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Collagenous Mucosal Inflammatory Diseases of the Gastrointestinal Tract

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Collagenous mucosal inflammatory diseases involve the columnar-lined gastric and intestinal mucosa and have become recognized increasingly as a significant cause of symptomatic morbidity, particularly in middle-aged and elderly women, especially with watery diarrhea. Still, mechanisms involved in the pathogenesis of this diarrhea remain poorly understood and require further elucidation. The prognosis and long-term outcome of these disorders has been documented only to a limited extent. Recent clinical and pathologic studies have indicated that collagenous mucosal inflammatory disease is a more extensive pathologic process that concomitantly may involve several sites in the gastric and intestinal mucosa. The dominant pathologic lesion is a distinct subepithelial hyaline-like deposit that has histochemical and ultrastructural features of collagen overlying a microscopically defined inflammatory process. An intimate relationship with other autoimmune connective tissue disorders is evident, particularly celiac disease. This is intriguing because these collagenous disorders have not been shown to be gluten dependent. Collagenous mucosal inflammatory disorders may represent a relatively unique but generalized inflammatory response to a multitude of causes, including celiac disease, along with a diverse group of pharmacologic agents. Some recent reports have documented treatment success but histopathologic reversal has been more difficult to substantiate owing to the focal, sometimes extensive nature, of this pathologic process.

Collagenous mucosal inflammatory diseases of the gastrointestinal tract increasingly have become recognized over the past 3 decades as a group of new disorders that involve only columnar-lined mucosa. These were identified first in the small intestine (ie, collagenous sprue), then the colon (ie, collagenous colitis), and, finally, the stomach (ie, collagenous gastritis). Recently, concomitant involvement of different sites within the gastrointestinal tract has been noted. The morphologically dominant lesion in this group of inflammatory disorders is a distinctive subepithelial hyaline-like deposit. This deposit displays both the histochemical and ultrastructural features of collagen. The present review describes the historical background and clinical features of these disorders, examines their etiopathogenesis, including their relationship to other autoimmune disorders such as celiac disease, and evaluates reported treatment options.

Collagenous Sprue (Collagenous Enteritis)

Background and Clinicopathologic Features

In 1970, Weinstein et al[1] described an unusual histologic abnormality in the small intestinal mucosa of a 51-year-old woman initially thought to have celiac disease with refractory malabsorption. The pathologic lesion detected with routine light microscopy consisted of an eosinophilic hyaline material in the lamina propria region of the small bowel. These deposits had the histochemical staining characteristics of collagen, and ultrastructural studies confirmed the presence of an electron-dense material with the characteristic 640 A axial periodicity of collagen fibers. A review of the patient's initial small-bowel biopsy specimens showed some features of celiac disease with flattened villi, but a gluten-free diet response did not occur. Subsequently, her clinical course deteriorated with worsening malabsorption, diarrhea, and weight loss. Corticosteroids transiently provided symptomatic amelioration of the diarrhea. She died within 4 years and detailed post mortem evaluation of the entire length of the small bowel revealed that most of the proximal small bowel was abnormal and completely devoid of villi, but short segments of normal intestine were defined more distally. Eosinophilic hyaline material with varying degrees of thickness was present in abnormal areas. Extensive studies failed to reveal a cause for this disorder, although the investigators suggested that an identical lesion may have been observed earlier by

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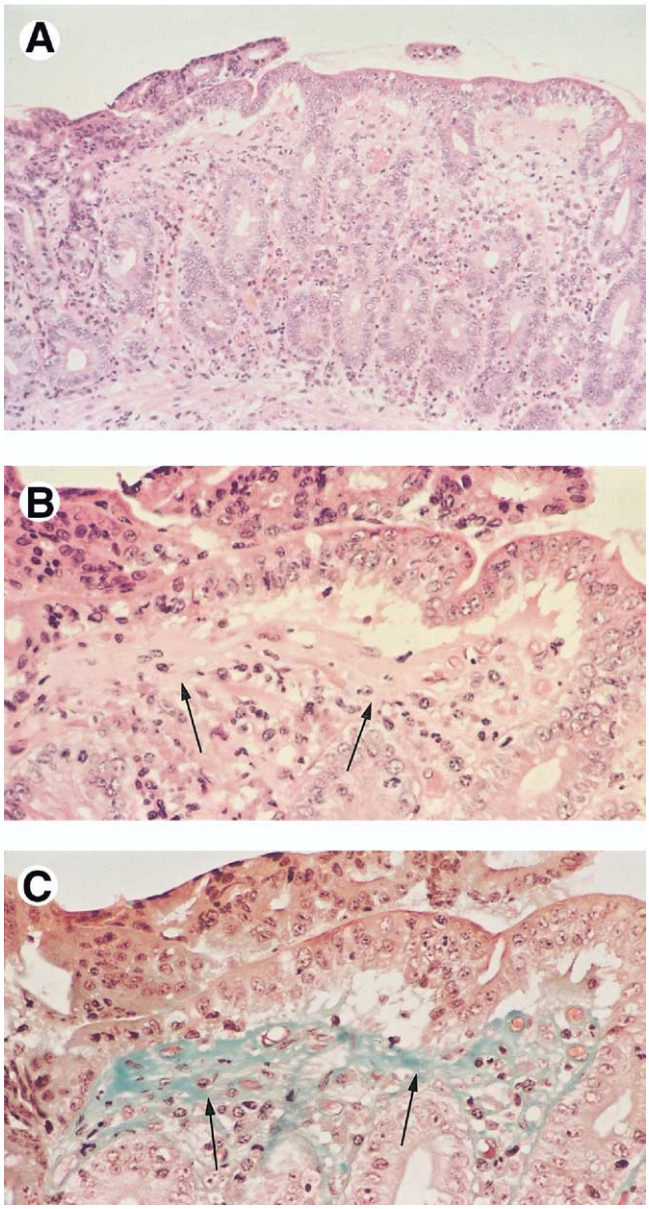

Figure 1. Collagenous sprue. (*A*) H&E-stained section of small bowel from an elderly woman with malabsorption and weight loss showing a moderately severe flat biopsy lesion (ie, crypt hyperplastic villous atrophy). Increased lamina propria lymphocytes and plasma cells are present with epithelial detachment. An eosinophilic subepithelial band–like deposit also is evident. (*B*) High-power view showing this subepithelial deposit with multiple cell types embedded in deposit matrix (*arrows*). (*C*) Adjacent section stained with trichrome, typical of collagen and showing subepithelial deposit (*arrows*).

Schein[2] in 1947 and by Hourihane[3] in 1963. In the latter description, ileal involvement also was present.

Rare reports of this disorder appeared later,[4–15] with similar clinical and pathologic features that included severe and long-standing malabsorption, flattened small intestinal villous architecture, and the distinctive subepithelial collagen deposits (Figure 1). In most cases, diarrhea and progressive weight loss were documented, and, rarely, abdominal pain, sometimes severe, was present occasionally with vasculitis.[1,10] Subepithelial collagen often was patchy or focal in its distribution rather than diffuse, and typically the collagen deposition was associated with variably severe alterations in villous structure. Collagen deposits also were variable in thickness, even in similar small intestinal regions.[1,11] Because the pathologic lesion was so patchy or focal in its distribution and the collagen deposit was so variable in thickness, convincing documentation of a histopathologic response to different treatments was difficult.

Relationship to Celiac Disease

The relationship of collagenous sprue to celiac disease has been controversial. Some initially believed that increased subepithelial collagen might represent only a prognostic histopathologic marker of a poor outcome in celiac disease[16] whereas others viewed collagenous sprue as an entirely new, previously unrecognized, small-bowel disorder that was poorly responsive to a gluten-free diet.[17] This issue still remains incompletely resolved although there are elements of a common or related pathogenesis because both disorders share some clinical, pathologic, and serologic features. For example, hyposplenism and immunoglobulin A antibodies to endomysium may be detected, not only in celiac disease but also in collagenous sprue.[18] Moreover, complications typically associated with celiac disease also occur in collagenous sprue. Atypical immunohistochemical changes with gene rearrangement defined by polymerase chain reaction recorded in refractory celiac sprue (or *sprue-like intestinal disease*) also have been noted in collagenous sprue.[19,20] Finally, malignant lymphoma may be seen during the clinical course of collagenous sprue.[21] As in celiac disease,[22] both T-cell and B-cell types have been recorded in collagenous sprue.[21,23]

Outcome and Treatment

In the past, the natural history of collagenous sprue has been characterized by unremitting malabsorption, usually of multiple nutrients, and an inevitably lethal outcome.[1,4,5,17] However, 2 recent independent reports with extensive biopsy studies[24,25] showed complete disappearance of these abnormal small intestinal collagen deposits after treatment with steroids for periods of up to almost 4 years.[25] Thus, at least in some instances, the lesion may be reversible temporarily for prolonged periods. Alternatively, it also is possible that the collagen deposits have heterogeneous causes, in some instances being steroid responsive.