Microscopic Colitis: Collagenous Colitis and Lymphocytic Colitis

Collagenous colitis and lymphocytic colitis are chronic relapsing diarrheal illnesses, which are often referred to together as microscopic colitis. It most commonly occurs in women in their fifth to sixth decade. The symptoms usually include profuse watery diarrhea and crampy abdominal pain. Laboratory and endoscopic studies are generally normal but microscopic inflammation is seen when colonic biopsies are performed. In collagenous colitis there is a subepithelial collagen band in addition to chronic inflammation in the lamina propria. The etiology is not known but multiple theories exist including autoimmune, infectious, and medication-induced. Although the course is generally benign, patients may have multiple relapses over many years. Treatment regimens vary and have included anti-diarrheals, antibiotics, 5-aminosalicylates, steroids, and immunosuppressive agents.

INTRODUCTION

Collagenous colitis (CC) (Figure 1) and lymphocytic colitis (LC) (Figure 2) are uncommon chronic relapsing diarrheal illnesses. The majority of patients are women in their fifth to sixth decade who complain of profuse, watery diarrhea, and crampy abdominal pain. Both conditions have normal mucosa when viewed endoscopically, however biopsy specimens show chronic mucosal inflammation. In CC there is a subepithelial collagen band of varying thickness in association with an inflammatory cell infiltrate in the lamina propria (1). The collagen band is absent in LC (2,3). The term microscopic colitis (MC) was originally used to describe patients with chronic diarrhea and normal endoscopic and barium enema studies, but who had evidence of mucosal inflammation when examined microscopically (4). This term is sometimes used interchangeably with collagenous and

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lymphocytic colitis, and sometimes used as an umbrella term for all forms of microscopic inflammation in the colon. In this review the term MC will be used to describe either collagenous colitis and/or lymphocytic colitis.

**EPIDEMIOLOGY**

Microscopic colitis can present in any age group but the majority of patients are in their fifth to sixth decade. While CC has a strong female predominance, with women accounting for 85%–90% of cases, LC has a roughly equal distribution between males and females (2,5). The incidence of CC has been reported as 1.0/10^5 in France (6), 1.8/10^5, in Sweden (7), and 1.1/10^5 in Spain (8). The prevalence of CC in Sweden is 15.7/10^5 (7). LC has been reported to have an incidence of 3.1/10^5 in Spain (8).

**CLINICAL FEATURES**

The most prominent feature of MC is diarrhea. In most patients it is described as profuse and watery, with up to ten bowel movements a day. Abdominal pain, cramping, fecal urgency, and nocturnal stools may also be associated. The onset is generally insidious but may be abrupt in up to 40% of cases (9). Neither bloody stools nor steatorrhea is usually seen, and dehydration is not a common complication. Weight loss has been associated with MC (9) but, if present, may suggest a more serious condition. The physical examination is unrevealing in the majority of patients as are routine laboratory tests, stool studies, radiology, and endoscopy (Table 1). Autoantibodies and increased serum IgM have been noted in some patients but the significance is not clear (10–12).
Table 1
Diagnosis

Symptoms
- Watery diarrhea
- Crampy abdominal pain

Laboratory
- Normal

Endoscopy
- Normal

Mucosal biopsy
- Chronic inflammatory infiltrate
- Thickened subepithelial collagen layer (collagenous colitis)

ASSOCIATED CONDITIONS

Microscopic colitis has been associated with other enteropathies and autoimmune diseases. Celiac disease has been associated with both CC and LC, with reports of LC patients having a 15%–27% incidence of celiac disease (13–15). There have been reports of CC associated with Crohn’s disease (16) as well as CC progressing to ulcerative colitis (17,18). There has also been a case reported of synchronous CC and pseudomembranous colitis (19). Although there is no clear autoimmune etiology of MC, it has been found in association with many autoimmune and rheumatologic diseases such as rheumatoid arthritis (20), systemic and discoid lupus erythematosus (21,22), spondyloarthritis (23), CRST syndrome (24), diabetes mellitus, pernicious anemia, Sjogren’s syndrome, autoimmune thyroid disease, linear IgA dermatosis (25), and primary biliary cirrhosis (26). Collagenous gastritis has been described in association with CC, suggesting a diffuse intestinal tract disorder (27). The relative risk of colorectal malignancy does not appear to be increased in these patients (28).

DIAGNOSIS

In a patient with the appropriate clinical history and unremarkable physical exam and laboratory studies, a flexible sigmoidoscopy or colonoscopy with biopsy is necessary to make the diagnosis. The endoscopic examination is in most cases grossly normal, but random mucosal biopsies will show evidence of microscopic chronic inflammation.

HISTOLOGY

Both LC and CC have evidence of chronic inflammatory cell deposition in the lamina propria (generally 20 lymphocytes per 100 surface epithelial cells is used for diagnosis (3)). Neutrophils, plasma cells, and eosinophils are seen less commonly (1). In CC there is an eosinophilic staining subepithelial band of collagen, which measures between 7 and 100 microns in thickness. The band thickness varies from each area of the colon and is an average of 9 microns (29). The superficial collagen layer has been shown to stain strongly for collagen types I, III, and VI, as well as the glycoprotein tenascin, which is involved in matrix remodeling (30). A labile imbalance between fibrogenesis and fibrolysis has been proposed as the mechanism that induces collagen band formation (31). Biopsies should be done from both the proximal and distal colon in order to most accurately classify the disorder because the collagen layer is generally less thick in the distal colon (5). Immunostaining of mucosal biopsies for tenascin and type VI collagen has recently been proposed as a sensitive and specific method for determining the presence of CC, especially in indefinite cases (32). The sensitivity of this method may allow for the diagnosis to be made from biopsies of the rectum and sigmoid colon, avoiding colonoscopy in some patients.

PATHOGENESIS

Multiple theories for the etiology of microscopic colitis exist: environmental, infectious, and autoimmune. No nutritional component or medication has been directly linked to the disorder, but NSAID use has been suggested to play an etiological role, with some patients’ symptoms improving after the withdrawal of the medication (33). There have been reports of CC associated with lansoprazole (34), and cimetidine (35), and reports of LC associated with ticlodipine (36–38), ranitidine

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Helicobacter pylori

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Table 1
Proposed Etiologies
- Environmental (medications, dietary)
- Bacterial toxins
- Autoimmune

(39), and acarbose (40). Fecal stream diversion surgery has been shown to induce histological remission with clinical and histologic recurrence after ostomy closure (41), suggesting that noxious luminal material may play a role. Bile salt malabsorption has also been postulated to play a role in pathogenesis (42). Others have raised the question of bacterial endotoxins as a cause of MC, with the toxin-binding resin cholestyramine shown to improve symptoms (43). A toxigenic strain of Bacteroides fragilis has been associated with MC (44), and there have been reports of CC associated with Clostridium difficile (19,45) infection. A small series reported collagenous colitis diagnosed after Yersinia enterocolitica infection (46), and a case of lymphocytic colitis was attributed to Campylobacter jejuni infection in one patient (47), raising the question of a post-infectious response causing MC. Additionally, treatment of Helicobacter pylori has been associated with improvement in CC (48) (Table 2).

Some authors have suggested an immune-mediated mechanism due to the high incidence of autoantibodies in these patients (2). Although there are associations with many autoimmune diseases as noted above, no clear autoimmune etiology has been postulated or proven.

The mechanism of diarrhea in patients with MC is not entirely clear. One hypothesis has been that the collagen band in collagenous colitis is responsible for the symptoms, but some believe that the collagen is a mere consequence of mucosal inflammation (49) and not the causative abnormality. In addition, the symptoms are similar between LC and CC, and there is no collagen band to alter mucosal permeability in LC. Eosinophil activation has been noted to be increased in the mucosa of patients with collagenous colitis (50), and has been suggested to be related to altered mucosal permeability (51). Increased numbers of mucosal mast cells and clinical response to an H1 antagonist was noted in one patient suggesting a role for this mechanism in the production of diarrhea (52). It is possible that bacterial toxins induce an altered host inflammatory cell response in some patients leading to diarrhea.

TREATMENT

A variety of therapeutic agents have been used in patients with microscopic colitis. Most regimens are supported by case-reports or small, uncontrolled series only. A recent double-blind placebo-controlled trial of 9 mg of oral budesonide versus placebo in 24 patients with CC showed both clinical and histological short-term response (53) with budesonide. This study, however, used a different formulation of budesonide than that currently available in the United States. An open label trial of bismuth subsalicylate in 13 patients with microscopic colitis showed it to be safe and efficacious (54). Case series or case reports have noted the successful use of many other agents. Antidiarrheals and verapamil have been used to control symptoms in some cases (55,56), and bismuth subsalicylate has been shown to have a prolonged response in some (54,57). The 5-aminosalicylates, sulphasalazine, and cholestyramine have been shown to be useful in some patients with more severe symptoms (9,58,59). Some patients may respond to variable courses of steroids (9,58), and the immunomodulatory drugs methotrexate and 6-mercaptopurine have been used with some success in patients who have refractory symptoms or who are steroid dependent (60–63) (Table 3).

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A SPECIAL ARTICLE

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SUMMARY

Microscopic colitis is a term that is often used to encompass the two similar disorders, lymphocytic colitis and collagenous colitis. Both disorders are characterized by chronic, relapsing watery diarrhea. The diagnosis is made in patients with the appropriate clinical presentation, who have normal radiographic, laboratory, and endoscopic findings, but have evidence of microscopic inflammation on colonic biopsy. Although many theories as to its cause exist, no etiology is currently known. Many treatments ranging from antiarrheals to immunosuppressants have shown efficacy, but controlled trials are lacking. The course of microscopic colitis is benign in the vast majority of cases.

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