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OBSERVATION

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# Update on collagenous sprue

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## Abstract

Collagenous sprue has traditionally been defined as a small intestinal mucosal disorder characterized by persistent diarrhea, severe malabsorption with multiple nutrient deficiencies and progressive weight loss. Pathologically, a severe to variably severe "flattened" mucosal biopsy lesion with distinctive sub-epithelial deposits in the lamina propria region is detected. Histochemical stains and ultrastructural studies have confirmed that these deposits contain collagens. Often, an initial diagnosis of celiac disease is considered but no continued response to treatment with a gluten-free diet occurs. Recent reports indicate an intimate relationship between collagenous sprue and celiac disease, sometimes with concomitant T-cell enteropathy. In addition, permanent disappearance of these deposits after resection of a localized colon cancer suggested that this disorder could actually represent a paraneoplastic morphologic marker of an occult malignancy. Studies showing either gastric or colonic involvement (or both) with this unusual collagenous inflammatory mucosal process may also reflect a far more extensive and heterogeneous process than previously appreciated.



**Key words:** Collagenous sprue; Celiac disease; Lymphoma; Paraneoplastic disease

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## INTRODUCTION

In 1970, Weinstein *et al*[1] reported on a small intestinal mucosal biopsy lesion from a 51-year-old female initially thought to have celiac disease as histopathological changes included severely flattened villi. However, a long-term response to a gluten-free diet failed to develop. Subsequently, routine hematoxylin-eosin stained biopsies showed a prominent band-like deposit of subepithelial hyaline material in the lamina propria region of the small bowel. The deposit had the histochemical features of collagen and ultrastructural studies confirmed an electron-dense material with the typical 640 A axial periodicity of collagen fibers. Her symptoms transiently improved with corticosteroids, but she then developed worsening diarrhea, severe malabsorption and progressive weight loss. Post-mortem examination showed very extensive pathologic changes in the proximal small intestine with sub-epithelial eosinophilic hyaline deposits of varying thickness. Short segments of normal mucosa were present in the distal small intestine. Two earlier reports by Schein[2] in 1947 and Hourihane[3] in 1963 may have reflected the same biopsy lesions (although in the latter, ileal involvement was also present).

Collagenous sprue was thought to be a "new" form of malabsorptive disorder with the specific clinical and pathological features: (1) persistent diarrhea with panmalabsorption causing nutrient deficiencies and progressive weight loss; (2) a biopsy lesion included a unique

morphologic marker, a sub-epithelial band-like deposit with histochemical and ultrastructural features of collagen; (3) other pathologic changes of untreated celiac disease were present, but not responsive to a gluten-free diet; and (4) diffuse and patchy mucosal changes of variable severity, localized mainly in the proximal small intestine.

## OTHER CAUSES OF SEVERE "FLAT" BIOPSY LESION

Traditionally, the diagnosis of celiac disease (or gluten-sensitive enteropathy) has been established pathologically and depended on two sequential criteria: first, documentation of the typical histopathologic features of untreated disease in small bowel biopsies, and, second, a response to a gluten-free diet. Otherwise, celiac disease, even if present, cannot be diagnosed with certainty. In some cases, a "flattened" biopsy appearance may be present, but a gluten-free diet response has not been documented. This may require months to years[4]. Some investigators have loosely labeled these cases as refractory celiac disease, but this label should be reserved for those who show an initial (and documented) response to a gluten-free diet followed by later development of recurrent symptoms and biopsy changes. The most commonly reported causes for recurrent symptoms and biopsy changes include poor dietary compliance or inadvertent ingestion of a ubiquitous gluten-containing food (e.g. pill capsules, communion wafers). In these cases, removal of the offending gluten should be sufficient to resolve symptoms and biopsy changes. A second or superimposed cause (e.g. infection, folate or zinc deficiency) could also develop. In addition, another entirely separate cause for a "flat" biopsy lesion could be present[5], as the initial true diagnosis (e.g. Crohn's disease in duodenum without mucosal granulomas) may have been missed[6] or an associated or complicating disease (e.g. collagenous colitis, lymphoma) could have developed. In these patients, symptoms and biopsy changes may be improved with specific treatment, but not with a gluten-free diet. Finally, another "wastebasket" group with a "flat" biopsy appearance that has never been responsive to a gluten-free diet may be present, so-called sprue-like intestinal disease or unclassified sprue[7].

## RELATIONSHIP WITH CELIAC DISEASE

Collagenous sprue has a "flat" biopsy appearance, like untreated celiac disease, but fails to show a persistent response to a gluten-free diet. In addition, collagenous sprue is characterized by the appearance of distinctive subepithelial collagen deposits. Some believed that this histopathological change might simply represent a prognostic pathologic marker for a poor outcome in celiac disease[8]. Others, however, viewed collagenous sprue as a new and previously unrecognized small bowel disorder[9]. Later reports have also described further elements between celiac disease and collagenous sprue. Common clinical features include hyposplenism and positive endomysial antibodies that have been documented in both entities[10]. In collagenous sprue, similar complications recorded in celiac disease may also occur, including both T-cell and B-cell lymphomas[11,12].

## NATURAL HISTORY AND LOCALIZATION

Collagen deposits may also be present in the colon (i.e. collagenous colitis) or even stomach (i.e. collagenous gastritis)[13]. An associated inflammatory process in either colonic or gastric mucosa, or both, is also present, usually with epithelial lymphocytosis. Interestingly, collagenous or lymphocytic colitis as well as collagenous or lymphocytic gastritis are all associated with biopsy-defined celiac disease[13-15]. These pathological changes also suggest that a far more extensive pathologic process may occur elsewhere in the gastrointestinal tract with collagenous sprue.

Previously published reports noted that the natural history of collagenous sprue was characterized by worsening malabsorption with an inevitably fatal outcome. In most patients, diarrhea and progressive weight loss occurred, and rarely, severe abdominal pain, sometimes with an associated vasculitis, was recorded[16]. However, more recently, independent reports with extensive biopsy studies have documented complete resolution of the lesion for prolonged periods after corticosteroid treatment[17,18] suggesting that the lesion may be reversed, at least temporarily, for extended periods, even years. Immunosuppressants have also been used in some cases.

## DISEASE HETEROGENEITY

The etiology and pathogenesis of these collagenous deposits are not known, however, different causes could be responsible. In addition to celiac disease, collagenous sprue has not only been complicated with T-cell lymphoma[12], but associated with its co-occurrence[19]. Finally, collagen deposits in both small and large intestines were detected with an apparently coincidental, but localized, colon cancer[20]. Later, clinical and histopathological changes were resolved after the cancer was resected, suggesting that these collagen deposits could represent a paraneoplastic morphologic marker of occult malignant disease.

## FUTURE DIRECTIONS

Recent reports suggest that collagenous sprue may be more heterogeneous than previously appreciated. This has been reflected in frequently associated, but variable collagenous mucosal inflammatory changes elsewhere in the gastrointestinal tract, differential responses to treatment, particularly with steroids, and its association with other conditions, including malignant disease as a possible paraneoplastic morphologic marker.

Treatment of this condition remains an empirical exercise. Steroids and/or immunosuppressant agents have been used, but, to date, this approach has resulted in only rare success.

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