61]

The indications for intestinal transplantation approved by the US Center for Medicare and Medicaid Services and from the position paper of the American Society of Transplantation are noted in Table 2.[62,63] Our patient was considered to be stable on parenteral nutrition and, therefore, was not considered an intestinal transplant candidate.

In the past, the natural history of CS has been characterized by unremitting malabsorption and an inevitably lethal outcome.[2,19] However, there are two reports with extensive biopsy studies that showed complete disappearance of these abnormal small intestinal collagen deposits after treatment with steroids.[13,24] Long-term high-dose corticosteroids remain the most effective treatment option for CS, but the dosing, tapering period, and side-effect management needs to be investigated. Other options that have been used to treat refractory CD may be useful in the treatment of CS. A combination of nutrition support, steroids, and immunosuppressors such as azathioprine, 6-mercaptopurine, cyclosporine, or tumor necrosis factor antibodies may be useful, but lack clinical trials.[59,64] Cytokines such as interleukin-10 have been shown to

Table 2. Indications for Intestinal Transplantation Approved by the US Center for Medicare and Medicaid Services and the Position Paper of the American Society of Transplantation

1. **Failure of HPN.**
   a. Impending (total bilirubin >3–6 mg/dL, progressive thrombocytopenia, and progressive splenomegaly) or overt liver failure (portal hypertension, hepatosplenomegaly, hepatic fibrosis, or cirrhosis) because of parenteral nutrition–liver injury.
   b. Central venous catheter–related thrombosis of 2 or more central veins.
   c. Frequent central line sepsis: 2 or more episodes per year of systemic sepsis secondary to line infections requiring hospitalization; a single episode of line-related fungemia; or septic shock or acute respiratory distress syndrome.
   d. Frequent episodes of severe dehydration despite intravenous fluid in addition to HPN.

2. **High risk of death attributable to the underlying disease.**
   a. Desmoid tumors associated with familial adenomatous polyposis.
   b. Congenital mucosal disorders (eg, microvillus atrophy, intestinal epithelial dysplasia).
   c. Ultra-short bowel syndrome (gastrostomy, duodenostomy, residual small bowel <10 cm in infants and <20 cm in adults).

3. **Intestinal failure with high morbidity or low acceptance of HPN.**
   a. Intestinal failure with high morbidity (frequent hospitalization, narcotic dependency) or inability to function (eg, pseudo-obstruction, high output stoma).
   b. Patient's unwillingness to accept long-term HPN (eg, young patients).

Adapted from Medicare coverage policy[62] and Buchman AL, et al.[63]

HPN=home parenteral nutrition.

have no effect on the treatment of refractory CD, but they may be useful in CS.[65] Small bowel transplant may be an option for those patients who are refractory to these immunosuppressive agents with severe malnutrition. Improvement in symptoms and clinical features may be the only way to define effective treatment. Because endoscopic appearance is usually normal and the pathologic lesion of CS may be patchy in its distribution, convincing documentation of a histopathologic response to different treatments is difficult.[7]

Summary

Clinical and pathologic features of CS have been delineated, but the mechanism involved in the characteristic malabsorption remains poorly understood and requires further elucidation. Standardized diagnostic criteria are needed to better define this disease. The prognosis and long-term outcome of CS are poorly documented. Future studies are necessary to better define possible treatment regimens.

References

1. Schein J. Syndrome of nontropical sprue with hitherto undescribed lesions of the intestine. *Gastroenterology*. 1947;8:438-460.
2. Weinstein WM, Saunders DR, Tytgat GN, Rubin CE. Collagenous sprue--an unrecognized type of malabsorption. *N Engl J Med*. 1970;283:1297-1301.
3. Robert ME, Ament ME, Weinstein WM. The histologic spectrum and clinical outcome of refractory and unclassified sprue. *Am J Surg Pathol.* 2000;24:676-687.
4. Hafkemeyer P, Herbst E, Köhler G, Fuhrmann K, Kreisel W. Collagenous sprue. *Dtsch Med Wochenschr*. 1995;120:1430-1434.
5. Holdstock DJ, Oleesky S. Successful treatment of collagenous sprue with combination of prednisolone and gluten free diet. *Postgrad Med J.* 1973;49:664-667.
6. Bossart R, Henry K, Doe WF, Booth CC. Proceedings: Collagenous basement membrane thickening in jejunal biopsies from patients with adult celiac disease. *Gut*. 1974;15:338.
7. Freeman HJ. Collagenous mucosal inflammatory diseases of the gastrointestinal tract. *Gastroenterology.* 2005;129:338-350.
8. Freeman HJ. Collagenous sprue associated with an extensive T-cell lymphoma. *J Clin Gastroenterol.* 2003;36:144-146.
9. Biagi F, Corazza GR. Defining gluten refractory enteropathy. *Eur J Gastroenterol Hepatol.* 2001;13:561-565.
10. Freeman HJ. Refractory celiac disease and sprue-like intestinal disease. *World J Gastroenterol.* 2008;14:828-830.
11. Gorgun OV, Portianko AS. Collagenous sprue: a case description [in Russian]. *Klin Med (Mosk).* 2007;85:70-72.
12. Medlicott SA, Beck PL, Loken S, Crabtree T. Synchronous collagenous sprue and enteropathy-type T cell lymphoma: variants of the same disease. *Can J Gastroenterol.* 2004;18:329-332.
13. Freeman HJ, Davis JE, Myers DM. Complete histological resolution of collagenous sprue. *Can J Gastroenterol.* 2004;18:333-336.
14. Maggiolo P, Klinger J, Arellano L. Collagenous sprue. Clinical case [in Spanish]. *Rev Med Chil.* 1998;126:1100-1102.
15. Jármay K, Várkonyi T, Hajnal-Papp R. Collagenous sprue--a rare form of celiac disease in adulthood. *Z Gastroenterol.* 1993;31:144-146.
16. Güller R, Anabitarte M, Mayer M. Collagenous sprue and ulcerative jejunoileitis in a patient with gluten-induced enteropathy. *Schweiz Med Wochenschr.* 1986;116:1343-1349.
17. Holtmann M, von Herbay A, Galle PR, Stremmel W. Long-term collagenous sprue--remission with a gluten-free diet. *Z Gastroenterol.* 1999;37:1163-1168.
18. Brandborg LL. Histologic diagnosis of diseases of malabsorption. *Am J Med.* 1979;67:999-1006.

19. Barry RE, Morris JS, Read AE. A case of small intestinal mucosal atrophy. *Gut.* 1970;11:743-747.
20. Doe WF, Evans D, Hobbs JR, Booth CC. Celiac disease, vasculitis, and cryoglobulinemia. *Gut.* 1972;13:112-123.
21. Sheehy TW, Staats OJ. Collagenous sprue. A case report. *Ala J Med Sci.* 1972;9:392-396.
22. Pepper HW, Brandborg LL, Shanser JD, Goldberg HI, Moss AA. Collagenous sprue. *Am J Roentgenol Radium Ther Nucl Med*. 1974;121:275-282.
23. Zeman RK, Tomer RG. Collagenous sprue. *Am J Gastroenterol*. 1978;70: 541-544.
24. Schreiber FS, Eidt S, Hidding M, Schmidt-Walczuch J, Werning C. Collagenous duodenitis and collagenous colitis: A short clinical course as evidenced by sequential endoscopic and histologic findings. *Endoscopy*. 2001;33:555.
25. Dowling RH, Henry K. Clinicopathological conference: Non responsive celiac disease [demonstrated at the Royal Postgraduate Medical school]. *Br Med J.* 1972;3:624-631.
26. Bossart R, Henry K, Booth CC, Doe WF. Subepithelial collagen in intestinal malabsorption. *Gut.* 1975;160:18-22.
27. Barry RE, Morris JS, Read AE. Collagenous sprue. *N Engl J Med.* 1971; 284:1041.
28. Hourihane DO. The histology of intestinal biopsies. *Proc R Soc Med.* 1963; 56:1073-1077.
29. Freeman HJ, Berean KW. Resolution of paraneoplastic collagenous enterocolitis after resection of colon cancer. *Can J Gastroenterol.* 2006;20:357-360.
30. Neale G. Clinicopathological conference. Case of adult celiac disease resistant to treatment. *Br Med J*. 1968;2:678-684.
31. Freeman HJ. Hyposplenism, antiendomysial antibodies and lymphocytic colitis in collagenous sprue. *Can J Gastroenterol*. 1999;13:347-350.
32. Samitier RS, Andreu EB, Martiner AG, et al. Esprue colageno. *Rev Esp Enferm Apar Dig.* 1979;6:583-588.
33. Woods CA, Foutch PG, Kerr DM, Haynes WC, Sanowski RA. Collagenous sprue as a cause for malabsorption in a patient with myotonic dystrophy: a new association. *Am J Gastroenterol*. 1988;83:765-766.
34. Eckstein RP, Dowsett JF, Riley JW. Collagenous enterocolitis: a case of collagenous colitis with involvement of the small intestine. *Am J Gastroenterol.* 1998;83:767-771.
35. Stolte M, Ritter M, Borchard F, Koch-Scherrer G. Collagenous gastroduodenitis on collagenous colitis. *Endoscopy*. 1990;22:186-187.
36. Meier PN, Otto P, Ritter M, Stolte M. Collagenous duodenitis and ileitis in a patient with collagenous colitis. *Leber Magen Darm*. 1991;21:231-232.
37. McCashland TM, Donovan JP, Strobach RS, Linder J, Quigley EM. Collagenous enterocolitis: a manifestation of gluten-sensitive enteropathy. *J Clin Gastroenterol.* 1992;15:45-51.
38. Armes J, Gee DC, Macrae FA, Schroeder W, Bhathal PS. Collagenous colitis: jejunal and colorectal pathology. *J Clin Pathol*. 1992;45:784-787.
39. Castellano VM, Munoz MT, Colina F, Nevado M, Casis B, Solis Herruzo JA. Collagenous gastrobulbitis and collagenous colitis. Case report and review of literature. *Scand J Gastroenterol*. 1999;34:632-638.
40. Freeman HJ, Piercey JR, Raine RJ. Collagenous gastritis. *Can J Gastroenterol.* 1989;3:171-174.
41. Colletti RB, Trainer TD. Collagenous gastritis. *Gastroenterology.* 1989;97: 1552-1555.
42. Pullimood AB, Ramakrishna BS, Mathan MM. Collagenous gastritis and collagenous colitis: a report with sequential histological and ultrastructural findings. *Gut.* 1999;44:881-885.
43. Vesoulis Z, Lozanski G, Ravichandran P, Esber E. Collagenous gastritis: a case report, morphologic evaluation and review. *Mod Pathol.* 2000;13:591-596.
44. Meunier S, Villard F, Bouvier R, Lachaux A, Bertrand Y. Collagen gastritis, an unusual cause of anemia in children. Report of 2 cases. *Arch Pediatr.* 2001;8:47-50.
45. Freeman HJ. Topographic mapping of collagenous gastritis. *Can J Gastroenterol.* 2001;15:475-478.
46. Lagorce-Pages C, Fabiani B, Bouvier R, Scoazec JY, Durand L, Fiejou JF. Collagenous gastritis: a report of six cases. *Am J Surg Pathol.* 2001;25:1174-1179.
47. Daum S, Foss HD, Schuppan D, Riecken EO, Zeitz M, Ullrich R. Synthesis of collagen I in collagenous sprue. *Clin Gastroenterol Hepatol.* 2006;4:1232-1236.
48. Sasaki M, Kashima M, Ito T, Watanabe A, Izumiyama N, et al. Differential regulation of metalloproteinase production, proliferation and chemotaxis of human lung fibroblasts by PDGF, interleukin-1beta and TNF-alpha. *Mediators Inflamm.* 2000;9:155-160.
49. McGaha TL, Le M, Kodera T, Stoica C, Zhu J, et al. Molecular mechanisms of interleukin 4 induced upregulation of type 1 collagen gene expression in murine fibroblasts. *Arthritis Rheum*. 2003;48:2275-2284.
50. Jinnin M, Ihn H, Yamane K, Tamaki K. Interleukin-13 stimulates the transcription of the human alpha2(I) collagen gene in human dermal fibroblasts. *J Biol Chem*. 2004;279:41783-41791.
51. Azouz A, Razzaque MS, El-Hallak M, Taguchi T. Immunoinflammatory responses and fibrogenesis. *Med Electron Microsc*. 2004;37:141-148.
52. Günther U, Schuppan D, Bauer M, Matthes H, Stallmach A, et al. Fibrogenesis and fibrolysis in collagenous colitis: patterns of procollagen types 1 and 4, matrix metalloproteinase-1 and 13, and TIMP-1 gene expression. *Am J Pathol.* 1999;155:493-503.
53. Pender SL, Tickle SP, Docherty AJ, Howie D, Wathen NC, MacDonald TT. A major role for matrix metalloproteinases in T-cell injury in the gut. *J Immunol.* 1997;158:1582-1590.
54. Saarialho-Kere UK. Patterns of matrix metalloproteinase and TIMP expression in chronic ulcers. *Arch Dermatol Res*. 1998;290(suppl):S47-S54.
55. Schuppan D, Koda M, Bauer M, Hahn EG. Fibrosis of liver, pancreas and intestine: common mechanisms and clear targets? *Acta Gastroenterol Belg.* 2000;63:366-370.
56. Matthes H, Stallmach A, Matthes B, Herbst H, Schuppan D, Riecken EO. Indications for different collagen metabolism in Crohn's disease and ulcerative colitis [in German]. *Med Klin (Munich).* 1993;88:185-192.
57. Birkedal-Hansen H. Proteolytic remodeling of extracellular matrix. *Curr Opin Cell Biol.* 1995;7:728-735.
58. Iredale JP, Murphy G, Hembry RM, Friedman SL, Arthur MJ. Human hepatic lipocytes synthesize tissue inhibitor of metalloproteinases: implications for regulation of matrix degradation in liver. *J Clin Invest.* 1992;90:282-287.
59. Goerres MS, Meijer JW, Wahab PJ, Kerckhaert JA, Groenen PJ, et al. Azathioprine and prednisone combination therapy in refractory coeliac disease. *Aliment Pharmacol Ther*. 2003;18:487-494.
60. Abdulkarim AS, Burgart LJ, See J, Murray JA. Etiology of nonresponsive celiac disease: results of a systematic approach. *Am J Gastroenterol.* 2002;97:2016-2021.
61. Pironi L, Forbes A, Joly F, Colomb V, Lyszkowska M, et al. Survival of patients identified as candidates for intestinal transplantation: a 3-year prospective follow-up. Home Artificial Nutrition Working Group of the European Society for Clinical Nutrition and Metabolism (ESPEN). *Gastroenterology.* 2008;135:61-71.
62. Medicare coverage policy. Decisions. Intestinal and multivisceral transplantation (CAG-00036). October 4, 2000.
63. Buchman AL, Scolapio J, Fryer J. AGA technical review on short bowel syndrome and intestinal transplantation. *Gastroenterology*. 2003;124:1111-1134.
64. Longstreth GF. Successful treatment of refractory sprue with cyclosporine. *Ann Intern Med.* 1993;119:1014-1016.
65. Mulder CJ, Wahab PJ, Meijer JW, Metselaar E. A pilot study of recombinant human interleukin-10 in adults with refractory coeliac disease. *Eur J Gastroenterol Hepatol.* 2001;13:1183-1188.

Review

Collagenous Sprue: A Distinctive and Heterogeneous Clinicopathologic Disorder

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In 1970, Weinstein and associates[1] described a distinctive abnormality in small bowel biopsies from a 51-year-old woman initially thought to have celiac disease. The changes in the present case report by Xiao and colleagues[2] are similar to this original case study. In the original report, biopsies stained with hematoxylin and eosin showed a prominent band of subepithelial eosinophilic hyaline material in the lamina propria. The deposits were notable due to their histochemical features of collagen, and ultrastructural evaluation confirmed the presence of an electron-dense material with the typical 640 A axial periodicity of collagen fibers. Prior biopsies showed changes of untreated celiac disease with flattened villi, but response to a gluten-free diet failed to occur. Later, her clinical course worsened with severe diarrhea, malabsorption, and weight loss. Symptoms transiently improved with corticosteroids. She died approximately 4 years later, and a postmortem examination showed abnormal and very extensive pathologic changes in the proximal small intestine with subepithelial eosinophilic hyaline of varying degrees of thickness. In addition, short segments of normal intestine were present in the distal small intestine. The investigators noted two earlier reports by Schein[3] in 1947 and Hourihane[4] in 1963 possibly representing the identical biopsy lesion (though in the latter, ileal involvement was evident).

Thus, this distinctive and intriguing disorder was initially shown to have the following features: persistent diarrhea with pan-malabsorption causing nutrient deficiency and weight loss; distinctive histopathologic changes that include a unique morphologic marker, a subepithelial band with the histochemical (and ultrastructural) features of collagen; other histopathologic changes similar to untreated celiac disease but not responsive to a gluten-free diet; and diffuse and patchy mucosal changes of variable severity, localized mainly in the proximal small intestine. In the case presented by Xiao and coworkers, the diagnosis of collagenous sprue was supported by at least the first two features (though ultrastructural studies were not performed). However, a gluten-free diet provided for only 2 weeks would not be adequate to exclude concomitant celiac disease, as duodenal biopsy improvement may require months or even years, particularly in older adults.[5] Finally, overall severity and extent of the changes along the length of the small intestine could not be fully detailed.

This case emphasizes a very important clinical issue. The diagnosis of celiac disease (or gluten sensitive enteropathy) is pathologically-based and has traditionally depended upon two sequential criteria: documentation of the typical histopathologic features of untreated disease in small bowel mucosal biopsies; and response to a gluten-free diet. Otherwise, celiac disease, even if present, cannot be defined. In some cases, a "flattened" biopsy appearance may be present, but a gluten-free diet response has not been documented. Some of these cases have been loosely labeled as refractory celiac disease, but this label should be reserved for those that show an initial response to a gluten-free diet followed by later development of recurrent symptoms and biopsy changes. The most common causes for this scenario in celiac disease include poor dietary compliance or inadvertent ingestion of a ubiquitous gluten-containing food source (eg, pill capsules, communion wafers). A second cause or a superimposed cause (eg, infection, folate or zinc deficiency) for recurrence could also occur. Moreover, a different cause for a "flattened" biopsy appearance may be responsible,[6] the initial correct diagnosis (eg, Crohn's disease in the duodenum without mucosal granulomas) may have been missed,[7] or an associated or complicating disease (eg, collagenous colitis, lymphoma) may have developed. Finally, a miscellaneous or "wastebasket" group with a "flat" biopsy appearance may be present with no evidence that a gluten-free diet response had ever occurred. This group does not meet the two traditional criteria for celiac disease (or even refractory celiac disease). More precise terms are sprue-like intestinal disease or unclassified sprue.[8] In the present case, a specific cause for clinical and pathologic changes could be defined because of the unique pathologic features found in collagenous sprue.

The possible relationship to celiac disease was also raised here. Some physicians originally believed that increased subepithelial collagen may simply represent only a prognostic pathologic marker for a poor outcome in celiac disease.[9] Others, however, viewed collagenous sprue as an entirely new, previously unrecognized small bowel disorder that is poorly responsive to a gluten-free diet.[10] More recent studies have also noted some other

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shared elements between celiac disease and collagenous sprue. For example, common clinical features have been documented (eg, hyposplenism, positive endomysial antibodies)[11] as well as complications, including both T-cell and B-cell lymphoma in both entities.[12,13]

The present case also illustrates another intriguing aspect of collagenous sprue that continues to be explored. Collagen deposition was also present in the colon as in earlier reports demonstrating collagen deposits in the colon (ie, collagenous colitis) or even the stomach (ie, collagenous gastritis).[14] An associated inflammatory process in either colonic or gastric mucosa, or both, is usually present, often including epithelial lymphocytosis. Interestingly, collagenous or lymphocytic colitis or gastritis have all been associated with biopsy-defined celiac disease.[14-16] Together, these findings suggest a far more extensive pathologic process and may also represent an important clue to a far more heterogeneous process than has been previously appreciated.

Historically, published reports have suggested that the natural history of collagenous sprue is characterized by worsening malabsorption, usually of multiple nutrients, with an inevitably fatal outcome. In most cases, diarrhea and progressive weight loss were documented, and on rare occasions, abdominal pain, sometimes severe, was present, often with vasculitis.[17] However, independent reports with extensive biopsy studies have also demonstrated complete histologic resolution of the lesion and disappearance of the abnormal collagen deposits after steroid therapy for prolonged periods of time.[18,19] This suggests that the lesion may occasionally be reversible, in some patients, at least temporarily for extended periods of years. In the present report, steroids were also used and a response was noted in the colon, but not in the small bowel. This differential treatment response suggests that these collagen deposits and their accompanying inflammatory processes could be quite heterogeneous along the length of the gastrointestinal tract.

The cause of these collagenous deposits may also be quite different from case to case. In addition to celiac disease, collagenous sprue has not only been complicated by T-cell lymphoma, but has been associated with its occurrence.[13] Finally, collagen deposits in both the small and large intestines were detected with an apparently coincidental, but localized, colorectal cancer.[20] Later, clinical and histopathologic changes resolved after the cancer was resected, suggesting that these collagen deposits could represent an important paraneoplastic morphologic marker of occult malignant disease.

Summary

Collagenous sprue is a small intestinal disorder marked by severe to variably severe architectural disturbance and distinctive subepithelial collagen deposits. Recent studies suggest that this disorder may be more heterogeneous than previously appreciated, as reflected in frequently associated collagenous mucosal inflammation elsewhere in the gastrointestinal tract, differential responses to treatment, particularly with steroids, and its association with other conditions, including malignant disease as a paraneoplastic morphologic marker.

References

1. Weinstein WM, Saunders DR, Tytgat GN, Rubin CE. Collagenous sprue—an unrecognized type of malabsorption. *N Engl J Med*. 1970;283:1297-1301.
2. Xiao Z, Dasari VM, Kirby DF, Bronner M, Plesec TP, Lashner BA. Collagenous sprue: a case report and literature review. *Gastroenterol Hepatol*. 2009;5:418-424.
3. Schein J. Syndrome of nontropical sprue with hitherto undescribed lesions of the intestine. *Gastroenterology*. 1947;8:438-460.
4. Hourihane DO. The histology of intestinal biopsies. *Proc R Soc Med.* 1963; 56:1073-1077.
5. Tursi A, Brandimarte G, Giorgetti GM, Elisei W, Inchingolo CD, et al. Endoscopic and histological findings in the duodenum of adults with celiac disease before and after changing to a gluten-free diet: a 2-year prospective study. *Endoscopy.* 2006;38:702-707.
6. Freeman HJ. Small intestinal mucosal biopsy for investigation of diarrhea and malabsorption in adults. *Gastrointest Endosc Clin N Am*. 2000;10:739-753.
7. Schuffler MD, Chaffee RG. Small intestinal biopsy in a patient with Crohn's disease of the duodenum. The spectrum of abnormal findings in the absence of granulomas. *Gastroenterology*. 1979;76:1009-1014.
8. Freeman HJ. Refractory celiac disease and sprue-like intestinal disease. *World J Gastroenterol.* 2008;14:828-830.
9. Bossart R, Henry K, Booth CC, Doe WF. Subepithelial collagen in intestinal malabsorption. *Gut.* 1975;16:18-22.
10. Perera DR, Weinstein WM, Rubin CE. Small intestinal biopsy. *Hum Pathol.* 1975;6:157-217.
11. Freeman HJ. Hyposplenism, antiendomysial antibodies and lympocytic colitis in collagenous sprue. *Can J Gastroenterol.* 1999;13:347-350.
12. Robert ME, Ament ME, Weinstein WM. The histologic spectrum and clinical outcome of refractory and unclassified sprue. *Am J Surg Pathol.* 2000;24: 676-687.
13. Freeman HJ. Collagenous sprue associated with an extensive T-cell lymphoma. *J Clin Gastroenterol.* 2003;17:111-113.
14. Freeman HJ. Collagenous mucosal inflammatory diseases of the gastrointestinal tract. *Gastroenterology*. 2005;129:338-350.
15. Wolber R, Owen D, DelBuono L, Appelman H, Freeman H. Lymphocytic gastritis in patients with celiac sprue and sprue-like intestinal disease. *Gastroenterology*. 1990;98:310-315.
16. Wolber R, Owen D, Freeman HJ. Colonic lymphocytosis in patients with celiac sprue. *Hum Pathol.* 1990;21:1092-1096.
17. Doe WF, Evans D, Hobbs JR, Booth CC. Celiac disease, vasculitis and cryoglobulinemia. *Gut*. 1972;13:112-123.
18. Schreiber FS, Eidt S, Hidding M, Schmidt-Walczuch J, Werning C. Collagenous duodenitis and collagenous colitis: a short clinical course as evidenced by sequential endoscopic and histologic findings. *Endoscopy.* 2001;33:555.
19. Freeman HJ, Davis JE, Myers DM. Complete histologic resolution of collagenous sprue. *Can J Gastroenterol*. 2004;18:333-336.
20. Freeman HJ, Berean KW. Resolution of paraneoplastic collagenous enterocolitis after resection of colon cancer. *Can J Gastroenterol*. 2006;20:357-360.