Microscopic Colitis in Patients with Diarrhea of Unknown Etiology: Diagnosis and Treatment

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ABSTRACT

Chronic diarrhea is a common reason for referral to a gastroenterologist. Microscopic colitis (MC) is fairly common cause of chronic non-bloody diarrhea. Microscopic colitis which was previously regarded rare, now has emerged as a common cause of chronic diarrhea. The condition is characterized clinically by chronic non bloody diarrhea, a macroscopically normal or near-normal colonic mucosa, but microscopic examination of mucosal biopsies reveals diagnostic histopathological changes. Microscopic colitis mainly includes two diseases, collagenous colitis (CC) and lymphocytic colitis (LC). In CC the most characteristic feature is thickening of the sub-epithelial collagen layer (SCL) beneath the basal membrane intra-epithelial lymphocyte (IEL) infiltration although not asprominent as in LC. The diagnosis of LC relies on a characteristic increase of IELs, which exceeds 20 IEL/100 surface epithelial cells compared with < 5 IEL/100 surface epithelial cells in normal colonic mucosa.

Randomized controlled trials (RCTs) assessing therapies for microscopic colitis have been performed. A previously published review showed that budesonide was effective in producing both clinical and histological responses in patients with collagenous colitis. This review will focus on epidemiology, clinical features and treatment of MC.

***Keywords**: chronic diarrhea, microscopic colitis, lymphocytic and collagenous colitis*

ABSTRAK

Diare kronik merupakan kasus yang sering dirujuk ke ahli gastroenterologi, sedangkan kolitis mikroskopik merupakan penyebab tersering dari diare kronik yang tidak berdarah. Sebelumnya, kasus kolitis mikroskopik jarang dilaporkan, namun saat ini sering dilaporkan sebagai penyebab tersering kasus diare kronik. Karakteristiknya adalah diare kronik tanpa darah dan pemeriksaan kolonoskopi mukosa kolon normal, sehingga diagnosisnya berdasarkan pemeriksaan histopatologi. Kolitis mikroskopik ini dibagi menjadi dua subtipe, yaitu kolitis kolagenous dan kolitis limfositik. Kolitis kolagenus ditandai oleh adanya penebalan lapisan kolagen pada membran basal meskipun tidak sejelas kolitis limfositik, sedangkan pada kolitis limfositik adanya infiltrasi limfosik yang meningkat > 20 sel imun intra-epitel limfosit/100 permukaan sel epitel dibandingkan dengan < 5 sel imun intra-epitel limfosit/100 permukaan sel epitel pada mukosa kolon normal.

Penelitian secara acak tersamar ganda pada kolitis mikroskopik khususnya pada kolitis kolagenus telah banyak dilaporkan, dan budesonide menunjukkan efektifitas yang baik terhadap perbaikan klinis dan histopatologi. Pada ulasan ini dibahas aspek epidemiologi, gambaran klinis dan terapi dari kolitis mikroskopik.

***Kata kunci**: diare kronik, kolitis mikroskopik, kolitis kolagenus dan limfositik*

INTRODUCTION

Chronic diarrhea with no obvious reason is one of the challenges in gastroenterology. In 1980, Read et al, introduced microscopic colitis (MC) characterized by chronic diarrhea with normal endoscopic and radiologic findings, but with increased colonic mucosal inflammatory cells and epithelial lymphocytic infiltration on histological examination.[1] Later, Levison et al, emphasized that MC covered all cases of colitis with normal colonoscopy, but abnormal histopathologic features and described lymphocytic colitis separately.[2] Collagenous colitis, which is a closely related condition, was first described in 1976 as a separate subtype with additional histological finding of increased sub-epithelial collagen band thickness.[3]

The prevalence of MC has been difficult to estimate. The symptoms of microscopic colitis have been frequently attributed to diarrhea predominant irritable bowel syndrome, often for many years before diagnosis. Diagnostic awareness of these conditions by physicians in the geographic area of interest significantly affects likelihood of diagnosis and, therefore, the prevalence. Clinical and histological characteristics of microscopic colitis have been well established.[4-8] However, limited data is available regarding the prevalence, pathogenesis and progress of the disease, and its treatment. The diagnosis is made only by histological examination and most of these patients are treated and followed up erroneously as irritable bowel syndrome. Recently, several studies from Sweden and Iceland reported high prevalence of microscopic colitis.[9-11]

MICROSCOPIC COLITIS AND DIARRHEA

Microscopic colitis, which is characterized by chronic watery diarrhea with normal radiological and endoscopic appearances, is diagnosed only by histopatologic examination. This condition which consists of two main subtypes, lymphocytic and collagenous colitis, is a relatively common cause of chronic watery diarrhea, often accompanied by abdominal pain and weight loss. Studies from different countries reported microscopic colitis rates between 4-13% in the cohort of population with non-bloody diarrhea of unknown origin.[10-15] The reported prevalence seems to change within years. In Sweden, microscopic colitis was reported in 4% of patients with non-bloody chronic diarrhea in 1993, but this rate was reported as 10% in 1998.[9,10,13] The prevalence of collagenous colitis in Sweden between 1984-1988 was 0.8/105 inhabitants, but increased to 6.1/105 inhabitants between 1996-1998.[9,10,13,15]

Recently, higher prevalence values have been reported from Iceland where the mean annual prevalence of collagenous colitis was 5.2/105 inhabitants and the mean annual incidence of lymphocytıc colıtıs was 4.0/105 inhabitants in the period 1995-1999.[11] In a study performed in Spain, lymphocytic colitis was found in 9.5% of patients who had undergone colonoscopy because of chronic diarrhea during a period of 5 years.[14] In this study, the prevalence of lymphocytic colitis was three times that of the prevalence of collagenous colitis, with female/male ratio in lymphocytic and collagenous colitis was 2.7/1 and 4.7/1, respectively. Female/male ratio were reported as 5/1 from Iceland and 2/1 from Sweden.[10-15] In reported series this ratio for collagenous colitis was reported as 4/1-20/1.[13-17] Marshall et al, encountered 13 lymphocytic colitis and 1 collagenous colitis in their 111 chronic-diarrhea patients with unexplained etiology.[16] In another study of 132 consecutive patients who had undergone colonoscopy for chronic diarrhea and abdominal pain, lymphocytic and collagenous colitis were found in 21 (16%) and 7 (5%) patients, respectively.[17] Mean ages of patients with lymphocytic and collagenous colitis in other studies were between 51-59 years, and 64-68 years, respectively.[13-17] In the study of Lazenby et al, the mean intra-epithelial lymphocyte (IEL)/100 intercryptal epithelial cells was 34.7 and 29.4, respectively.[5] In the current study, the mean IEL per 100 intercryptal epithelial cells was 28.2. Normal subjects may have up to 1 to 5 IEL per 100 intercryptal epithelial cells. Some studies have reported that biopsy specimens from all segments of the colon revealed similar number of IEL and, therefore, biopsy obtained only from sigmoid colon would be enough for diagnosis.[7,8,12]

COLONOSCOPY AND HISTOLOGY

Patients were prepared for colonoscopy with bowel cleansing. During colonoscopy two biopsies were taken from terminal ileum and all segments of the colon. Specimens were stained with hematoxyline eosin (HE) and Masson's Trichrome or Van Gieson dyes.[11]

DIAGNOSTIC CRITERIA

Increased chronic inflammatory infiltration in the lamina propria, increased intraepithelial lymphocytes (IELs), degeneration of surface epithelium and increased mitosis in crypts were sought to diagnose microscopic colitis. Over 20 IEL/100 intercryptal

epithelial cells (normal < 1-5/100) were deemed necessary for the diagnosis of lymphocytic colitis.[1,7,8] For collagenous colitis sub-epithelial collagen band thickness was measured by ocular micrometer in Masson's Trichrome stained specimens. Thickness over 10 μm was required to establish the diagnosis.[2,3,7,8,11,12]

Histopathologic criteria of lymphocytic colitis were chronic inflammatory infiltration in lamina propria, increased IELs, superficial epithelial degeneration and increased mitosis in crypts, IELs/100 intercryptal epithelial cell > 20/100. While, collagenous colitis were a diffusely distributed and thickened sub-epithelial, collagen band > 10 μm, chronic inflammatory infiltration in lamina propria.[2,3,5]

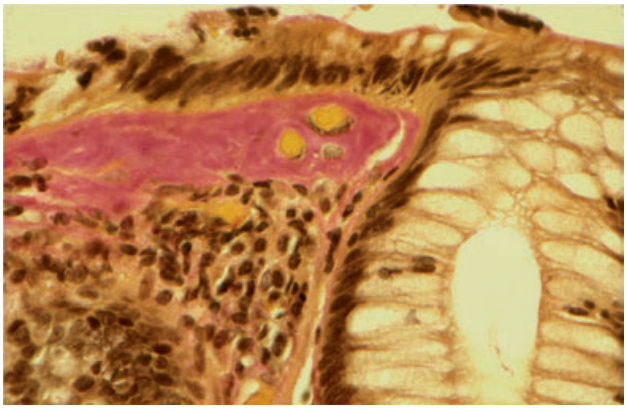

Figure 1. Biopsy from colon showing typical findings of collagenous colitis–increased sub-epithelial collagen layer, inflammation of lamina propria and epithelial lesions with intraepithelial lymphocytes[11]

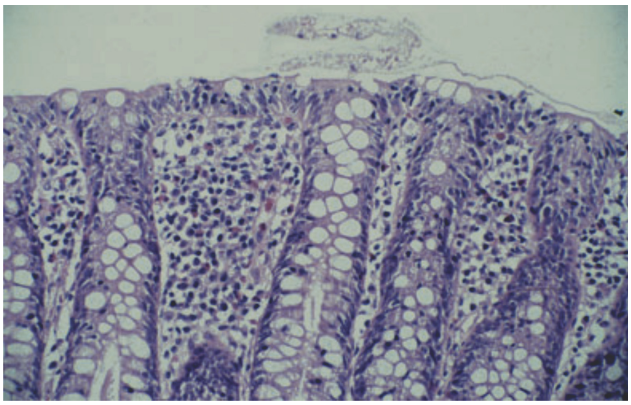

Figure 2. Biopsy from colon showing typical findings of lymphocytic colitis–epithelial lesions with intraepithelial lymphocytes and inflammation in the lamina propria[11]

ETIOLOGY

The cause of the diseases is largely unknown and probably multifactor. Collagenous and lymphocytic colitis are presently considered to represent specific mucosal responses in predisposed individuals to various noxious luminal agents. The luminal factor increased number of T lymphocytes in the epithelium has suggested that MC may be caused by an immunological response to a luminal agent in predisposed individuals.[11,12]

Gastrointestinal infections, a sudden onset of MC in a subset of patients and effect of various antibiotics support a possible infectious cause. *Yersinia enterocolitica* was found in three of six patients with collagenous colitis prior to diagnosis and another study showed that antibodies to *Yersinia* species were more common in collagenous colitis patients than in healthy controls. An association with MC and *Campylobacter jejuni* and *Clostridium difficile* has also been reported.[12]

Various drugs, about 17 drugs, were found to be associated with a high or intermediate probability of causality. A high likelihood of inducing MC was associated with acarbose, aspirin, Cyclo3 Fort, lanzoprazole, non-steroidal anti-inflammatory drugs (NSAIDs), ranitidine, sertraline and ticlopidine. Carbamazepine, flutamide, lisinopril, modopar (levodopa and benserazide), oxetorone, paroxetine, simvastatin, tardyferon and vinburine associated with an intermediate likelihood of inducing MC, were reported to be the causative factors.[12] Assessment of concomitant drug use in patients with MC is important to identify and consider withdrawal of drugs that might cause or worsen the condition.[11,12]

Bile acid malabsorption can coexist with MC, leading to worsening of symptoms. Concurrent bile acid malabsorption was found in 27–44% of patients with CC and in 9–60% of patients with lymphocytic colitis.[15] These observations are the rationale for recommendations of bile acid-binding treatment in MC.[12]

Some gastrointestinal rheumatologic disorders (celiac sprue, rheumatoid arthritis, uveitis, idiopathic pulmonary fibrosis, diabetes mellitus, pernicious anemia, autoimmune thyroiditis, etc) and positivity of some auto antibodies, particularly anti-nuclear antibody (ANA) may be associated with both lymphocytic and collagenous colitis.[14] Giardiello et al, found 4 ANA positive patients in their 12 lymphocytic colitis patients.[18] Whether secretory or osmotic diarrhea, the precise mechanism of diarrhea in MC is not fully clarified. In collagenous colitis, diarrhea has been regarded as secretory, caused by reduced net absorption of sodium and chlorine ions due to epithelial cell lesions, and the thickened collagenous layer as a co-factor causing a diffusion barrier, and by

an additional active chloride secretion. Fasting on the other hand, seems to reduce diarrhea, which would indicate an osmotic component in some patients as well.[12]

TREATMENT

In the past, treatment was based on anecdotal evidence, and the literature includes observational studies using traditional corticosteroids, budesonide, 5-ASA compounds, azathioprine/6 mercaptopurine, methotrexate, cyclosporine, antibiotics, bismuth subsalicylate, cholestyramine/colestipol, octreotide, ketotifen, verapamil, pentoxifylline, antidiarrheal agents, bulking agents and spasmolytics, dietary modification, or surgery.[19,20] Randomized controlled trials (RCTs) of therapies for microscopic colitis have been performed. A previously published review showed that budesonide was effective for producing both clinical and histological responses in patients with collagenous colitis.[19,20]

From a total of 11 RCTs, nine studies assessed treatment of active disease, including five which enrolled patients with collagenous colitis only, one which enrolled patients with lymphocytic colitis only, and three which enrolled patients with both collagenous and lymphocytic colitis. Two studies assessed maintenance of response and included patients with collagenous colitis only.[20]

CLINICAL AND HISTOLOGICAL RESPONSES OBSERVED

Collagenous Colitis

Induction of response: **bismuth subsalicylate vs. placebo**. In Fine 1999, all four bismuth subsalicylate patients (100%; 95% CI = 45–100%) achieved clinical and histological responses after 8 weeks, compared to 0 of 5 placebo patients (0%; 95% CI = 0–49%; p = 0.03 for each comparison). No adverse events were reported.[19]

Mesalamine vs. mesalamine + cholestyramine. In Calabrese et al, 8 of 11 patients (73%; 95% CI 43–91%) treated with mesalamine alone responded clinically after 6 months compared to 12 of 12 mesalamine + cholestyramine patients (100%; 95% CI = 72–100%; p = 0.14). Of 20, 18 patients (90%; 95% CI = 69–98%) in both groups who underwent a follow-up colonoscopy at 6 months had a histological response.[21] It was not clear from the report in which groups these patients were enrolled to obtain this information from the authors were unsuccessful. No adverse events were reported.

Prednisolone vs. placebo. In Munck et al, 5 of 8 prednisolone patients (63%; 95% CI = 30–87%) achieved a clinical response after 2 weeks of therapy, compared to 0 of 3 placebo patients (0%; 95% CI = 0–62%; p = 0.15).[22] Follow-up colonoscopy or sigmoidoscopy was not performed. Adverse events were common in the prednisolone group, but not severe enough to cause patient withdrawal.[20,22]

Budesonide vs. Placebo. A total of 94 patients were enrolled in three trials (Baert et al, Miehlke et al, and Bonderup et al). After 6–8 weeks of treatment, 38 of 47 patients (81%; 95% CI = 67–90%) treated with budesonide achieved a clinical response compared to 8 of 47 placebo patients (17%; 95% CI = 9–30%; p < 0.00001).[23-25] The number needed to treat (NNT) to achieve a clinical response to budesonide was two patients. The pooled odds ratio for response to budesonide therapy was 12.32 (95% CI = 5.53–27.46%). Baert et al, reported minor adverse events in both groups.[23] Conversely, Bonderup et al, did not report adverse events as an outcome.[24] Adverse events in Miehlke et al, were more common in patients treated with budesonide (39%) than placebo (12%).[25] Two patients (8%) in the budesonide group (one with nausea, headache, increase in body weight, and disturbed sleep, the other with upper abdominal discomfort) and one patient (4%) in the placebo group (arthralgia) withdrew from the study due to an adverse event.[24] All other events were minor.[20]

The definitions for histological response varied between trials. Therefore the data were not combined for analysis. In Baert et al, 10 of 11 budesonide patients (91%; 95% CI = 60–100%) and 4 of 12 placebo patients (33%; 95% CI = 14– 61%) had a histological response after 8 weeks (p = 0.01).[23] In Miehlke et al, 14 of 26 budesonide patients (54%; 95% CI = 35–71%) and 1 of 25 placebo patients (4%; 95% CI = 0–21%) had a histological response after 6 weeks (p = 0.002).[25] All 10 budesonide patients (100%; 95% CI = 68–100%) in Bonderup et al, had a histological response, compared to 3 of 10 placebo patients (30%; 95% CI = 10–61%; p = 0.02).[24]

Maintenance of response: **budesonide vs. placebo**. In Bonderup et al, and Miehlke et al, 80 of 90 patients with clinically active disease treated with open-label budesonide 9 mg per day for 6 weeks responded to therapy and met the inclusion criteria for study enrolment.[22,23] A total of 40 patients were randomized to budesonide 6 mg per day and 40 to placebo for 6 months, which resulted in 30 of 40 budesonide patients (75%; 95% CI = 60–86%) and 10 of 40 placebo

patients (25%; 95% CI = 14–40%) had maintained their response ($p < 0.0001$). The pooled odds ratio for maintenance of clinical response was 8.82 (95% CI = 3.19–24.37), with an NNT of 2 patients.[24,25]

Probiotics vs. placebo. In Wildt et al, 6 of 21 probiotic patients (29%; 95% CI = 14–50%) achieved a clinical response after 12 weeks compared to 1 of 8 placebo patients (13%; 95% CI = 3–48%; $p = 0.38$).[26] There was no histological response in either group. The median short inflammatory bowel disease questionnaire score in the placebo group was unchanged from baseline (53.5) till the end of the study (59.5) but increased from 46 to 55 in the probiotics group ($p < 0.05$). After correction for multiple comparisons this difference was no longer statistically significant. Seven mild adverse events were considered possibly related to probiotic treatment, but none led to study withdrawal.[20,26,27]

Lymphocytic Colitis

There is less evidence for treating lymphocytic colitis. Budesonide 9 mg daily for 6 weeks was found to be effective in producing clinical and histological responses and was well tolerated.[20] The utility of this therapy for maintaining a long-term response is not known, and warrants further study. Bismuth seemed to be beneficial at producing a clinical response, although the number of patients was too small to make any meaningful conclusions. Mesalamine with or without cholestyramine produced clinical and histological responses in an unblinded study. The treatments were well tolerated and warrant further study.[20,23] Collagenous and lymphocytic colitis were once thought to be rare disorders, but it is now apparent that they are relatively common causes of chronic diarrhea in middle-aged and elderly patients.[20]

The etiology is not fully understood, however altered gut immunity has a role in its pathogenesis.[20,23] Despite this better understanding of microscopic colitis, there is relatively little evidence from RCTs assessing therapy.[23,28] The results here demonstrate budesonide to be an effective treatment, and suggest that bismuth subsalicylate, prednisolone, and mesalamine with or without cholestyramine may be beneficial.[28] However, these studies all have small sample sizes, and larger randomized trials need to be performed. Some of the studies reviewed here included patients with collagenous or lymphocytic colitis only whereas others reported the effectiveness of these therapies in both disorders. In the past, some studies used the more general term "microscopic colitis" and included patients with both of these disorders, making conclusions about treatment effectiveness for the two subtypes difficult.[20]

Although collagenous and lymphocytic colitis share some epidemiological, clinical, and histological features, it is not certain if all treatments for one subtype of microscopic colitis will necessarily be effective for treating the other subtype. Future studies will need to enroll, follow, and report outcomes of patients with the two disorders separately. Over time it may become clearer if treatments for the two subtypes of microscopic can be used interchangeably.[20]

The difference between "response" and "remission" in microscopic colitis may be important. As standardized definitions of clinical and histological remission do not exist, the outcome measures defining "response" vary between trials, and thus the effectiveness of therapies at inducing and maintaining true disease remission are unknown. In addition, inclusion criteria defining histological features of collagenous and lymphocytic colitis and clinical activity are variable, so that patients in different trials may not be comparable. Once standardized definitions for clinical and histological features, disease activity, and remission are established, trials studying therapies could use uniform inclusion criteria and outcome measures. This would allow more accurate assessment of treatment effectiveness for therapies of microscopic colitis.[20]

CONCLUSION

Microscopic colitis is a chronic diarrheal disease with normal colonoscopic, but with abnormal histopathologic features. It is a disease with two subtypes of similar clinical but different histological features, lymphocytic colitis which is characterized by pronounced colonic mucosal lymphocyte infiltration and collagenous colitis which is characterized by increased sub-epithelial collagenous band thickness. In limited number of studies from various countries the rates of microscopic colitis in patients with chronic diarrhea have been reported between 4-13%.

Although the number of the cases was not enough to answer the question of how many biopsies should be taken and from which part of the colon, the fact that histopathological criteria were determined on all colonic regions in patients with lymphocytic colitis on whom biopsy was performed is promising in terms of diagnostic convenience.

Considering 11.5% of the patients with chronic diarrhea of unknown etiology and normal colonoscopy would have microscopic colitis, biopsy should be

taken during colonoscopy in this subset of patients. RCTs of therapies for microscopic colitis have been performed. A previously published review showed that budesonide was effective in producing both clinical and histological responses in patients with collagenous colitis.

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