Microscopic colitis is a chronic inflammatory bowel disease characterized by chronic nonbloody diarrhea and specific histopathology features. Active disease, defined as 3 or more stools or 1 or more watery stools per day, significantly reduces quality of life. Epidemiologic studies have found the incidence and prevalence of microscopic colitis to be comparable with those of Crohn’s disease and ulcerative colitis. Nevertheless, microscopic colitis is still under-recognized in clinical practice—most health care workers know little about its etiology and pathophysiology. Furthermore, there are many challenges to the diagnosis and treatment of patients. We review the epidemiologic and clinical features of this disorder and discuss its pathogenesis. We also outline the criteria for histopathologic evaluation of microscopic colitis, recently published by the European Consensus on Inflammatory Bowel Disease, and discuss a treatment algorithm created by the European Microscopic Colitis Group. Treatment options for patients with budesonide-refractory disease are discussed.

Keywords: Colon; EMCG; Immune Response; Therapy.

During the past decade, microscopic colitis (MC) has emerged as a common cause of chronic nonbloody diarrhea, especially in the elderly population. Up to 10% to 20% of patients with chronic diarrhea are diagnosed with MC. A normal or nearly normal endoscopic picture is typically seen and only histology can confirm the diagnosis, differentiating between its major subtypes: collagenous colitis (CC) or lymphocytic colitis (LC). Affected individuals present with frequent loose or watery stools, leading to urgency and, ultimately, fecal incontinence. Abdominal pain and weight loss are common. Hence, patients with active MC have a severely deteriorated quality of life (QoL). The only drug that has been tested in multiple randomized controlled trials (RCT) and that fulfills the criteria of evidence-based medicine is budesonide. This drug is highly effective and achieves clinical remission in approximately 80% of patients. However, symptom relapse occurs in 60% to 80% of patients after withdrawal of treatment, necessitating a discussion regarding maintenance therapy in patients with an active chronic course.

The cause of MC is unknown, but it is believed that a luminal agent triggers an uncontrolled immunologic response in the mucosa of genetically predisposed individuals. On a scientific level, MC has not received the same attention as other inflammatory bowel diseases (IBDs) (ie, ulcerative colitis and Crohn’s disease). Therefore, knowledge of MC among physicians as well as pathologists is limited.

Epidemiology

Epidemiologic studies have been performed mainly in Europe, North America, and Canada. However, reports on cases and smaller cohorts from Africa, Asia, Latin America, and Australia have indicated that MC is a worldwide disease. The most comprehensive population-based studies have been performed in Olmsted County, Minnesota, and in Örebro, Sweden. Since 1984, continuous epidemiologic follow-up evaluation in both centers has shown a parallel trend with an initial increase in incidence that has stabilized during the last decade (Figure 1). Overall, the annual incidence rates are between 2.6 and 10.8 per 105 inhabitants for CC and between 2.2 and 14 per 105 inhabitants for LC. The prevalence of MC was 219 of 105 cases in Olmsted County (in 2010) and 123 of 105 cases in Örebro (in 2008). These figures show that MC is nearly as common as classic IBD (ie, Crohn’s disease and ulcerative colitis). Consistent in all studies is a strong female predominance that is less pronounced in LC than in CC. Typically, MC is a disease of the elderly, with an average age at diagnosis of approximately 65 years. However, younger patients with chronic diarrhea also should be evaluated for the disease because 25% of MC patients are younger than age 45. MC in childhood is a rare phenomenon, but some cases reports have been published.

Clinical Presentation

Regarding symptoms and clinical presentation, LC and CC are not distinguishable from each other. The key clinical feature is chronic nonbloody diarrhea, which is
MC commonly is associated with other autoimmune diseases. In a recent Swedish multicenter study, autoimmune disorders occurred in a third of patients, most commonly celiac disease (12%), autoimmune thyroid disease (10.3%), but also Sjögren’s syndrome (3.4%), diabetes mellitus (1.7%), as well as skin and joint diseases (6.0%). In most cases, the diagnosis of associated autoimmune disease preceded that of MC. Notably, patients had an earlier onset of colitis and more severe gastrointestinal symptoms.

The relative risk of overall malignancy and overall mortality in CC is not different compared with the general population despite an increased risk of lung cancer in women, which may be related to smoking habits.

**Histopathology**

MC remains a histologic diagnosis, but only in patients with chronic diarrhea. This clinical information always should be provided to the pathologist. A recent large retrospective analysis showed that history of diarrhea per se does not identify patients at higher risk of abnormal histology, but those older than age 60 had a markedly increased likelihood of a specific histologic abnormality, and MC was the most common diagnosis. Histology is necessary not only to make the diagnosis, differentiating between the 2 major subtypes (ie, LC and CC), but also to rule out other causes of chronic diarrhea. On endoscopic evaluation, the mucosa of the colon is almost always normal, but occasionally may show subtle changes, such as edema, erythema, altered vascular pattern, or even mucosal defects.

In MC, the morphologic findings may be patchy and not continuous. A systematic analysis of patients with CC from 2 large prospective multicenter trials showed that a collagenous band more than 10 μm in thickness was more common in the right colon (with the highest levels in the cecum and ascending colon), and less frequent in the sigmoid and rectum, whereas the mononuclear inflammation in the lamina propria was found to be distributed evenly among the different segments of the large bowel. It is recommended to take multiple biopsy specimens throughout the whole colon because biopsy specimens obtained only from the rectum or from the rectum and sigmoid colon may miss 41% or 21% of cases, respectively. The biopsy specimens should be submitted, preferably, in separate containers.

**Lymphocytic Colitis**

The predominant histologic feature of LC is intraepithelial lymphocytosis (ie, an increased number of surface intraepithelial lymphocytes [IELs] with little or no crypt architectural distortion) (Figure 2). Most investigators refer to a cut-off value of 20 or more IELs per 100 surface epithelial cells (normal, <5), but some investigators refer to 15 or more IELs. Aiming at
standardization of the histologic diagnosis, the cut-off value of 20 or more IELs recently was recommended in the European Consensus on the Histopathology of Inflammatory Bowel Disease, which was published on behalf of the European Society of Pathology and the European Crohn’s and Colitis Organisation. The terminal ileum may be affected in LC (and also CC) with a mean villous IEL count greater than 5.

On sections stained with H&E, IELs are characterized by mostly round, compact nuclei with a dense chromatin pattern, slightly irregular nuclear outline, and perinuclear halo. The surface epithelium may show degenerative changes of the surface epithelium (Figure 3). High-power view of IELs. Note the degenerative changes of the surface epithelium (original magnification: 250×).

Collagenous Colitis

The predominant histologic feature of CC is a thickened collagen band underneath the surface epithelium. The band is most evident between the crypts. It has an irregular jagged appearance at the deeper border. It may contain entrapped capillaries, red blood cells, and inflammatory cells. Damage to the surface epithelium usually is pronounced and is more common than in LC, with sloughing of surface epithelial cells from subepithelial collagen being a characteristic finding (Figure 3). An increased number of IELs is seen, but not to the same amount as in LC. Similar to LC, the cellularity in the lamina propria is increased by a predominantly mononuclear inflammatory infiltrate, and IBD-like features, such as active crypt inflammation with occasional crypt abscess formation, may occur (Table 1). According to the European Consensus on the Histopathology of Inflammatory Bowel Disease, the thickness of the collagen band should exceed 10 µm (normal, <3 µm) on well-oriented biopsy specimens (ie, biopsy specimens cut perpendicular to the mucosal surface). In most cases, the diagnosis can be established on the basis of H&E-stained slides without problems. In borderline cases, additional stains, such as Masson trichrome or immunohistochemistry with antibodies directed against tenascin, which is not present in normal adult mucosa and is synthesized by subepithelial myofibroblasts (indicative of matrix remodeling), may be helpful.

Variants and Differential Diagnosis

Different variant forms have been reported under separate names for patients who have clinical features of MC but fall short of fulfilling the morphologic criteria of LC or CC. In these cases, histology shows an increased inflammatory infiltrate in the lamina propria and an abnormal collagenous band less than 10 µm or an increased number of IELs less than 20 per 100 epithelial

Table 1. Histologic Key Features of Different Forms of MC

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<th>LC</th>
<th>CC</th>
<th>MCI or MCnos</th>
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<tbody>
<tr>
<td>IELs</td>
<td>&gt;20 IELs</td>
<td>Normal to slightly increased</td>
<td>5–20 IELs</td>
</tr>
<tr>
<td>Subepithelial collagen layer</td>
<td>Normal to slightly thickened</td>
<td>&gt;10 µm</td>
<td>5–10 µm</td>
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<tr>
<td>Surface epithelium damage</td>
<td>+</td>
<td>++</td>
<td>(+)</td>
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<tr>
<td>Lamina propria inflammation</td>
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MCI, microscopic colitis incomplete; MCnos, microscopic colitis not otherwise specified.
cells. The following terms, which reflect variations in histology, but not clinical differences, have been suggested: borderline LC, MC incomplete, MC not otherwise specified, or paucicellular LC. The histology of these atypical forms of MC cannot be discussed here in detail and we refer to the review by Chang et al for further information. These histologic categories are still somewhat controversial and not universally accepted. In addition, it may be difficult to separate these milder forms from irritable bowel syndrome.

**Pathophysiology**

The etiology and pathophysiology of MC is not well understood but is likely to be multifactorial, involving mucosal immune responses to luminal factors in a genetically predisposed individual. This theory is best supported by observations made in patients undergoing surgery with ileostomy. In these patients, fecal stream diversion leads to regression of intestinal inflammation and mucosal barrier dysfunction and, in turn, reconstruction of bowel continuity leads to reappearance of the classic histologic features of MC. The following section is a selection of relevant results of mainly small observational studies describing different factors and mediators that might be involved in the pathogenesis of MC. However, it still largely is unclear which of these findings have true pathogenic relevance.

**Genetics**

Familial occurrence of MC has been reported, but the exact role of genetic factors remains to be defined. HLA studies have shown an association of MC with HLA-DQ2 or DQ1/3 and a higher frequency of HLA-DR3DQ2 haplotype and TNF2 allele carriage compared with controls. Furthermore, allelic variation of the matrix metalloproteinase-9 gene does appear to be associated with CC. In contrast to Crohn’s disease, functional polymorphism in the nucleotide-binding oligomerization domain-containing protein 2 and caspase recruitment domain-containing protein 15 (NOD2/CARD15) gene has not been detected.

**Epithelial Barrier Function**

Another factor may be a defect in mucosal barrier function, leading to increased transmucosal permeability of antigens and bacteria, thereby promoting intestinal inflammation. In vitro experiments on colonic biopsy specimens showed significant mucosal barrier dysfunction in CC patients in clinical remission, which was aggravated in active disease presenting with increased transmucosal uptake of nonpathogenic bacteria. Mucosal barrier dysfunction persisted despite short-term, clinically effective treatment with budesonide. Tagkalidis et al observed reduced E-cadherin and zona occludens 1 expression (induced by interferon [IFN]γ) in CC, which is indicative of altered epithelial barrier function. Burget et al noted reduced expression of the tight junction proteins occludin and claudin 4. Their findings...
correlated with reduced epithelial resistance, indicating increased paracellular permeability.

**Mechanism of Diarrhea**

By using an Ussing chamber technique, Burgel et al. described the mechanism of diarrhea in CC as a consequence of reduced Na⁺ and Cl⁻ absorption accompanied by active Cl⁻ secretion. The clinical observation that fasting can reduce diarrhea indicates an osmotic component, making it likely that watery stools in MC are driven by a combination of osmotic and secretory components.

Because MC can present with abdominal pain, urgency, and fecal incontinence, the question arises whether MC patients have normal anal-rectal function. In a small study, patients with active CC had normal anal function and rectal compliance. Furthermore, there were no signs of visceral hypersensitivity.

**Immunology**

CD8⁺ T lymphocytes predominate in both the epithelium and the lamina propria with increased proportions of Ki67⁺ and CD45RO⁺ CD8⁺ mucosal T cells. CD4⁺ T lymphocytes are comparably rare in the lamina propria.

MC shows a Th1 mucosal cytokine profile with IFNγ as the predominantly increased cytokine in CC, tumor necrosis factor α (TNF-α) in LC, and increased mucosal messenger RNA levels of interleukin (IL)8 and IL15. More recent immunologic studies showed a mixed Th17/Tc17 and Th1/Tc1 mucosal cytokine profile. Mucosal messenger RNA levels of IFNγ, IL12, IL17A, IL21, and IL22 were up-regulated significantly compared with controls, and these correlated with higher clinical activity. Significantly enhanced IL21 and TNF-α protein levels were noted in both CC and LC.

**Risk Factors**

**Drugs**

Drug intake has been suggested to act as an environmental risk factor in causing or triggering MC. Beaugerie and Pardi proposed a scoring system with varying grades of certainty, and drugs with a high likelihood to cause MC were acarbose, aspirin, cyclo3 fort, lansoprazole, nonsteroidal anti-inflammatory drugs, ranitidine, sertraline, and ticlopidine. In a recently published systematic review, nonsteroidal anti-inflammatory drugs and proton pump inhibitors were identified as the 2 drugs with the highest likelihood to cause MC, but the investigators stressed that confirmation of drug-induced MC is still lacking. Most of the drugs that have been associated with MC are known to have diarrhea as a side effect. Hence, higher use of colonoscopy plus biopsies in patients with drug-induced diarrhea may simply increase the frequency of MC diagnoses, rather than these medications being a causative or triggering factor in MC development. Therefore, considering a drug to cause MC should include clinical improvement, but also disappearance of histologic findings after withdrawal and recurrence after rechallenge.

**Smoking**

Studies on smoking habits in MC patients have indicated that smoking is an equal risk factor for MC for men and women and that smokers develop the disease earlier than nonsmokers (by a median of 14 years). This risk is most prominent in current smokers (adjusted odds ratio, 5.36; 95% confidence interval, 2.63–11.13 for CC, and adjusted odds ratio, 3.81; 95% confidence interval, 1.92–7.12 for LC).

**Treatment**

The primary aim of therapy is to achieve clinical remission and to improve the patient’s QoL. Whether or not histologic remission is an important goal is currently unknown. Before embarking on medical therapy, the possibility of drug-induced MC always should be taken into account, and the patient’s medication should be reviewed carefully for drugs with high likelihood to cause MC. Discontinuation of such drugs, if possible, may lead to resolution of symptoms. Smoking cessation can be considered but the evidence for this is still weak. It is advisable that patients register their bowel movements in a diary before initiation and during follow-up treatment.

The strongest treatment evidence is currently available for budesonide, a locally active corticosteroid with extensive first-pass metabolism in the liver and low systemic exposure. In a meta-analysis, budesonide was effective, with response rates greater than 80%, and was well tolerated for inducing and maintaining remission with a “number needed to treat” of 2 for CC and 3 for LC. More recently, 2 larger RCTs have confirmed the good efficacy of budesonide induction therapy in active CC with significant improvement of QoL. Two additional RCTs of CC showed that clinical remission and histologic response can be maintained with budesonide 6 mg/d for 6 months. However, 6 mg/d might be too high in the long run and bears the risk of developing side effects such as a skin hematoma, cataract, or increased serum blood sugar level. After withholding short-term budesonide treatment or maintenance therapy (6 mg), relapse rates are high (60%–80%).

Currently, there are no evidence-based alternatives to budesonide. Antidiarrheals such as loperamide are used frequently in MC, although they have never been tested formally in RCTs. Clinical experience suggests improvement of symptoms in some patients. However,
sustained clinical remission rarely is achieved and impact on colonic inflammation is unlikely. Thus, antidiarrheals may be used alone or in conjunction with other therapies, depending on symptom severity.

Prednisolone has been investigated mainly in retrospective studies. In a recent population-based study, budesonide had a higher rate of complete response than prednisolone (82.5% vs 52.9%). Furthermore, MC patients treated with budesonide were less likely to experience a recurrence than those treated with prednisolone. Therefore, prednisolone appears to have no value for patients who do not respond to budesonide.

Bismuth subsalicylate has been tested in a small RCT that was never fully published. A clinical and histologic response was noted in all 7 bismuth subsalicylate MC patients compared with none of the 7 placebo recipients. Larger randomized trials are necessary to determine the value of bismuth subsalicylate in the treatment of MC.

Mesalazine achieved results comparable with placebo in a recent RCT of CC patients, clearly showing that mesalazine should not be used as induction therapy.

Although evidence is limited, immunosuppressive therapies may be considered in patients with severe symptoms who are refractory or intolerant to budesonide. According to results from RCTs, MC patients are expected to achieve clinical remission within 4 weeks on induction therapy with 9 mg budesonide or maintain clinical remission on 6 mg or less of budesonide. Approximately 10% to 20% of short-term budesonide-treated patients are nonresponders and may be candidates for immunosuppressive therapy. How many patients develop intolerance or lose effect on budesonide maintenance therapy has not been reported.

To date, only a few case reports have been published showing the beneficial effects of anti-TNF agents (infliximab and adalimumab) in selected CC patients. The regimen and dose applied were equal to those normally used for classic IBD. Because these approaches are experimental, solid recommendations cannot be given because of a lack of data, and the following remarks are based mainly on personal experience. Budesonide nonresponders often have a long history of diverse treatment failures. The chronic active disease with highly frequent watery stools binds the patient to the toilet, causing severely impaired QoL. Initiation of biological therapy always should be considered on an individual basis, taking age and comorbidity into account. A thorough risk-benefit calculation is necessary to avoid serious side effects and regular follow-up evaluation is important. The advantage of anti-TNF agents compared with thiopurines may lie in faster relief of symptoms. However, experience is limited and data on long-term treatment with biologicals are not available yet.

Azathioprine (AZA) or mercaptopurine have been tested in a small group of patients (N = 9) with steroid-dependent or refractory CC, showing a response rate of 89% and a steroid-sparing effect. In a larger retrospective multicenter case series, 28% of patients treated with AZA achieved and maintained clinical remission for up to 57 months, however, the majority of patients developed an intolerance to AZA, causing cessation of treatment. Thirteen of the 31 AZA-intolerant patients were put on mercaptopurine, of whom 6 patients (48%) regained clinical remission, resulting in an overall response rate of 41%. These results indicate that thiopurine might be considered in chronic active MC primarily as maintenance therapy, but prospective RCTs are necessary and eagerly awaited.

In a retrospective case series oral methotrexate has shown beneficial effect on symptoms of CC patients naive to budesonide. However, in a recent case series of 9 patients intolerant or not responding to budesonide, methotrexate was administered subcutaneously at a dose of 15 to 25 mg/wk for a period of 12 weeks. None of the patients achieved clinical remission and 4 patients experienced reversible adverse events leading to cessation of medication. The limited data are conflicting and further studies are required for methotrexate, especially in budesonide nonresponders.

Surgical intervention in MC should be regarded as the last treatment option in patients refractory to any medical therapy. Diverting ileostomy, subtotal colectomy, or ileal pouch-anal anastomosis have been performed successfully in individual cases.

Based on the currently available evidence, an algorithm for the treatment of MC was proposed by the European Microscopic Colitis Group. According to this algorithm, a treatment attempt with antidiarrheals and/or cholestyramine may be justified in patients with only mild symptoms. However, patients with active disease should be treated primarily with short-term budesonide (6–8 wk). In patients initially responding to this treatment, budesonide can be re-administered in case of relapse, either as intermittent therapy or as low-dose continuous therapy, always aiming to identify the lowest dose that maintains clinical remission. In patients lacking response to budesonide and mild symptoms, cholestyramine, bismuth, or loperamide, even in combination, may be given. In more severe cases and in patients with low risk for side effects (age, comorbidity), anti-TNF-α antibodies may be justified to restore remission and improve QoL. As maintenance treatment, immunomodulators such as AZA or mercaptopurine can be considered. Surgical treatment is a therapeutic option in patients refractory to all medical therapies.

Future Considerations

Epidemiologic data clearly show that MC has become a common gastrointestinal disorder and physicians and pathologists should be aware of the disease. All patients, especially elderly patients with chronic diarrhea, should be referred for colonoscopy and biopsy specimens should be obtained to confirm or rule out MC. On a
practical level, patients should be asked to use a diary to monitor symptoms. The criteria for disease activity presented by Hjortswang et al\textsuperscript{13} are recommended for treatment decision making. Because MC mainly presents with a chronic relapsing course, regular follow-up evaluation is needed and the definition of disease activity can be applied to improve patient empowerment.

On a scientific level, continuous epidemiologic studies should be encouraged not only to monitor incidence data but also to focus on environmental factors, such as drugs, infections, or food that might play a pathogenic role. The most striking finding in epidemiology is the consistent female predominance. This notion causes speculation on the pathogenetic role of specific hormones or may simply reflect women as more prone to develop autoimmune diseases. Large-scale genetic studies are warranted to identify genetic variants associated with MC and focus on susceptibility genes that overlap with variants seen in other immune-related conditions. Basic science should concentrate on the investigation of immunologic abnormalities that occur in MC. Improved knowledge of the underlying immune processes could be the key to a better understanding of patients with treatment failure and could stimulate the development of future treatment strategies. Despite the fact that many patients respond to budesonide, patients who become refractory or intolerant to the drug are a clinical challenge and physicians have to make therapeutic decisions tailored to individual patient needs because evidence-based data are unavailable. To overcome this shortcoming, future clinical trials should focus on the treatment of budesonide nonresponders and investigate the efficacy and safety of therapies on maintaining clinical remission. For this task, it would be desirable if biological markers or objective parameters could be developed to monitor disease activity.

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