

Collagenous Sprue, a Heterogeneous Small Bowel Disorder

Hugh James Freeman*

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

*Corresponding author: hugfree@shaw.ca

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Abstract Collagenous sprue is a disorder characterized by severe diarrhea, progressive malabsorption of multiple nutrients, protein depletion and weight loss accompanied by a pathognomonic small bowel biopsy lesion characterized by a villus atrophy and a band-like subepithelial mucosal deposit containing collagen. It has been closely linked to celiac disease, tends to be refractory to treatment and prognosis has been poor with only anecdotes of successful therapy. In recent years, the disorder has been detected in different settings, including early malignancies as a paraneoplastic phenomenon and due to the toxic effects of some medications including non-steroidal anti-inflammatory drugs (NSAIDs) and the angiotensin II receptor antagonist, olmesartan. Here, dramatic reversal to normal of the clinical and pathological changes have been documented so that a medication history is critical in any patient presenting with sprue-like intestinal disease.

Keywords: collagenous sprue, celiac disease, non-responsive celiac disease, refractory celiac disease, refractory sprue, olmesartan

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1. Introduction

Collagenous sprue (enteritis) is a mucosal small intestinal disorder characterized by a very distinct histopathological lesion marked by persistent diarrhea, severe malabsorption with multiple nutrient deficiencies, protein wasting and progressive weight loss. The disorder is rare and recent clinical studies suggest that the disorder likely has multiple causes, possibly with differing prognoses depending on the cause. The treatment is not known, in part, because most specialist physicians, even in large referral centres, only accumulate a limited extended experience over a lifetime of clinical practice and well done clinical treatment trials in large patient groups are simply not available.

2. Pathological Lesion

A small bowel mucosal biopsy shows a sub-epithelial band-like deposit with the histochemical and ultrastructural features typical of collagen. With a hematoxylin-eosin stain, the band stains pink often with entrapped cells. With a trichrome stain, the band is characteristically blue or blue-green, typical of collagen. Photomicrographs illustrating these features can be located elsewhere in journal reviews or authoritative textbooks on gastrointestinal pathology [1,2]. Other changes may be present, including "flattening" of the villus architecture, increased lamina propria lymphoid

and plasma cells, increased numbers of intra-epithelial lymphocytes and a peculiar sloughing from the intestinal surface of single cells and strips of epithelial cells. In extensive biopsy studies along the length of the small intestine, the architectural changes may be described as variable to severe, patchy or diffuse and localized mainly in the proximal small intestine. In some cases, there may be associated and similar collagenous deposits in gastric and/or colonic mucosa, so-called and more generalized collagenous mucosal inflammatory disease [1].

3. Historical Clinicopathological Descriptions

The earliest reports of this entity may have been recorded by Schein in 1947 [3] and Hourihane in 1963 [4]. However, Weinstein et al [5] provided the most detailed description of the clinical and pathological features in a 51-year old female initially believed to have celiac disease as the histopathological changes in the small bowel included severely flattened villi. A long-term response to a gluten-free diet failed to occur and subsequent biopsy studies resulted in a detailed description of the pathological changes of this entity, including histochemical and ultrastructural features, in particular electron-dense material with the typical 640 Å axial periodicity of collagen fibres. Treatment with steroids provided some symptomatic improvement, but eventually, worsening diarrhea, severe malabsorption and progressive weight loss developed. Post-mortem studies confirmed extensive small intestinal

changes, particularly prominent in the proximal small intestine (although ileal involvement was previously documented).

Subsequent reports confirmed some common clinical features with celiac disease. These included: hyposplenism or splenic atrophy [6], small bowel ulceration with free perforation [7], lymphocytic colitis [6] and collagenous mucosal involvement elsewhere, including collagenous colitis [1,8]. While collagenous sprue was usually viewed as a possible complication of long-standing celiac disease that had become refractory to a gluten-free diet [2], some collagenous sprue cases appeared to develop in the absence of underlying and long-standing celiac disease, in other words, a truly unrecognized form or new cause for malabsorption with a distinctive mucosal lesion.

4. Natural History

Indeed, the majority of earlier reports and early clinical experience suggested that the natural history of collagenous sprue was typically characterized by progressive and worsening malabsorption with an inevitably fatal outcome [2]. In most, diarrhea with protein loss and a progressive depletion in weight occurred, sometimes with an associated vasculitis (possibly an early clue that collagenous sprue was a truly heterogeneous entity) [9]. Initially, intense nutritional supplementation with parenteral nutrition was required. However, rare reports (after detailed and extensive biopsy studies) suggested that some responded, at least temporarily, to steroids or treatment with immune suppressive drugs. In one such treatment-responsive case [8], collagen deposits were also noted in the colon suggesting a more extensive, but entirely different clinical and pathological entity. In this setting of treatment success (given decades of clinical experience of treatment failure in many centers), new forms or causes of this complex clinicopathological entity seemed possible. Recent reports of collagenous sprue in patients with malignancies, drug toxicities and immunoglobulin deficiency states also deserve further exploration as these may also reflect the different entities that may precipitate this pathological mucosal response (Table 1).

Table 1. Heterogeneous Causes/Associations of Collagenous Sprue

Celiac disease
Generalized collagenous mucosal inflammatory disease Collagenous gastritis Collagenous colitis
Lymphoid malignancies T-cell enteropathy B-cell lymphoma
Paraneoplastic syndrome with colonic adenocarcinoma
Drug toxicity Non-steroidal anti-inflammatory drugs Angiotensin II receptor antagonist (olmesartan)
Immune disorders Lymphoid hyperplasia with selective IgA deficiency Common variable immunodeficiency

5. Malignancy

Although extensive lymphoma (both B and T-cell types) have been documented to complicate established and

pre-existing collagenous sprue [10,11], a temporal relationship has been difficult to precisely define. However, in a later report [12], a 64-year old female with synchronous onset of collagenous sprue and an enteropathy-type T-cell lymphoma was described leading to the hypothesis that collagenous sprue may be a non-invasive component of the lymphoma, essentially a paraneoplastic process. Interestingly, this paraneoplastic development of collagenous sprue was later recorded in a patient with colon cancer [13]. A 52 year old female developed an illness characterized by profound diarrhea and weight loss. A early stage colonic adenocarcinoma was detected and removed in a rural hospital but earlier extensive studies for a cause of the diarrhea proved to be negative. Subsequent referral and review of earlier biopsies revealed previously unrecognized collagenous sprue (along with collagenous colitis). Interestingly, after the resection, her symptoms completely resolved and repeated biopsy studies of the small and large intestine were normal. The collagen deposition throughout the intestinal tract completely resolved confirming that a true paraneoplastic event had occurred, essentially the pathological changes of collagenous sprue, and then completely resolved after resection of the colon cancer. She remains well over a decade later without any subsequent requirement for medications. The intriguing relationship to her malignancy has not been determined.

6. Drug Toxicity

A number of drugs have been documented to be associated with development of collagenous sprue and resolution after cessation of drug use. Vasant *et al* [14] described a 43 year old female with longstanding use of non-steroidal anti-inflammatory drugs and collagenous sprue followed by complete resolution of symptoms and histological resolution after 6 months of cessation of the drug as well as a gluten free diet. Most dramatic, however, have been numerous reports of collagenous sprue associated with use of olmesartan, an angiotensin II receptor antagonist for treatment of hypertension [15,16,17]. This agent has been shown to be associated with a sprue-like enteropathy that usually resolves with cessation of the drug [18]. Similar findings of a sprue-like enteropathy have been reported with other sartans, including valsartan and telmisartan [19,20] suggesting a possible drug class effect. To date, however, the distinct pathological features of collagenous sprue has only been reported with olmesartan along with improved symptoms and histological resolution after cessation of its use [15,16,17]. These appear to be critically important to recognize since many patients have documented complete remission (including the collagenous lesions) with drug cessation.

7. Others

As noted earlier [1], collagenous sprue may occur alone, or associated with other collagenous inflammatory mucosal disorders, including collagenous gastritis and collagenous colitis. In addition, collagenous sprue has

been associated with nodular lymphoid hyperplasia of the small and large intestine along with selective IgA deficiency [21]. Recently, collagen deposits in the gastrointestinal tract were also described in patients with common variable immunodeficiency [22].

8. Summary

Collagenous sprue has been shown to represent a distinctive small intestinal disorder that may have multiple causes or associations and this may impact the form of treatment. Some of these, particularly malignant disorders and drug-induced forms of collagenous sprue, may be entirely reversible. More importantly, the natural history of this small bowel disease may be dependent on identification of a specific association. Clearly, any patient presenting with an apparently refractory form of sprue, particularly collagenous sprue, should have their medications carefully reviewed.

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