The Collagenous Gastroenteritides

Similarities and Differences

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Collagenous gastritis, collagenous sprue, and collagenous colitis share striking histologic similarities and occur together in some patients. They also share some drug and disease associations. Pediatric cases of collagenous gastritis, however, lack most of these associations. The etiologies of the collagenous gastroenteritides are not known, so it is not clear whether they are similar because they share pathogeneses, or because they indicate a common histologic response to varying injuries. The features, disease and drug associations, and the inquiries into the pathogenesis of these disorders are reviewed.

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During the past several decades a set of gastrointestinal inflammations have become recognized that are characterized by subsurface collagen deposition and are so histologically similar that common sense would suggest they must be related by etiology or pathogenesis. This set of disorders includes collagenous gastritis, collagenous sprue, and collagenous colitis. A survey of the medical literature reveals associations between these entities in enough patients to support the notion that they must be related. Still, there is enough heterogeneity in the clinical presentations and responses to therapy to thwart attempts to neatly unite the collagenous gastroenteritides into 1 family of diseases. A brief review of what we know about these inflammatory conditions follows a representative case.

REPORT OF A CASE

A 56-year-old previously healthy man presented with complaints of nausea, vomiting, abdominal pain, loss of appetite, and weight loss during the past 6 to 7 months. Biopsies were taken from the esophagus, stomach, and duodenum with endoscopic findings of “esophagitis, gastritis, and duodenitis.”

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RESULTS

Multiple gastric biopsies were taken for microscopic evaluation. Histologic findings included patchy lamina propria inflammation composed of plasma cells, lymphocytes, and eosinophils (Figure 1), patchy surface epithelium lymphocytosis (Figure 2), and deposition of eosinophilic material resembling collagen within the superficial lamina propria (Figure 3). This subsurface deposition was highlighted with Masson trichrome staining (Figure 4). This set of histologic features is typical of collagenous gastritis.

COMMENT

Collagenous Gastritis

Collagenous gastritis is an unusual form of gastritis that was first described in 1989.1 Since then, the literature discussing it has consisted mainly of case reports and small series ranging from 2 to 12 cases.1–6 The histologic features of collagenous gastritis include lamina propria lymphoplasmacytosis with eosinophils, patchy surface lymphocytosis, patchy subepithelial collagen deposition of variable thickness that can be highlighted with Masson trichrome stain (Figure 4), injury and detachment of surface epithelium, and glandular atrophy.

There is a slight female predominance2 and while collagenous gastritis is more common in adults, the ages in reported cases range from 1 to 77 years.3 Clinical symptoms and endoscopic findings of collagenous gastritis differ between the pediatric and adult patient populations. In the pediatric age group, patients typically present in their early teens with iron-deficiency anemia, frequently severe, and thought to arise from the entrapped capillaries in the subepithelial collagen layer exposed by sloughing of the surface epithelium.4,5 Endoscopic nodular, erythematous mucosa is typical of these cases.5 The depressed areas around the nodules most likely correspond to the patchy subsurface collagen deposition that is present histologically.4,5 In pediatric collagenous gastritis, abnormalities are limited to the stomach.5

In contrast to the pediatric cases, adult collagenous gastritis is a heterogenous disease that often has more diffuse involvement of the gastrointestinal tract. Most adult patients with collagenous gastritis present with watery diarrhea, and many patients have associated collagenous colitis, collagenous sprue, and/or celiac disease.6,8 There have been reports of adult patients with collagenous gastritis having associated lymphocytic gastritis, lymphocytic colitis, ulcerative gastritis,5 or an

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underlying autoimmune disease such as Sjögren syndrome. Adult collagenous gastritis has also been seen in patients with concurrent Helicobacter pylori gastritis. Endoscopic findings in adult patients with collagenous gastritis either include mucosal atrophy or show no changes to correspond with the histologic appearance of the biopsies. They do not generally have the nodular endoscopic gastric mucosa of pediatric patients with collagenous gastritis.

Treatment of collagenous gastritis in adult and pediatric populations differs. Successful treatment in adults depends on the presence, if any, of an associated disease. Adult patients with collagenous gastritis and celiac disease may respond to a gluten-free diet, while patients with a concurrent collagenous sprue may have poor response to dietary changes and/or corticosteroids. Adult patients with collagenous gastritis and associated collagenous colitis may respond well to steroids, specifically budesonide. Different therapies have been attempted in the pediatric population, including hypoaergic inetic diets and various drugs, such as ranitidine, sucralfate, misoprostol, and 5-aminosalicylic acid, all with minimal success. Otherwise, there is limited information about the treatment of collagenous gastritis.

Collagenous Sprue

Collagenous sprue is a rare enteropathy that shares some clinical and histologic features with gluten-sensitive enteropathy (celiac disease). Some patients have a history of celiac disease, documented by biopsy and/or serology, before developing collagenous sprue, in which case this development is a marker of poor outcome. Others present with collagenous sprue and have no past or current evidence of celiac disease.

Collagenous sprue often affects middle-aged to elderly females and presents with symptoms of malabsorption including diarrhea, weight loss, and sometimes abdominal pain. Histologic features of collagenous sprue are villous blunting, which can range from total and diffuse to subtotal and patchy, and increased lamina propria cellularity composed of lymphocytes, plasma cells, and occasional eosinophils and neutrophils (Figure 5). The subepithelial collagen deposition is apparent on routine hematoxylin-eosin staining and can be enhanced with histochemical stains for collagen, such as Masson trichrome (Figure 6). Surface epithelial detachment and superficial ulceration is also common. Intraepithelial lymphocytosis is variable and is more frequent in patients with a history of celiac disease. Collagenous sprue, like refractory celiac disease, may have a lamina propria infiltrate composed of monoclonal T cells; however, most of these patients do not develop an overt lymphoma. In addition to its association with collagenous gastritis and celiac disease, collagenous sprue has been seen in patients with collagenous colitis, lymphocytic colitis, lymphocytic gastritis, and ulcerative jejunitis.

The outcome of collagenous sprue is not as dismal as was once believed. While many patients have a progressive downhill course and die from malnutrition or malnutrition-related conditions, nearly half of patients will respond to a combination of a gluten-free diet and immunosuppressive therapy. There can be resolution of the changes seen on biopsy following treatment as well.

Collagenous Colitis

Interestingly, the histologic features of collagenous gastritis and collagenous sprue are similar to those seen in collagenous colitis. Collagenous colitis more commonly affects women older than seventy years and presents with chronic watery diarrhea, with or without abdominal pain, and weight loss. The diagnosis is made by biopsy in this clinical setting. Multiple biopsies are needed, from at least as high as the transverse colon, as the findings may be patchy and may be absent in the descending colon. Endoscopically, the colonic mucosa generally appears normal. The characteristic features on biopsy include a hypercellular lamina propria containing plasma cells.

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Figure 3. The subsurface collagen deposition in collagenous gastritis is patchy and usually visible without special stains (hematoxylin-eosin, original magnification \( \times 100 \)).

Figure 4. A special stain for collagen, such as this Masson trichrome stain, highlights the subsurface collagen deposition in collagenous gastritis (original magnification \( \times 100 \)).

Figure 5. In this case of collagenous sprue, the flat surface, lamina propria lymphoplasmacytosis, detached surface epithelium, and subsurface collagen are evident (hematoxylin-eosin, original magnification \( \times 200 \)).

Figure 6. The collagen deposition in this case of collagenous sprue extends deep into the lamina propria (Masson trichrome, original magnification \( \times 100 \)).

Figure 7. In collagenous colitis, the architecture is normal but the lamina propria is hypercellular, with surface lymphocytosis, and a band of subsurface collagen may be obvious on routine stains (hematoxylin-eosin, original magnification \( \times 100 \)).

Figure 8. Some cases of collagenous colitis have subtler amounts of subsurface collagen that is only appreciated with a special stain for collagen (Masson trichrome, original magnification \( \times 100 \)).
lymphocytes, and eosinophils; normal crypt architecture; and patchy surface lymphocytosis. There is also detachment of the surface epithelium and patchy increased deposition of subepithelial collagen, which is often appreciated on routine staining with hematoxylin-eosin (Figure 7). Special stains for collagen, such as Masson trichrome, are sometimes required to highlight the increase in subepithelial collagen (Figure 8).

Collagenous colitis has been associated with multiple medications as well as autoimmune disorders such as thyroid diseases, rheumatoid and psoriatic arthritis, systemic lupus erythematosus, and Sjögren syndrome. Associated gastrointestinal diseases include celiac disease (20%), lymphocytic colitis, collagenous sprue, and lymphocytic gastritis.

Collagenous colitis has a variable clinical course. Most patients (85%) have chronic, but intermittent symptoms, while others (13%) have chronic, continuous symptoms. A few patients (2%) have a single episode that resolves. Because of the variability in clinical symptoms, it is difficult to gauge the efficacy of treatments. The best treatment results for collagenous colitis have been found with budesonide, a glucocorticoid with good mucosal activity, but little systemic activity, owing to extensive first-pass metabolism. Less effective have been treatments with bismuth, salicylates, prednisolone, mesalamine, cholestyramine, and antibiotics. Finally, some patients with collagenous colitis have proven bile acid malabsorption, possibly related to inflammation of the small bowel, and respond to bile acid–binding resin therapy; however, this is not common.

Collagenous gastritis, sprue, and colitis share similar histologic features, are associated with each other in some cases, and are also associated with other gastrointestinal and extragastrointestinal diseases in adults. However, not much is known regarding the pathogenesis of these entities, or whether their pathogeneses are related. Theories regarding the pathogenesis of collagenous gastritis and collagenous sprue suggest that the evolution of these diseases is similar to that of collagenous colitis, but there are few data to support or refute this.

The pathogenesis of collagenous colitis has been studied most extensively of all the collagenous gastroenteritides, although the exact mechanism of its pathogenesis is still unknown. Studies have focused on several different areas including extracellular matrix production and degradation, nitric oxide production, drugs, and bacterial toxins. An earlier hypothesis describes the subepithelial collagen deposition in collagenous colitis as replacement of plasma proteins that have seeped through blood vessel walls into the superficial lamina propria in the absence of inflammation, and relates this to the entrapped capillaries in the subepithelial collagen. Others describe an association between pericryptal myofibroblasts and subepithelial collagen deposition. A number of studies support the conclusion that there is an imbalance in extracellular matrix production and degradation that leads to an accumulation of collagens I, III, IV, and VI and tenasin in the lamina propria. This could be carried out by decreased activity of matrix metalloproteinases, which play an important role in collagen degradation, and/or increase in tissue inhibitor of matrix metalloproteinase (TIMP-1). Also, an increase in expression of transforming growth factor β, vascular endothelial growth factor, and basic fibroblast growth factor, which promotes angiogenesis, increased leakage of plasma proteins, and decreased fibrinolysis, have been shown. Activation of eosinophils and neutrophils may also be involved. At this point, despite clues to the cause of the collagen deposition, the fundamental cause(s) of collagenous colitis is (are) not known.

Although some drugs have been associated with collagenous colitis, the mechanism by which they may cause colitis is not known. Nonsteroidal anti-inflammatory drugs, usually used for greater than 5 years, are among the most common drugs associated with collagenous colitis. Other drugs that have been implicated are selective serotonin reuptake inhibitors, bisphosphonates, simvastatin, lansoprazole, omeprazole, cimetidine, and ticlopidine. A few individual case studies have reported bacterial toxins that injure colonic mucosa and lead to inflammation and collagen deposition; however, these are anecdotal reports.

The etiology of the diarrhea in collagenous colitis is also not well understood. Upregulation of nitric oxide synthase activity may lead to increased production of nitric oxide in colonic mucosa, which may lead or contribute to the diarrhea experienced by patients with collagenous colitis. The diarrhea is secretory and has components of sodium chloride absorption and active chloride secretion. The severity of diarrhea in collagenous colitis correlates with the inflammation and not the thickness of the collagen deposits. The collagen deposition seems to be a cofactor, but not the sole cause of diarrhea in patients with collagenous colitis.

**SUMMARY**

The collagenous gastroenteritides are a group of inflammations that have similar histologic features, but little is known regarding their relationships with each other. The clinical settings and associations are often similar in adults, who may have combinations of collagenous gastritis, collagenous colitis, and celiac disease. Collagenous sprue differs from the others, with half of patients developing a progressive malabsorption that may lead to death. In the pediatric population, the same associations do not seem to occur. Children with collagenous gastritis present with blood loss, rather than diarrhea or malabsorption. Pediatric collagenous gastritis is not usually associated with other collagenous or lymphocytic gastroenteritides.

The exact pathogenesis of the collagenous gastroenteritides is not known, and there may be several different causes for each that result in a set of histologic changes that are essentially identical. At this time, treatment is similar for the adult collagenous gastroenteritides in that if the diagnosis is made, it is important to determine whether there is underlying celiac disease because these patients can be successfully treated with a gluten-free diet. Adult patients with collagenous gastritis without an associated disease may have a limited clinical course and are most likely to benefit from immunosuppressive therapies.

**References**


