CONCISE REVIEW

Microscopic Colitis: A Concise Review for Clinicians

June Tome, MD; Amrit K. Kamboj, MD; and Darrell S. Pardi, MD, MS

Abstract

Microscopic colitis (MC) is an inflammatory disease of the colon and a common cause of chronic watery diarrhea, predominantly in older patients. Microscopic colitis encompasses 2 different subtypes, lymphocytic colitis and collagenous colitis. The colon typically appears normal endoscopically in MC, and the diagnosis requires histologic evaluation. Whereas recent studies suggest that the incidence of MC has plateaued, given the aging of the population, the prevalence of MC will likely increase. Risk factors for MC include increasing age; female sex; presence of other autoimmune diseases; and possibly use of certain medications, including proton pump inhibitors, nonsteroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, and statins. The clinical presentation of MC is nonspecific and includes watery nonbloody diarrhea, nocturnal stools, fecal urgency, abdominal pain, arthralgias, and weight loss. The disease course of MC is variable; some patients experience occasional, intermittent symptoms, and others demonstrate more chronic and even progressive symptoms. The approach to treatment is similar for both lymphocytic colitis and collagenous colitis and should be guided by the severity of the patient’s symptoms. Offending medications...
highly associated with MC should be eliminated as clinically possible. In patients with mild symptoms, antidiarrheals such as loperamide are the initial choice; for moderate-severe disease, budesonide is recommended for induction of clinical remission. In those with recurrent symptoms, low-dose budesonide may be required for maintenance therapy with close monitoring for potential adverse effects. In rare cases, immunomodulators may be required.

Microscopic colitis (MC) is an inflammatory disease of the colon and a common cause of chronic watery diarrhea, especially in older patients. The colon appears normal endoscopically in MC, and the diagnosis requires histologic evaluation. Microscopic colitis encompasses 2 different subtypes, namely, lymphocytic colitis (LC) and collagenous colitis (CC). The 2 subtypes have characteristic histologic features including intraepithelial lymphocytosis with dense inflammatory infiltrate in the lamina propria, with (CC) or without (LC) expansion of the subepithelial collagen band. The clinical presentation of MC is nonspecific and includes chronic or intermittent watery nonbloody diarrhea, often with nocturnal stools, fecal urgency, abdominal pain, arthralgias, and weight loss. The severity of symptoms is variable, and in severe cases, electrolyte derangements and dehydration may also be present. In addition, MC has a variable disease course; some patients experience occasional, intermittent symptoms, and others demonstrate more chronic and even progressive symptoms. Moreover, some patients achieve spontaneous remission, whereas others can require long-term maintenance therapy.

Epidemiology and Risk Factors
Population-based studies from North America and Europe had reported increasing incidence of MC in the late 20th century. However, more recent data suggest a plateau in MC incidence rates. The estimated incidence of MC ranges between 1 and 25 per 100,000 person-years. A systematic review and meta-analysis demonstrated a pooled incidence of 4.14 per 100,000 persons for CC and 4.85 per 100,000 persons for LC, although updated data from Olmsted County, Minnesota, indicated significantly higher rates (9.9 and 15.8 per 100,000, respectively). In that systematic review, the prevalence was estimated to be 49.2 cases per 100,000 person-years for CC and 63.1 cases per 100,000 person-years for LC, whereas in Olmsted County, it was much higher at 100 and 146 cases per 100,000, respectively.

Risk factors for MC (Table 1) include increasing age; female sex; presence of other autoimmune diseases; and possibly use of certain medications, including proton pump inhibitors (PPIs), nonsteroidal anti-inflammatory drugs (NSAIDs), statins, and selective serotonin reuptake inhibitors (SSRIs). Smoking has been associated with an increased frequency of watery stools in MC as well as with an increased risk of persistent disease with a lower probability of achieving clinical remission. In a French multicenter prospective study, MC was associated with age older than 50 years (odds ratio [OR], 3.1; 95% CI, 1.6 to 5.9), autoimmune diseases (OR, 5.5; 95% CI, 2.5 to 12.0), and new offending medications (OR, 3.7; 95% CI, 2.1 to 6.6). Patients with celiac disease (CD) have a 50 to 70 times greater risk of MC, although in patients with MC, the presence of CD ranges from 2% to 9%. Thus, clinicians should consider the possibility of MC in patients with CD who have persistent diarrhea despite adherence to a gluten-free diet. In contrast, not every patient with MC needs to be tested for CD unless the individual fails to respond to appropriate therapies for MC.

Pathophysiology
Although the pathophysiologic process of MC is not currently well understood, there are several proposed mechanisms. These include autoimmunity, genetic predisposition, an immune or inflammatory response to luminal antigens, certain medications, abnormal collagen metabolism, and several
others. These proposed models, however, are based on studies with relatively small sample sizes with often inconsistent results.

As previously described, MC is associated with other autoimmune diseases, such as hypothyroidism or hyperthyroidism, CD, rheumatoid arthritis, and type 1 diabetes mellitus. The female predominance of MC, a characteristic of many autoimmune disorders, is further suggestive of an autoimmune component. However, there are no current serologic antibody tests that are sensitive or specific for MC. Studies have supported a possible genetic predisposition of MC with infrequent familial cases of MC as well as an association with certain human leukocyte antigen haplotypes. More recently, MC has been associated with potential polymorphisms in the serotonin transporter gene promoter and other immunologic pathways.

Another proposed mechanism for the development of MC is the body’s response to a luminal antigen, including dietary antigens, bile salts, various medications, and infectious antigens such as bacterial toxins. Microscopic colitis is more common in patients with CD, and histologic changes resembling LC can be seen in patients with CD who consume gluten. Similarly, in patients with bile acid malabsorption, histologic changes resembling LC can be observed. As such, bile acid sequestrants may play a role in a subset of patients with MC. Last, infectious antigens may play a role as patients with MC have alterations in the fecal microbiome and have been reported to respond to antibiotic therapy. Nonetheless, no causative organism has been definitively linked to MC.

Medications such as PPIs, NSAIDs, statins, SSRIs, and histamine H₂ receptor antagonists have been implicated in MC. A British case-control study of more than 1200 patients with MC demonstrated an increased risk of disease in patients with current exposure to medications such as NSAIDs, PPIs, or SSRIs in addition to prolonged use for 4 to 12 months. However, a recent multicenter study from the United States showed an inverse association with some of these medications in comparison to a control group with chronic diarrhea. Therefore, it is possible that these drugs do not actually cause MC but rather worsen diarrhea and bring the diagnosis to attention. Despite reports of improvement in patients’ symptoms after discontinuation of offending drugs, there is a paucity of literature regarding drug rechallenges in MC. However, when drug-induced MC is suspected, the causative medication should be discontinued if possible as this may lead to symptom response.

Other postulated pathophysiologic mechanisms for CC include abnormal collagen deposition due to a primary abnormality of collagen synthesis vs a normal or exaggerated reparative response to chronic inflammation. Mediators of fibrosis including vascular endothelial growth factor, transforming growth factor β, and fibroblast growth factor are often up-regulated in CC. Despite this association with abnormal collagen metabolism, the severity of diarrhea in MC has been more strongly correlated

<table>
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<th>TABLE 1. Risk Factors for and Associations With Microscopic Colitis</th>
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<td>Risk factors</td>
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<tr>
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<td>Autoimmune diseases</td>
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Varying degrees of association between medications and microscopic colitis have been reported in prior studies.
with the degree of inflammatory infiltrate compared with the thickness of collagen deposition.\textsuperscript{16}

However, pathophysiologic studies in MC are typically small and often demonstrate conflicting results between studies, making it difficult for definite conclusions to be drawn about the different postulated mechanisms.\textsuperscript{12}

**DIAGNOSIS**

Microscopic colitis should be considered in middle-aged to older patients with chronic watery diarrhea. The risk factors and associated conditions are discussed earlier. In evaluating patients for MC, the differential diagnosis includes other causes of chronic diarrhea, such as infections (ie, *Clostridium difficile*), CD, inflammatory bowel disease (IBD), and irritable bowel syndrome. These conditions can be differentiated from MC by a combination of patient history, laboratory studies, and endoscopic evaluation with biopsy (Table 2). A careful history should include recent travel to endemic areas; recent antibiotic exposure; family history of autoimmune diseases, such as IBD or CD; presence of bloody diarrhea; and relationship of abdominal pain and bowel movements. Physical examination findings are usually nonspecific and unlikely to further aid in refining the differential diagnosis in most cases. Extraintestinal manifestations, such as fatigue and arthralgias, can occur in both MC and IBD, although skin findings of pyoderma gangrenosum or erythema nodosum would support a diagnosis of IBD, and dermatitis herpetiformis can be seen in those with CD. Stool culture specimens and microscopy for ova and parasites can be obtained to further evaluate for infectious causes. Laboratory studies, such as anti–tissue transglutaminase antibody and complete blood count with inflammatory markers, may be helpful in evaluating for CD and IBD, respectively. Upper endoscopy and colonoscopy with biopsy can further differentiate MC, IBD, and CD on the basis of histopathologic findings.

The diagnosis of MC requires biopsy of the colonic mucosa and histopathologic assessment. In MC, the colon typically appears normal endoscopically, although erythema or edema may sometimes be present. Laboratory test results, such as for fecal leukocytes, are nonspecific, although some studies suggest using fecal calprotectin to monitor disease activity.\textsuperscript{17} The presence of colonic ulceration is highly suggestive of an alternative cause, such as IBD, ischemia, or NSAID-induced changes. On histologic evaluation, the hallmark of MC is intraepithelial lymphocytosis. It is currently unknown whether LC and CC represent 2 distinct entities or whether they are a single disorder. There are reports demonstrating findings of both LC and CC on biopsy specimens from a single individual at 1 time, in addition to patients transitioning from 1 MC subtype to another over time.\textsuperscript{18} At present, both LC and CC are considered to be along the same spectrum of disease and approached similarly. There is no current international consensus on the optimal location in the colon from which to obtain biopsy specimens. In general, a colonoscopy with random biopsy samples throughout the colon is preferred. However, if a patient had a recent colonoscopy (ie, for colon cancer screening), flexible sigmoidoscopy with random biopsy samples above the rectum could be considered.\textsuperscript{12}

Lymphocytic colitis is defined by more than 20 intraepithelial lymphocytes per 100 surface epithelial cells (normal, <5; Figure 1A). Both acute and chronic inflammatory cells, including lymphocytes, neutrophils, eosinophils, and mast cells, are found in the lamina propria. Collagenous colitis is defined by the presence of a subepithelial collagen band that is typically greater than 7 to 10 μm (normal, <5 μm; Figure 1B). In CC, a chronic inflammatory cell infiltrate is also found in the lamina propria; the intraepithelial lymphocytosis is often less prominent than in LC and may not always be present. There is a subset of patients who do not meet these histologic criteria. These patients may be diagnosed with “microscopic colitis, not otherwise specified” or “microscopic colitis, incomplete.” Additional research is needed to further clarify the
clinical utility of these expanded histologic definitions and whether they accurately represent a form of MC.

**MANAGEMENT**

The first step in managing patients with MC is to evaluate for factors that may exacerbate diarrhea, such as dietary components (lactose, artificial sweeteners), and medications associated with diarrhea or MC. Although modification of these factors can lead to symptom improvement, most patients with MC will require drug treatment to achieve complete remission. Studies suggest that the 2 subtypes of MC respond similarly to medical therapies.

In general, treatment should be guided by the severity of the patient’s symptoms. In patients with mild symptoms, antidiarrheals such as loperamide may be sufficient to control diarrhea. Loperamide can easily be obtained over the counter, and the dose is titrated to effect (maximum, 16 mg daily). For patients with mild-moderate symptoms refractory to antidiarrheal medications, bismuth subsalicylate (three 262-mg tablets 3 times daily for 6 to 8 weeks) may be used. Long-term use of high-dose bismuth subsalicylate, however, is not recommended because of a potential risk of neurotoxic effects. In patients who do not respond to bismuth and those with more severe disease, an 8-week course of budesonide (9 mg daily) is recommended for induction of clinical remission (Figure 2). Budesonide is preferred to the use of other medications, such as mesalamine, especially for severe disease, although bile acid sequestrants, such

<p>| TABLE 2. Differential Diagnosis in Considering Microscopic Colitis |
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<th><strong>Differential diagnosis</strong></th>
<th><strong>Diagnostic features</strong></th>
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<td>Microscopic colitis</td>
<td>Watery diarrhea with intraepithelial lymphocytosis (lymphocytic colitis) or thickened subepithelial collagen band (collagenous colitis)</td>
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<tr>
<td>Infection (ie, <em>Clostridium difficile</em>)</td>
<td>Watery diarrhea and detection of toxin by polymerase chain reaction or positive reaction on stool studies</td>
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<tr>
<td>Celiac disease</td>
<td>Steatorrhea with positive celiac serologic test results and duodenal biopsy specimen demonstrating crypt hyperplasia with villous atrophy</td>
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<tr>
<td>Inflammatory bowel disease</td>
<td>Bloody diarrhea with colonoscopy demonstrating friability, erosions, edema, and crypt abscesses (ulcerative colitis) or skip lesions, cobblestone mucosa, transmural inflammation, and noncaseating granulomas (Crohn disease) Biopsy specimens should demonstrate chronic colitis (both ulcerative colitis and Crohn disease)</td>
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<td>Irritable bowel syndrome</td>
<td>Normal physical examination findings, laboratory values, and colonoscopy with biopsy</td>
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**FIGURE 1.** A, Biopsy specimen demonstrating lymphocytic colitis with intraepithelial lymphocytosis. B, Biopsy specimen demonstrating collagenous colitis with a thickened subepithelial collagen band. (A and B courtesy of Catherine Hagen, MD, Department of Pathology, Mayo Clinic, Rochester, Minnesota.)
as cholestyramine (starting at 4 g daily and titrating to 4 g 4 times daily as needed), may be an effective noncorticosteroid strategy that has shown some efficacy.21

The American Gastroenterological Association guidelines recommend budesonide as first-line therapy for induction of clinical remission in MC on the basis of several randomized, placebo-controlled studies.19 Compared with placebo, budesonide was greater than 3 times more effective in achieving both short- and long-term clinical response.22 A Cochrane systematic review reported a pooled OR of 12.32 (95% CI, 5.53 to 27.46) compared with placebo to induce symptom response in CC during 6 months, with a number needed to treat of 2.23 Budesonide also increases quality of life in MC. It is preferred to other corticosteroids, such as prednisone, given its high first-pass metabolism with fewer systemic adverse effects. However, after discontinuation of budesonide, relapse is common, ranging from 40% to 81% in various studies, and many patients ultimately require long-term maintenance.23,24

Older age, longer duration of symptoms, and high stool frequency on presentation are risk factors for relapse after the discontinuation of budesonide. For patients who do not respond to (or tolerate) long-term budesonide, immunosuppressant medications such as thiopurines, methotrexate, and biologic agents (tumor necrosis factor α inhibitors or vedolizumab) can be considered,23 although studies on the use of these therapies in MC are limited. In those with persistent or refractory symptoms, clinicians often use low-dose budesonide (no more than 6 mg per day, although many patients can maintain symptomatic response with 3 mg per day or every other day) for maintenance therapy. In those requiring long-term budesonide use, the lowest possible dose should be used, and patients should be monitored for potential adverse effects, such as metabolic bone disease, hypertension, and hyperglycemia. Patients receiving long-term budesonide may also need to be monitored for ophthalmologic disorders including glaucoma and cataracts. Although budesonide has fewer corticosteroid-related adverse effects compared with other corticosteroid formulations, data on its safety long term in MC are limited.

Unlike for other IBDs such as ulcerative colitis, there does not appear to be an increased risk of MC and colon adenocarcinoma. Some studies have even demonstrated a decreased risk for development of colonic adenomas compared with patients with chronic diarrhea without MC.26

SUMMARY AND FUTURE DIRECTIONS

Microscopic colitis should be considered in patients with chronic watery diarrhea, especially in the presence of certain clinical features, such as older age, female sex, presence of other autoimmune conditions, and use of certain associated medications. Whereas recent studies suggest that the incidence of MC has plateaued, given the aging population, the prevalence of MC will likely increase. Careful evaluation of exacerbating factors is essential in MC management, and budesonide is the recommended first-line therapy for moderate-severe symptoms. Given the high risk of relapse, maintenance therapy is often required. Ongoing research is needed to investigate the overlapping phenotypes of LC and CC, to validate the role of fecal inflammatory markers in the
monitoring of MC, and to explore the long-term safety outcomes with budesonide. Further research is also needed to evaluate the role of immunomodulators and newer biologic agents, including infliximab, vedolizumab, and ustekinumab, as treatment options for patients with refractory disease.

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Histopathology images courtesy of Catherine Hagen, MD, Department of Pathology, Mayo Clinic, Rochester, Minnesota.

Abbreviations and Acronyms: CC = collagenous colitis; CD = celiac disease; IBD = inflammatory bowel disease; LC = lymphocytic colitis; MC = microscopic colitis; NSAID = nonsteroidal anti-inflammatory drug; OR = odds ratio; PPI = proton pump inhibitor; SSRI = selective serotonin reuptake inhibitor

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Correspondence: Address to Darrell S. Pardi, MD, MS, Division of Gastroenterology and Hepatology, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (pardi.darrell@mayo.edu; Twitter: @DarrellPardi).

ORCID
June Tome: https://orcid.org/0000-0001-9914-1695

REFERENCES