Selected luminal mucosal complications of adult celiac disease

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

Abstract: Celiac disease is a gluten-dependent intestinal disorder that appears to be associated with several clinical conditions. Some involve the luminal mucosa of the stomach and intestinal tract and may, occasionally, complicate the course of celiac disease. Collagenous colitis has been associated with celiac disease and may lead to chronic diarrhea. Conversely, some of these clinical disorders that involve the luminal mucosa of the stomach and intestine may represent the initial clinical presentation of celiac disease. These disorders should be considered in patients with celiac disease who develop recurrent or refractory symptoms despite adherence to a strict gluten-free diet. Detection of collagenous disorders that affect the luminal mucosa of the stomach or intestinal tract may result in recognition of underlying celiac disease.

Keywords: celiac disease, collagenous gastritis, collagenous sprue, collagenous colitis, gluten-free diet

Adult celiac disease is a chronic gluten-dependent intestinal disorder that is estimated to affect about 0.5% to 1% of the population in Europe and North America, and the disorder is becoming increasingly recognized. Celiac disease in the adult, even in the very elderly, usually presents with chronic diarrhea and weight loss. Some may present without diarrhea, but instead with iron deficiency or altered chemistry values (eg, low serum albumin levels). Alternatively, a closely linked disorder may be evident, such as autoimmune thyroid disease, insulin-dependent diabetes, or dermatitis herpetiformis. Finally, positive screening blood test results (eg, tissue transglutaminase antibodies) may lead to eventual diagnosis of celiac disease. In recent years, fewer patients presenting with diarrhea and more patients presenting with positive serology have been noted.

Diagnosis of celiac disease depends on documentation, prior to treatment, of typical changes in proximal small bowel mucosal biopsies. These have been previously detailed and include: absent or rudimentary villi, increased lamina propria lymphoid cell elements (ie, plasma cells, lymphocytes), increased intra-epithelial lymphocytes and crypt epithelial cell hyperplasia. A second critical step in documentation of celiac disease is definition of an unequivocal clinical and/or pathological response to a gluten-free diet. In adults, resolution of diarrhea, weight gain and normalization of abnormal blood and chemistry values on a gluten-free diet is usually sufficient to provide a convincing clinical diagnosis. However, if limited symptoms were initially evident, then additional biopsies may be needed to show histological improvement. With a gluten-free diet, the mucosa reverts towards normal, although prolonged periods of dietary modification may be needed, particularly in older adults.

Celiac disease causes changes along the length of the small intestine. The extent of this change correlates better with clinical status than the severity of the biopsy changes in the proximal small bowel. In classic disease with malabsorption, severe changes...
may extend well into the jejunum. Less severe mucosal alterations are detected in the ileum, even though the ileal mucosa has been shown to be highly susceptible to gluten (infused through long intestinal tubes). It is possible that this proximal-to-distal gradient in the severity of pathological changes reflects the higher concentrations of dietary gluten (or its derivative peptides) in the proximal small intestine. Alternatively, changes may be indirect, resulting from immune-mediated effects of circulating memory T-cells. With extensive involvement of the small intestine, diarrhea and malabsorption of many nutrients occur. With less involvement, deficits may be limited, and diarrhea or weight loss may not be evident. Moreover, resolution of abnormal histological changes tends to occur initially in the distal small intestine, and later in the more proximal sites.

In celiac disease, other superimposed luminal mucosal disorders may occur in the stomach or the intestinal tract. Usually, most develop with established celiac disease, but these may also represent the presenting clinical feature of celiac disease in the adult. In celiac disease with recurrent or refractory symptoms, a number of possible causes require consideration. Most often, poor compliance or intentional lack of compliance to a gluten-free diet or ingestion of a source of unrecognized gluten are the most common causes. But other associated disorders, including pancreatic exocrine failure, or neoplastic disorders, particularly lymphoproliferative and other intestinal malignancies may be important. Persistent or recurrent symptoms may also be due to other causes, including the collagenous mucosal inflammatory disorders. Some are rarely encountered, and as a group, may have a limited prevalence in some centers, however, increased awareness of these conditions by specialist clinicians may lead to increased recognition in adult celiac disease.

**Collagenous sprue**

In 1970, a 51-yr-old female with apparent celiac disease was recorded with refractory malabsorption. An unusual histological abnormality in the small intestine was described consisting of an eosinophilic sub-epithelial hyaline-like material in the lamina propria. The deposits had histochemical staining characteristics of collagen, and ultra-structural studies confirmed the presence of an electron-dense material with the characteristic 640. A axial periodicity of collagen fibers. Her subsequent clinical course was characterized by worsening malabsorption, diarrhea and weight loss. Steroids caused temporary resolution of her diarrhea. Later reports described severe and long-standing malabsorption with diarrhea and progressive weight loss, flattened small intestinal villous architecture, and these same distinctive sub-epithelial collagen deposits.

A relationship between collagenous sprue and celiac disease was controversial. Some felt that the collagen deposits simply represented a prognostic marker of a poor outcome in celiac disease. Others considered the disorder to be an entirely new, previously unrecognized, entity poorly responsive to a gluten-free diet. Both entities share many common elements. Hyposplenism and positive endomysial antibodies have been detected in both disorders. Moreover, some complications ordinarily associated with celiac disease have been associated with collagenous sprue. Small intestinal ulceration and perforation may develop. Atypical immunohistochemical changes with gene rearrangement defined by polymerase chain reaction reported in refractory sprue (or sprue-like intestinal disease) have been noted in collagenous sprue. Malignant lymphoma may develop during the clinical course of collagenous sprue. As in celiac disease, both T-cell lymphoma and B-cell lymphoma have been recorded in collagenous sprue.

The natural history of collagenous sprue has been characterized by continued malabsorption, usually of multiple nutrients, and a lethal outcome. Some recent reports, however, with extensive biopsy studies have also noted complete disappearance of these abnormal collagen deposits after treatment with steroids for periods of up to almost four years. Thus, the lesion may be reversible, at least temporarily, for prolonged periods. It may also be that the collagen deposits have different causes, in some instances being steroid-responsive. Of note, in a recent report, collagen deposits completely resolved after resection of a localized colon cancer, suggesting a possible paraneoplastic phenomenon, expressed as this histopathologic marker in the intestinal mucosa.

**Collagenous colitis**

In 1976, similar deposits were detected in the colon in patients with a watery diarrhea syndrome. Colorectal biopsies showed lamina propria sub-epithelial hyaline deposits similar to the deposits reported in the small intestine with collagenous sprue. Although the endoscopic appearances were normal or near-normal, a microscopic mucosal inflammatory process was also present with increased lymphocytes and plasma cells. Intra-epithelial lymphocytes were also increased. The hyaline deposits stained positively with trichrome, characteristic of collagen and ultrastructural studies confirmed the presence of collagen fibers.

Later reports from large registries further detailed the clinical features. Most patients were middle-aged or
elderly females, however, collagenous colitis has also been
detected in males and children.24 Diarrhea was usually watery,
nonbloody, and sometimes nocturnal, often with intermittent
abdominal pain and weight loss. Often, the diarrhea was
present for weeks or months, resolving spontaneously for
variable periods of time, then recurring with remissions and
relapses over many years.

The pathogenesis of the diarrhea in collagenous colitis has
been evaluated but still needs to be elucidated. Some func-
tional studies of the small bowel and pancreas were normal.25
Interestingly, however, some early case studies both adult and
childhood celiac disease in collagenous colitis.26–28 Serological
investigations failed to show a linkage with celiac disease29 and
two retrospective studies of small bowel biopsies in collagenous
colitis were contradictory.30,31 However, a long-term prospec-
tive small bowel biopsy study in collagenous colitis docu-
mented celiac disease in over 20% of subjects.32 Recognition
of celiac disease may be important from a therapeutic perspective
because a gluten-free diet may resolve the diarrhea without need
for other pharmacologic treatment. In addition, other autoim-
mune disorders such as thyroiditis may be seen in collagenous
colitis at similar frequencies to that recorded in celiac disease.32
Finally, splenic hypofunction, often seen in celiac disease, has
been recorded in collagenous colitis.33

Some have classified collagenous colitis as a form of
microscopic colitis. In part, this is due to a clinical para-
digm that differentiates this entity from other inflammatory
bowl disease disorders (eg, ulcerative colitis, Crohn’s
disease) with macroscopically visible changes detected
during endoscopic evaluation. Another type of microscopic
colitis is lymphocytic colitis that serves to emphasize the
predominant cell type in cases of watery diarrhea with mac-
roscopically normal mucosa. Some believe that there may
be an hypothetical relationship between lymphocytic colitis
and collagenous colitis, however, the absence of collagen
deposits (in lymphocytic colitis) may simply reflect their
patchy and focal distribution in collagenous colitis. Interest-
ingly, though, increased epithelial lymphocytosis (without
collagen deposits) has been defined in colorectal mucosal
biopsies from patients with celiac disease.34 Bloody diarrhea
is very unusual in collagenous colitis and usually suggests
that another disorder is present and, recently, evolution of
collagenous colitis into severe and extensive ulcerative colitis
has been documented.35

Complications of collagenous colitis may also occur, and
these may be seen in adult celiac disease with concomitant
collagenous colitis. Surface epithelial sloughing is commonly
seen in colonic biopsies leaving a “naked” sub-epithelial
collagen deposit. In some, altered mucosal permeability
has been recorded and protein-losing enteropathy has been
noted in the absence of small intestinal disease.3 Submucosal
“dissection” has been described.36 Colonic fracturing after
endoscopic instrumentation, possibly related to air insuffl a-
tion and barotraumas, or insertion of barium contrast agents,
has been recorded.37 Recently, a report entitled “cat scratch
colon” emphasized the macroscopic changes in the colon in
collagenous colitis.38 Spontaneous peritonitis with colonic
perforation has also been recorded.39 A rarity of malignant
disease has been noted in collagenous colitis, such as colonic
carcinoma.40 Other neoplasms have also been recorded
including lymphoproliferative disorders41 and carcinoids.42

Gastric inflammatory disorders
Although lymphocytic gastritis was originally noted in
patients with celiac disease or sprue-like intestinal disease,43
other chronic gastritis types may occur. In 1989, a form of
chronic gastritis was initially described characterized by
gastric sub-epithelial collagen deposits with a background
inflammatory process.44 The presence of collagen in these
deposits was confirmed using ultrastructural methods and
observed in both adults and children.45 Later, this entity was
noted in celiac disease.46 Some recent studies have shown
concomitant collagen deposits elsewhere in the intestinal
mucosa, suggesting that, in some instances, collagenous
disease may be a far more extensive inflammatory disease
process.47

Conclusion
Diagnosis of celiac disease is usually straightforward, but
occasionally, it may prove to be difficult. Once established,
however, the clinician should be alert to other luminal mucosal
disorders, such as collagenous colitis, that may complicate
the clinical course of celiac disease. Conversely, collagenous
colitis or other specific luminal mucosal disorders may be the
presenting manifestation of underlying celiac disease.

Disclosure
The author reports no conflicts of interest in this work.

References
1. Freeman HJ. Pearls and pitfalls in the diagnosis of adult celiac disease.
2. Lo W, Sano K, Lebwohl B, Diamond B, Green PH. Changing presenta-
   findings in the duodenum of adults with celiac disease before and after
   changing to a gluten-free diet: a 2-year prospective study. Endoscopy.