

# Collagenous sprue

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Collagenous sprue is a small bowel mucosal lesion that has been historically associated with persistent diarrhea, progressive weight loss and severe malabsorption causing multiple nutrient deficiencies. A severe to variably severe mucosal lesion with distinct subepithelial collagen deposits occurs. Celiac disease has been intimately linked to collagenous sprue and, similar to celiac disease, small bowel ulceration, perforation and lymphoma may complicate the clinical course of collagenous sprue. In collagenous sprue, concomitant collagen deposits may also occur in gastric or colonic mucosal sites (or both), indicating that this unusual mucosal process may be very heterogeneous and far more extensive in the intestinal tract than previously appreciated. Moreover, reports of diagnosis during infancy suggest that the natural history of the disorder could be more prolonged than is currently appreciated. Finally, the collagen deposits, per se, may be due to different causes and, in some, even represent a novel paraneoplastic histopathological marker. Future studies are needed to more precisely define molecular and genetic biomarkers that identify homogeneous groups and permit the development of improved treatment strategies for this increasingly recognized disorder.

**Key Words:** *Celiac disease; Collagenous sprue; Malabsorption; Refractory celiac disease; Sprue-like intestinal disease; T cell lymphoma*

In 1970, Weinstein et al (1) described a small bowel biopsy lesion in a middle-age woman initially believed to have celiac disease. Although the typical 'flattened' biopsy appearance of untreated celiac disease was present, a long-term response to a gluten-free diet failed to occur. Later, hematoxylin and eosin-stained biopsies showed a prominent band-like deposit of subepithelial hyaline material with the histochemical features of collagen. Ultrastructural studies confirmed an electron-dense material with the typical 640 Å axial periodicity of collagen fibres. Later, the patient developed worsening diarrhea, severe



**Figure 1)** Endoscopic view of descending duodenum in collagenous sprue showing relatively feature-less mucosa with nonspecific loss of vascular pattern. Slight mucosal scalloping present

## La sprue collagène

La sprue collagène est une lésion muqueuse de l'intestin grêle qui s'associe à une diarrhée persistante, à une perte de poids progressive et à une malabsorption marquée entraînant de multiples carences nutritives. On observe une lésion muqueuse grave à variable accompagnée de collagène sous-épithélial distinct. La maladie cœliaque est intimement liée à la sprue collagène et, à l'instar de cette maladie, des ulcérations, des perforations et des lymphomes de l'intestin grêle peuvent en compliquer l'évolution clinique. En présence de sprue collagène, des dépôts concomitants de collagène peuvent également se déclarer dans des foyers muqueux gastriques ou coliques (ou les deux), ce qui démontre la grande hétérogénéité possible de ce processus muqueux inhabituel et la possibilité qu'il soit beaucoup plus étendu dans le tractus intestinal qu'on le croyait auparavant. De plus, des comptes rendus de diagnostic pendant la première enfance laissent supposer que l'évolution naturelle du problème pourrait être plus prolongée qu'on le croyait jusqu'à maintenant. Enfin, les dépôts mêmes de collagène peuvent être attribuables à diverses causes et, chez certains, représenter un nouveau marqueur histopathologique paranéoplasique. D'autres études s'imposent pour définir avec plus de précision les biomarqueurs moléculaires et génétiques qui permettent de repérer les groupes homogènes et pour élaborer de meilleures stratégies thérapeutiques à l'égard de ce trouble de plus en plus reconnu.

malabsorption and progressive weight loss. Postmortem studies showed extensive pathological changes, particularly in the proximal small bowel. These deposits varied in thickness and short segments of normal mucosa were also seen, especially in the distal small bowel. Reports by Schein (2) in 1947 and Hourihane (3) in 1963 were noted, while others (4) suggested that subepithelial collagen in celiac disease may simply represent a marker of poor prognosis. Subsequently, endoscopic changes have been noted, but are usually nonspecific (Figures 1 and 2), while pathological changes may vary in severity with a patchy distribution (Figure 3).

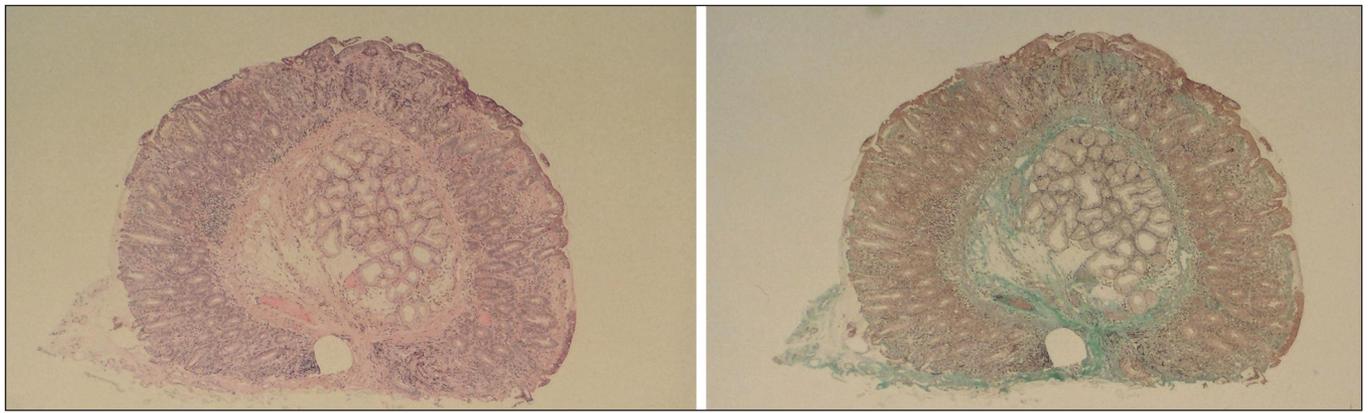


**Figure 2)** Endoscopic view of duodenal bulb in collagenous sprue showing pale mucosal appearance with slight mucosal scalloping. Nonspecific and patchy loss of vascular pattern is evident

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**Figure 3)** Photomicrographs of parallel biopsy sections from a duodenal bulb (note Brunner's glands in the submucosa) in collagenous sprue. The left panel is stained with hematoxylin and eosin, and the right panel is stained with trichrome. Subepithelial hyaline material is evident and also stains with trichrome. The subepithelial deposits are patchy in distribution and vary in thickness, even in the same biopsy. Inflammatory cells are trapped in the deposits, and the surface epithelium is separated in some areas from the underlying deposits. Reproduced with permission from reference 16

The clinical and pathological features of collagenous sprue include the following: first, the presence of persistent diarrhea with panmal-absorption causing multiple nutrient deficiencies and progressive weight loss that fail to respond to a gluten-free diet; and second, detection of a distinct proximal small bowel mucosal lesion with a unique morphological marker, a subepithelial band-like collagen deposit, usually with inflammatory cells 'trapped' in the deposit, along with characteristic 'separated' or sloughed surface epithelial cells.

#### 'REFRACTORY' MUCOSAL DISEASE

Traditionally, celiac disease (or gluten-sensitive enteropathy) has been a pathologically based diagnosis. Two sequential criteria have been historically required: first, typical histopathological changes of untreated celiac disease in proximal small bowel biopsies and, second, a response to a gluten-free diet.

The clinical response may be dramatic, with resolution of diarrhea and significant weight gain. A 'flat' biopsy appearance may completely normalize, but in some patients, the response to a gluten-free diet may be difficult to define or cannot be documented. A histopathological response may require months to years (5), especially in elderly patients (6). Some have labelled these cases as refractory celiac disease; however, this term should be strictly reserved for individuals who show an initial – and documented – response to a gluten-free diet followed by recurrent symptoms and biopsy changes.

In celiac disease that becomes refractory to a gluten-free diet, causes include poor dietary compliance or inadvertent ingestion of a ubiquitous gluten-containing food source (eg, pill capsules and communion wafers). This is very common, and removal of the offending gluten source should be sufficient to resolve symptoms and biopsy changes. In celiac disease, a second or superimposed cause (eg, infection, folate or zinc deficiency) could also occur. Possibly, another entirely independent cause for a 'flat' biopsy lesion could be present (7) because the diagnosis may have been initially erroneous (eg, Crohn's disease in the duodenum without mucosal granulomas) (8). Finally, an associated or complicating illness (eg, collagenous colitis or lymphoma) may develop.

Another important 'wastebasket' group with 'flattened' biopsies may be seen: so-called sprue-like intestinal disease or unclassified sprue (9,10). This is a heterogeneous group that appears to be completely refractory from the outset without evidence of any improvement despite a strict gluten-free diet. It is likely that there are multiple causes. Some have previously unrecognized collagenous sprue with the

distinct pathologically defined collagen deposits. Others may have an autoimmune enteropathic process with positive epithelial cell antibodies (11). Finally, some patients in this group with 'refractory' disease may eventually prove to have an occult or 'cryptic' lymphoma (10).

#### CELIAC DISEASE LINKAGES

Collagenous sprue may share some elements with celiac disease including: hyposplenism and seropositivity with immunoglobulin (Ig)A endomysial antibodies (12). Positive IgA tissue transglutaminase (tTG) antibodies were seen in a report of celiac disease complicated by collagenous sprue (although tTG antibodies actually resolved with a gluten-free diet before detection of collagenous sprue) (13). Finally, recognized complications of celiac disease (13) have been described in collagenous sprue, including small bowel ulceration and free perforation (14) as well as both T cell and B cell lymphomas (15,16). Free perforation, dissection and mucosal 'fracturing' occurs in other collagenous mucosal diseases. In collagenous colitis, this has been described either as a spontaneous colonic perforation with peritonitis (17) or with endoscopic instrumentation (18,19). In collagenous gastritis, similar changes have recently been recorded following air insufflation during endoscopic evaluation (20).

#### HETEROGENEITY OF COLLAGEN LOCALIZATION

If collagen deposits are found in the small bowel, similar deposits may be concomitantly present in colonic (ie, collagenous colitis) and/or gastric mucosa (ie, collagenous gastritis) (21). An inflammatory process with intraepithelial lymphocytosis may also occur in these different sites. Interestingly, collagenous or lymphocytic colitis as well as collagenous or lymphocytic gastritis have all been associated with biopsy-defined celiac disease (22-24). Indeed, collagenous colitis, if detected, should prompt exploration for underlying occult small bowel disease, particularly celiac disease (22). Similar findings have been independently confirmed (25,26) along with a recent report showing these extensive histopathological changes in the accumulated experience by gastrointestinal biopsy pathologists from Europe, North America and Australia (27).

Because a far more extensive pathological process in the gastrointestinal tract may occur in collagenous sprue, detection of collagen deposits in the small bowel should prompt further endoscopic assessment and biopsy elsewhere in the gastrointestinal tract (27).

#### NATURAL HISTORY

Contemporary information is based predominantly on older adults. A recent case report (28), however, served to emphasize that even young infants may be affected before one year of age, implying that the

natural history of this intriguing disorder could hypothetically extend over many decades. Most early case reports suggested that the natural history of collagenous sprue was limited and associated with a dismal prognosis, typically with progressive malabsorption and an inevitably fatal outcome. In most patients, diarrhea and progressive weight loss occur and, rarely, severe abdominal pain, sometimes with associated vasculitis, has been recorded (29). However, more recent and independent reports, with extensive biopsy studies (30,31) have documented clinical resolution and pathological disappearance of the lesion for prolonged periods after corticosteroids or following additional treatment with immunosuppressive agents, suggesting that the lesion may be reversed, at least temporarily, for extended periods, even years. In addition, successful treatment with biological agents, such as infliximab, has been documented (32,33), although reports describing development of lymphoproliferative diseases, particularly T cell type hepatosplenic lymphomas, may temper this treatment approach (34) because this malignancy also occurs in celiac disease (35). Interestingly, recent series (36,37) have reported additional cases with positive clinical outcomes. Collectively, these reports suggest that some patients with these collagen deposits in the small intestine have the potential to clinically and histopathologically resolve. To date, however, no single clinical marker or pathological signature appears to predict which patients might be responsive to treatment.

### DISEASE HETEROGENEITY

The pathogenesis of these collagen deposits is not understood, but different causes could be responsible. In addition to its intimate linkage with celiac disease, collagenous sprue has not only been complicated by T cell lymphoma (15,16), but has been associated with its co-occurrence (38). Finally, collagen deposits in both the small and large intestine

were detected with an apparently coincidental, but localized, colon cancer (39). Later, clinical changes resolved and histopathological changes completely resolved after the cancer was resected, suggesting that these collagen deposits represent a paraneoplastic morphological marker of occult malignant disease. Indeed, collagen deposits in the stomach or intestine could be due to celiac disease, but may also represent a more generalized pathological response to different causes.

Collagenous sprue is a very heterogeneous disorder as reflected in concomitant collagen deposition in gastric and colonic mucosa in some cases, its recognition at different ages from infancy to old age, and its close linkage with celiac disease and recognition with different malignancies.

### FUTURE DIRECTIONS

Recent studies suggest that these collagenous changes may be associated with different disorders, and may be more heterogeneous than previously appreciated as reflected in variable mucosal inflammatory changes with similar deposits elsewhere in the gastrointestinal tract, different responses to treatment and its association with other conditions including malignant disease as a possible paraneoplastic morphological marker.

Unfortunately, treatment remains an empirical and often frustrating clinical exercise. In part, this likely reflects the heterogeneity of the disorder. Its rare occurrence also poses a difficulty for any single physician or centre to accumulate significant treatment expertise. Future investigative endeavours that produce precise molecular and genetic markers are needed to permit definition of homogeneous forms of collagenous sprue that enable more specific avenues of therapy.

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