Drug-induced Collagenous Sprue: 
A Reversible Small Bowel Mucosal Disorder

Hugh James Freeman*

Department of Medicine (Gastroenterology), University of British Columbia, Vancouver, BC, Canada

*Corresponding author: hugfree@shaw.ca

Received April 03, 2021; Revised May 09, 2021; Accepted May 18, 2021

Abstract Collagenous sprue is an unusual small intestinal mucosal disorder characterized by flattened small intestinal mucosa, unusual sub-epithelial collagen deposits, increased intra-epithelial lymphocytes, often denuded epithelial cells and resistance to therapy, including a gluten-free diet. The disorder is heterogeneous with several potential causes now identified. Similar to sprue-like intestinal disease, collagenous sprue may be caused or precipitated by different pharmaceutical agents. Olmesartan, an angiotensin II inhibitor, often employed in treatment of hypertension, may cause a drug-induced form of sprue-like small intestinal disease with the pathological features of untreated celiac disease refractory to gluten-free diet treatment. In addition, collagenous sprue may be precipitated by olmesartan. Recognition and cessation of the medication has led to resolution of the small intestinal mucosal disorder without steroids or other treatment.

Keywords: collagenous sprue, sprue-like intestinal disease, drug-induced small bowel disease, malabsorption, olmesartan

Cite This Article: Hugh James Freeman, “Drug-induced Collagenous Sprue: A Reversible Small Bowel Mucosal Disorder.” International Journal of Celiac Disease, vol. 9, no. 2 (2021): 35-37. doi: 10.12691/ijcd-9-2-6.

Collagenous sprue (enteritis) is an unusual and rare intestinal disorder characterized by a “flattened” or atrophic small bowel mucosa and several very characteristic histopathological features, particularly a band of sub-epithelial collagen-containing deposit that histochemically stains with trichrome [1]. Electron microscopy has also confirmed 640 A fibers within these deposits, typical of collagen. Changes may be diffuse or patchy within the small intestine. Other important pathological features have been well documented including increased numbers of intra-epithelial lymphocytes and epithelial cell denudation from the luminal surface. In some, but likely the minority of patients with collagenous sprue, histopathologic changes with similar collagen deposits have also been occasionally documented in either gastric (i.e., collagenous gastitis) or colonic mucosa (i.e., collagenous colitis), or both [1]. To date, a number of associated conditions, some “autoimmune”, or other “causes” of collagenous disease in the gastrointestinal mucosa have been identified and previously detailed [1]. Prominent among these are celiac disease and some suspected medications, particularly, non-steroidal anti-inflammatory drugs.

The initial clinical description of collagenous sprue was reported in a woman with celiac disease non-responsive to a gluten-free diet [2], and later, her clinical course worsened with a fatal outcome. At autopsy, the pathological lesion was limited to multiple sites within the small bowel and, as noted in the first description of this entity, the mucosal pathological features were apparently similar to changes published in earlier descriptive reports [3,4]. Usually, the condition has been described in middle-aged to older adults, often, but not exclusively, female. However, the heterogeneous nature of the small intestinal mucosal disorder has been further emphasized in recent years [1] with definition of a much more extensive gastrointestinal disorder in occasional patients having both/either gastric and/or colonic mucosa involvement.

This enteropathy has often been described as so-called “sprue-like intestinal disease” due to some of its histopathologic similarities to untreated celiac disease, but with evidence of failure to respond to a gluten-free diet and, often, negative celiac serology (i.e., specifically, IgA-tissue-transglutaminase antibodies). Clinical experience over many decades has also indicated that involvement of the small intestine with this disorder usually predicted a poor prognosis. Most suffered an intractable clinical course with on-going diarrhea and severe pan-malabsorption of multiple nutrients and eventually, in most, a fatal outcome [1,2]. Some may have an acute or sub-acute clinical presentation with free perforation of the small intestine [5] or develop an associated extensive T-cell lymphoma [6,7]. In recent years, there have been rare anecdotal reports of improved clinical and pathological outcomes, even resolution with steroids and immunosuppression [8,9]. However, evidence in large numbers of patients, especially with histopathological resolution, has been limited, in part, because the disorder is uncommon.

In contrast to this experience, others suggested that most patients with collagenous sprue appeared to respond to a gluten-free diet and addition of oral enteric-coated steroids [10]. This conclusion of a surprisingly positive
outcome seemed puzzling and confounding factors may have played a role. Notable in this report were use of medications actually implicated in development of sprue-like intestinal disease, including some collagenous mucosal disorders per se (e.g., collagenous colitis, non-steroidal anti-inflammatory drugs or gastric anti-secretory agents). In addition, 8 of 30 collagenous sprue patients had received the anti-hypertensive agent, olmesartan. Later, the authors acknowledged that a positive clinical course may have been due to hospitalization alone [11]. Cessation of the medication alone may have been responsible for improvement, rather than added steroid. Together, these publications [10,11] suggested the potentially significant role of medications, in the pathogenesis of sprue-like small intestinal disease, and relevant here, some cases of collagenous sprue.

Olmesartan enteropathy was noted to have similar histopathological features to untreated celiac disease, and previously detailed in this journal [12]. The drug is a specific angiotensin II receptor antagonist, often used in treatment of hypertension. Olmesartan enteropathy is now appreciated to cause a drug-induced sprue-like small intestinal disorder (although the drug may also may cause a colonic inflammatory reaction, colitis, leading to a further exacerbation of diarrhea). The small bowel effects may be an adverse clinical event with diarrhea, malabsorption and weight loss following chronic long-term clinical use in hypertension, often years [12]. Serological studies in this setting, particularly for IgA tissue transglutaminase antibodies, are also usually negative and there is often a failure to respond to a gluten-free diet [12], leading often to an incorrect label of refractory celiac disease. Cessation of the medication, however, may lead to resolution [12]. This was first described in 3 reports in 2012, all by separate authors, including 2 independent descriptions from the same institution [11,13,14].

An increasing list of medications has been reported to cause drug-induced changes in the small intestine [15], especially in recent years. In some, a direct drug effect may be responsible. In others, a byproduct of the drug from hepatic and/or intestinal drug metabolism may be causative. For many, resultant mucosal changes in the small bowel may be difficult to distinguish with any degree of certainty from changes of untreated celiac disease. And, the list is growing (reflective of the evolving armamentarium of pharmaceutical agents) so that a suspect diagnosis of celiac disease should only be confirmed after medications have been excluded as a causative factor along with documentation of a response to a gluten-free diet. An editorial in 1970 warned clinicians then about “sprue by any other name” [16] and the characteristic, but non-specific nature of the pathological changes in untreated celiac disease, an issue that has continued to frustrate clinicians to the present era [17].

A new chapter in this histopathological narrative has also emerged during the past decade or so. Since the first description of collagenous colitis [18], different medications have been associated with its appearance, including ticlopidine, proton pump inhibitors, histamine receptor antagonists, anti-depressants and, especially, non-steroidal anti-inflammatory drugs (NSAIDS) [19].

Riddell et al [20], for example, provided added evidence that NSAIDS might cause collagen deposition, particularly in collagenous colitis, usually after long-term use. In 3 patients, diarrhea resolved with cessation of medication, and in 1, re-challenge resulted in recurrent symptoms. Biopsy studies were not repeated with symptom resolution or with re-challenge-induced recurrence in this study. However, Vasant et al [21] noted both clinical resolution and resolution of collagen in small intestinal biopsies from a patient with celiac disease receiving NSAIDS. The patient was labeled with collagenous sprue, treated solely with a gluten-free diet and discontinuation of NSAIDS. Repeated endoscopic studies 6 months later were normal with no intestinal mucosal collagen deposition.

Later, 3 different reports on collagenous sprue noted resolution of symptoms and normalization of small intestinal mucosal changes, simply with discontinuation of olmesartan [22,23,24]. Re-challenge studies were not done with olmesartan, but after 1 year, biopsies had normalized off olmesartan, and after long-term follow-up for 3 years there was no symptom recurrence [24].

Other medications have also now been noted to be linked, specifically to collagenous sprue. For example, mycophenolate mofetil, a medication often used for immune suppression after transplantation, has been associated with development of sprue-like small intestinal disease and pathological changes similar to untreated celiac disease [25] as well as colitis [26]. Celiac serological studies, however, have usually been negative and a gluten-free diet was not effective in improvement of the altered small bowel mucosa. Instead, in a recent report [27], the changes evolved into collagenous sprue.

In patients with changes characteristic of celiac disease, particularly if refractory to a gluten-free diet, it has long been appreciated that other causes should be considered. The histopathologic changes are not specific and may be mimicked by several causes, including a variety of medications. Additionally, collagenous sprue is increasingly becoming appreciated as heterogeneous, and a growing number of medications may be important in its development. Most important, removal of a responsible medication alone may result in reversal of the intestinal disease process with complete recovery from an otherwise devastating outcome. Physicians need to be alert to the medication profile of patients with newly diagnosed small bowel disease.

References

[1] Freeman HJ. Collagenous mucosal inflammatory diseases of the gastrointestinal tract. Gastroenterology 2005: 129: 338-350.
[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] Schein J. Syndrome of non tropical sprue with histerto undescribed lesions of the small intestine. Gastroenterology 1947; 8: 438-460.
[4] Hourihane DO. Diarrhea of small bowel origin. The histology of intestinal biopsies. Proc R Soc Med 1963; 56: 1073-1077.
[5] Freeman HJ, Webber DO. Free perforation of the small intestine in collagenous sprue. World J Gastroenterol 2009; 15: 4446-4448.
[6] 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.
Freeman HJ. Collagenous sprue associated with an extensive T-cell lymphoma. J Clin Gastroenterol 2003; 36: 144-146.

Freeman HJ, Davis JE, Myers DM. Complete histological resolution of collagenous sprue. Can J Gastroenterol 2004; 18: 333-336.

Freeman HJ, Berean KW. Resolution of paraneoplastic collagenous enterocolitis after resection of colon cancer. Can J Gastroenterol 2006; 20: 357-360.

Rubio-Tapia A, Talley NJ, Gurudu SR, Wu T-T, Murray JA. Gluten-free diet and steroid treatment are effective therapy for most patients with collagenous sprue. Clin Gastroenterol Hepatic 2010; 8: 344-349.

Rubio-Tapia A, Herman ML, Ludvigsson JF, Kelly DG, Mangan TF, Wu T-T, Murray JA. Severe sprue-like enteropathy associated with olmesartan. Mayo Clinic Proc 2012; 87: 732-738.

Freeman HJ. Olmesartan enteropathy, Inter J Celiac Dis 2016; 4: 24-26.

de Fonseka A, Turkey A, Moskalul C. A case of olmesartan-induced enteropathy. Inflamm Bowel Dis 2012; 18: S17.

Talbot GH Small bowel histopathologic findings suggestive of celiac disease in an asymptomatic patient receiving olmesartan. Mayo Clin Proc 2012; 87: 1231-1232.

Freeman HJ. Drug-induced sprue-like intestinal disease. Inter J Celiac Dis 2014; 2: 49-53.

Rubin CE, Eidelman S, Weinstein WM. Sprue by any other name. Gastroenterology 1970; 58: 409-413.

Freeman HJ. Sprue-like intestinal disease. Int J Celiac Dis 2014; 2: 6-10.

Freeman HJ, Weinstein WM, Shnitka TK, Wensel RH, Sartor VE. Watery diarrhea syndrome associated with a lesion of the colonic basement membrane (BM)—lamina propriety (LP) interface. Ann Royal Coll Phys Surg Can 1976; 9: 45.

© The Author(s) 2021. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).