Microscopic Colitis: Clinical and Pathologic Perspectives

Andreas Münch* and Cord Langner‡

*Division of Gastroenterology and Hepatology, Department of Clinical and Experimental Medicine, Faculty of Health Science, Linköpings University, Linköping, Sweden; and ‡Institute of Pathology, Medical University of Graz, Graz, Austria

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.[1] Up to 10% to 20% of patients with chronic diarrhea are diagnosed with MC.[2] 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).[3] The only drug that has been tested in multiple randomized controlled trials (RCT) and that fulfills the criteria of evidence-based medicine is budesonide.[4] 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,[5] 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.[1] 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 10^5 inhabitants for CC and between 2.2 and 14 per 10^5 inhabitants for LC.[1] The prevalence of MC was 219 of 10^5 cases in Olmsted County (in 2010)[6] and 123 of 10^5 cases in Örebro (in 2008).[7] 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.[8] MC in childhood is a rare phenomenon, but some cases reports have been published.[9]

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

Abbreviations used in this paper: AZA, azathioprine; CC, collagenous colitis; IBD, inflammatory bowel disease; IEL, intraepithelial lymphocyte; IFN, interferon; LC, lymphocytic colitis; MC, microscopic colitis; QoL, quality of life; RCT, randomized controlled trial; TNF, tumor necrosis factor.

1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2013.12.026

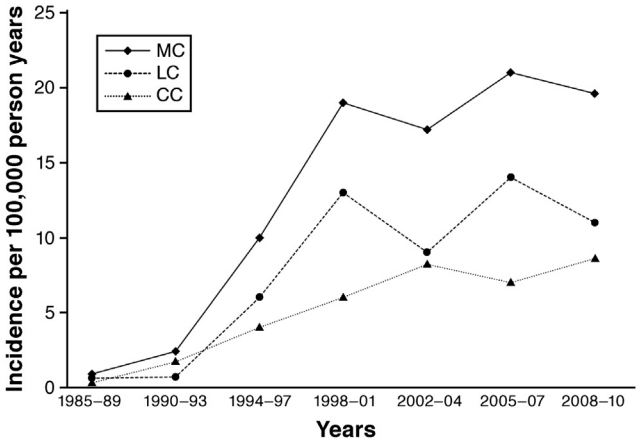

Figure 1. Incidence of MC in Olmsted County (1985–2011). Figure courtesy of Darrell Pardi (Mayo Clinic).

typically watery, leading to urgency (70% of patients) and, ultimately, fecal incontinence (40% of patients).[10] In severe cases, bowel movements can exceed 15 per day and nocturnal diarrhea is common (50%).[10] Despite considerable fluid loss, serious dehydration, electrolyte changes, or other complications are rare. The natural course of MC is not well investigated but more recent prospective studies have shown that the risk of relapse is high (60%–80%) after cessation of budesonide treatment, indicating that the course of many patients is chronic relapsing.[5,11]

Active disease leads to impaired health-related QoL and often results in severe social handicap.[3] Studies have shown that not the stool frequency as such but rather the stool consistency is the main determining factor for changes in QoL.[3,12] One watery stool per day already impairs QoL significantly and therefore disease activity in MC is defined according to Hjortswang et al[13] as 3 or more stools/day or 1 or more watery stools/day (mean of a 1-week registration). Thus, treatment decisions should focus primarily on bowel consistency and can be justified in patients with fewer than 3 bowel movements per day if the stools are watery. Several RCTs have shown that budesonide improves QoL significantly, and the earlier-mentioned criteria for disease activity have been proven useful in clinical trials.[12]

Abdominal pain is a common symptom in MC.[8,10] Abdominal discomfort or cramps may occur in up to 50%, and the differential diagnosis between MC and irritable bowel syndrome may be challenging in these patients. In a recent prospective cohort study, 43% of MC patients fulfilled the ROME II criteria.[14] Intermediate or severe pain is observed in periods with active disease and is ameliorated with budesonide treatment (unpublished data, 2013). Weight loss can occur in active disease and is observed in nearly half of patients.[8,10] It is uncertain whether this is purely an effect of fluid loss or a consequence of eating habits because patients may eat less to decrease bowel frequency. In patients with significant weight loss concomitant celiac disease should be ruled out.

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.[15]

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.[16]

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.[17] 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.[18]

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.[19] 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.[1,19,20]

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).[21–23] 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.[24] Aiming at