Microscopic Colitis

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Microscopic colitis has 2 main subtypes, collagenous colitis and lymphocytic colitis, that are similar clinically and histologically and are distinguished mainly by the presence or absence of a thickened subepithelial collagen band. Microscopic colitis accounts for approximately 10% of chronic watery diarrhea and may be associated with abdominal pain and mild weight loss. It is typically diagnosed in the sixth to eighth decade of life, and there is a female predominance that is more striking for collagenous colitis than for lymphocytic colitis. Endoscopic and radiographic findings of the colon appear normal. Diagnosis is made by colonic biopsy, which shows an intraepithelial lymphocytosis and a mixed inflammatory infiltrate in the lamina propria. Many potential treatments have been reported, but few have been subjected to controlled treatment trials. A stepwise approach to therapy often leads to satisfactory control of symptoms. *Mayo Clin Proc.* 2003;78:614-617

The term microscopic colitis was first used in 1980 to describe a group of patients with chronic diarrhea, normal findings on endoscopy and barium enema, and inflammation on colonic biopsy. Collagenous colitis, described in 1976, has similar clinical and histological features but is also characterized by a thickened subepithelial collagen band. It is unclear whether these conditions are distinct or are part of the spectrum of one disease. In fact, a review of some early cases of “microscopic colitis” showed that many of these patients had collagenous colitis. Furthermore, there are reports of patients diagnosed as having one type of colitis that was changed to the other over time or patients for whom there is a “mixed” histology. Thus, current nomenclature uses microscopic colitis as an umbrella term with 2 major subsets: collagenous colitis (with chronic mucosal inflammation and a thickened subepithelial collagen band) and lymphocytic colitis (with inflammation but no collagen thickening).

EPIDEMIOLOGY

In Europe, collagenous and lymphocytic colitis each have an incidence of 1 to 3 cases per 100,000 people per year and a prevalence of 10 to 16 cases per 100,000 people. In elderly women, the incidence may be as high as 20 cases per 100,000 people. No epidemiological data are available from North America.

In referral centers, microscopic colitis accounts for about 10% of patients examined for chronic diarrhea, and the number of patients with lymphocytic and collagenous colitis is similar. Microscopic colitis typically presents in the sixth to eighth decade of life, although a wide age range has been reported. A female predominance has been described, particularly for collagenous colitis, which has a female-to-male ratio as high as 20:1. The female predominance in lymphocytic colitis is less striking. There is a report of familial occurrence of microscopic colitis, but it is unclear whether a true familial predisposition exists.

CLINICAL FEATURES AND COURSE

The characteristic symptom in microscopic colitis is chronic or intermittent watery diarrhea, which can include nocturnal stools. Many patients have abdominal pain or weight loss (typically mild), whereas nausea and fecal incontinence are seen in only a minority. Fecal leukocytes may be present, but high fever, vomiting, or hematochezia should suggest another diagnosis. Steatorrhea may be seen but also should suggest another diagnosis, such as concomitant celiac sprue. Unlike chronic ulcerative colitis, chronic microscopic colitis does not appear to be associated with an increased risk of colon cancer.

Arthralgias and various autoimmune conditions occur commonly in patients with microscopic colitis. In addition, an elevated erythrocyte sedimentation rate and various autoimmune markers, including positive antinuclear antibodies, have been reported in some patients.

Of note is the association between microscopic colitis and celiac sprue. Up to one third of patients with celiac sprue have findings suggestive of microscopic colitis on colonic biopsy, whereas 2% to 10% of patients with microscopic colitis have small bowel mucosal changes consistent with celiac sprue. Serologic tests for celiac sprue can be positive in up to 17% of patients with microscopic colitis. Thus, celiac sprue should be considered in patients with...
microscopic colitis, particularly those whose conditions are refractory to standard therapies. In this group, small bowel biopsies would be appropriate.

**DIAGNOSIS**

In patients with microscopic colitis, findings on endoscopic and radiographic evaluation of the colon should be normal or have mild nonspecific changes such as erythema or edema. Therefore, a diagnosis of microscopic colitis depends on a colonic mucosal biopsy, the most distinctive feature of which is an intraepithelial lymphocytosis with more than 10 lymphocytes per 100 epithelial cells. In addition, the biopsy reveals a mixed inflammatory infiltrate in the lamina propria and often surface epithelial damage. Detachment of the epithelium may be seen, despite the normal endoscopic appearance of the mucosa. In collagenous colitis, the subepithelial collagen band is abnormally thickened, often with an irregular inferior edge and with entrapped erythrocytes and inflammatory cells. However, the changes of microscopic colitis are nonspecific, with similar histological findings occasionally reported in various other conditions and in patients without diarrhea.

Biopsy findings from the descending colon should be reasonably accurate; thus, flexible sigmoidoscopy is sufficient to diagnose microscopic colitis in most patients. If left-sided colonic biopsy findings are normal, but clinical suspicion is high, a colonoscopy with proximal biopsies can be considered; however, left-sided biopsies probably miss fewer than 5% of cases.

**PATHOPHYSIOLOGY**

There are many reports on potential pathophysiological mechanisms in microscopic colitis. Several hypotheses exist, ranging from immune dysregulation/autoimmunity to drug effect to infection. However, these data typically come from small studies that often give conflicting results; thus, it is difficult to draw firm conclusions on pathophysiology. Perhaps the clinicopathologic term *microscopic colitis* encompasses several different diseases or pathophysiological mechanisms with a similar histological expression. The proposed mechanisms have been reviewed in detail recently and are not discussed further here.

**TREATMENT**

Extremely few treatment trials of patients with microscopic colitis have been published; only bismuth subsalicylate and budesonide have been used in placebo-controlled studies. Thus, therapy is directed primarily by anecdotal reports and case series. Nonsteroidal anti-inflammatory drugs (NSAIDs) may play a pathophysiological role in microscopic colitis; if possible, NSAIDs and other agents that might exacerbate diarrhea (eg, dairy products, excess caffeine or alcohol) should be discontinued. Antidiarrheal therapy with loperamide hydrochloride or diphenoxylate hydrochloride/atropine can be extremely effective, and these drugs are often the first therapy chosen, particularly for mild to moderate diarrhea. If these agents are unsuccessful, bismuth subsalicylate at a dosage of 8 tablets (262 mg each) per day taken in 3 or 4 divided doses is beneficial in many patients.

If the patient’s diarrhea does not respond to bismuth, the next therapeutic intervention considered is often mesalamine or sulfasalazine, although 2 large retrospective series have reported benefit in less than half the patients treated. Cholestyramine may be more effective, although many patients cannot tolerate its texture.

Patients with microscopic colitis refractory to the previously described medications may respond to corticosteroids; however, before corticosteroids are used, alternative diagnoses such as coexistent celiac sprue or infection should be excluded if not done so previously. Budesonide, a synthetic corticosteroid with low systemic bioavailability and less risk of adverse effects, was reported to be superior to placebo in several trials in patients with collagenous colitis. Because of the proven efficacy of budesonide, at least in collagenous colitis, it would be reasonable to consider this agent if a patient does not respond to antidiarrheal medications or bismuth subsalicylate, rather than considering mesalamine or cholestyramine. Other corticosteroids also appear to be extremely effective for microscopic colitis. However, relapse rates after corticosteroid discontinuation are high, and patients may become corticosteroid dependent. For patients with microscopic colitis refractory to corticosteroids or for patients who are corticosteroid dependent, immune modifiers such as azathioprine or 6-mercaptopurine can be used, although clinical experience with these drugs is limited.

Other treatments of potential benefit include octreotide, methotrexate, cyclosporine, and antibiotics. Rarely, surgery is necessary for medically refractory disease. The response rates to various medications from 2 large series are listed in Table 1.

Most patients experience a waxing-and-waning course with microscopic colitis, and spontaneous or treatment-induced resolution has been reported. For example, patients treated with bismuth subsalicylate for 8 weeks have entered remissions lasting longer than 2 years. Thus, when an agent is found that controls the diarrhea, the drug may be discontinued after 6 to 8 weeks. Most patients will respond to this treatment, but the optimal duration of therapy is unclear. For patients who have an early recurrence of symptoms, maintenance therapy can be used.
Table 1. Response to Medications for Microscopic Colitis*

<table>
<thead>
<tr>
<th>Study</th>
<th>Pardi et al,*</th>
<th>Bohr et al,†</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>lymphocytic colitis</td>
<td>colligenous colitis</td>
</tr>
<tr>
<td>No. of patients treated</td>
<td>74</td>
<td>69</td>
</tr>
<tr>
<td>Patient response (%)</td>
<td>73</td>
<td>71</td>
</tr>
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<td></td>
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<tr>
<td>Antidiarrheal agents</td>
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<td>69</td>
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<tr>
<td>Bismuth</td>
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<td>NA</td>
</tr>
<tr>
<td>Sulfasalazine</td>
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<td>108</td>
</tr>
<tr>
<td>Mesalamine</td>
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<td>16</td>
</tr>
<tr>
<td>All 5-ASA</td>
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<td>139</td>
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<tr>
<td>Cholestyramine</td>
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<td>44</td>
</tr>
<tr>
<td>Corticosteroids</td>
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<td>41</td>
</tr>
<tr>
<td>Azathioprine/6-MP</td>
<td>5</td>
<td>NA</td>
</tr>
</tbody>
</table>

*ASA = aminosalicylates; 6-MP = 6-mercaptopurine; NA = not applicable.
†Patient response includes complete and partial responders. Response percentages are determined by clinical experience and are not the results of controlled trials; therefore, results for different drugs are not directly comparable.

**SUMMARY**

Microscopic colitis is a major cause of chronic diarrhea. Colonic biopsies are required to make a diagnosis and should be performed in all patients undergoing flexible sigmoidoscopy or colonoscopy for unexplained diarrhea. The 2 subtypes of microscopic colitis, colligenous colitis and lymphocytic colitis, are similar histologically and clinically and may represent variants of the same disease. Although there are few controlled treatment trials, the approach outlined in this article often gives satisfactory control of diarrhea in these patients.

**REFERENCES**


**Questions About Microscopic Colitis**

1. Which one of the following statements regarding the epidemiology of microscopic colitis is **false**?
   a. Microscopic colitis accounts for most otherwise unexplained chronic diarrhea in adults
   b. Microscopic colitis is most common in the sixth to eighth decade of life
   c. Microscopic colitis is more common in women than in men
   d. Microscopic colitis may be associated with NSAID use
   e. Collagenous colitis is about as common as lymphocytic colitis

2. Which one of the following statements regarding the diagnosis of microscopic colitis is **correct**?
   a. Collagenous colitis is distinguished from lymphocytic colitis by a thickened subepithelial collagen band instead of mucosal inflammation
   b. Thickening of the subepithelial collagen band is specific for collagenous colitis and should not be seen in other conditions or in subjects without diarrhea
   c. Sigmoidoscopic biopsies are usually sufficient to diagnose microscopic colitis
   d. Accurate diagnosis of microscopic colitis requires biopsies from the left and right colon
   e. Fecal leukocytes should not be seen in patients with microscopic colitis
3. Which one of the following statements regarding the clinical features of microscopic colitis is true?
   a. Abdominal pain is unusual
   b. Weight loss is unusual
   c. Fever is common
   d. Patients who have microscopic colitis for longer than 10 years have an increased risk of colon cancer
   e. In patients with microscopic colitis who do not respond to antidiarrheal medications and bismuth subsalicylate, celiac sprue should be considered

4. Which one of the following statements regarding the treatment of microscopic colitis is correct?
   a. Microscopic colitis can resolve spontaneously
   b. Bismuth subsalicylate is corticosteroid sparing in severe microscopic colitis
   c. For mild microscopic colitis, the anti-inflammatory properties of NSAIDs may be sufficient to control diarrhea
   d. Mesalamine is beneficial in most patients with microscopic colitis
   e. Currently there are no controlled data in favor of corticosteroid use in microscopic colitis

5. Which one of the following statements regarding microscopic colitis is true?
   a. Microscopic colitis is more common in the United States than in Europe
   b. The endoscopic changes in severely active microscopic colitis can mimic ulcerative colitis
   c. Patients with microscopic colitis often have alternating diarrhea and constipation
   d. Most patients with microscopic colitis respond to nonspecific antidiarrheal medications (eg, loperamide, diphenoxylate)
   e. First-degree relatives of a patient with microscopic colitis have a 3-fold increased risk of getting the disease

Correct answers: 1. a, 2. c, 3. e, 4. a, 5. d