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TOPIC HIGHLIGHT

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Diagnosis and management of microscopic colitis

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Abstract

Microscopic colitis, comprising collagenous and lymphocytic colitis, is characterized clinically by chronic watery diarrhea, and a macroscopically normal colonic mucosa where diagnostic histopathological features are seen on microscopic examination. The annual incidence of each disorder is 4-6/100 000 inhabitants, with a peak incidence in 60-70-year-old individuals and a noticeable female predominance for collagenous colitis. The etiology is unknown. Chronic diarrhea, abdominal pain, weight loss, fatigue and fecal incontinence are common symptoms, which impair the health-related quality of life of the patient. There is an association with other autoimmune disorders such as celiac disease, diabetes mellitus, thyroid disorders and arthritis. Budesonide is the best-documented short-term treatment, but the optimal long-term strategy needs further study. The long-term prognosis is good and the risk of complications including colonic cancer is low.

Key words: Microscopic colitis; Collagenous colitis; Lymphocytic colitis; Chronic diarrhea; Budesonide

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INTRODUCTION

Chronic diarrhea, reported in 4%-5% of individuals in Western populations, is a common cause for consulting a physician in general practice or in internal medicine, and for referral to a gastroenterologist[1]. Microscopic colitis (MC), previously regarded as rare, and certainly overlooked, has now emerged as a common cause of chronic diarrhea especially in elderly women. The condition is characterized clinically by chronic watery diarrhea, and a macroscopically normal or almost normal colonic mucosa, where microscopic examination of mucosal biopsies reveals characteristic histopathological changes[2]. MC comprises the two entities collagenous colitis (CC) and lymphocytic colitis (LC), which have indistinguishable clinical presentations but are separated by histopathological characteristics. This review will highlight epidemiology, clinical features, diagnosis and management of MC.

EPIDEMIOLOGY

CC and LC, first described in 1976[3] and in 1989[4], respectively, have mostly been reported from European or North American centers, but the disease is found worldwide[5-10]. Currently, epidemiological data have been reported from seven different regions (Table 1)[5,6,11-17]. Long-term epidemiological data from Sweden and US since the 1980s show a rising incidence, which seems to have levelled off during the last study periods in the Swedish study. Whether the increasing incidence figures are an artefact, reflecting an increased awareness and improved diagnosis of the condition, or in fact represents a true rise is at present unknown. MC may be diagnosed in 10%-20% of cases investigated for chronic

Table 1 Annual incidence/100 000 inhabitants in population-based epidemiological studies of CC and LC[5,6,11-17]

Region and study period	CC	LC
Örebro, Sweden 1984-1988	0.8	
Örebro, Sweden 1989-1993	2.7	
Örebro, Sweden 1993-1995	3.7	3.1
Örebro, Sweden 1996-1998	6.1	5.7
Örebro, Sweden 1999-2004	5.2	5.5
Terassa, Spain 1993-1997	2.3	3.7
Iceland 1995-1999	5.2	4.0
Olmsted County, USA 1985-1989	0.3	0.5
Olmsted County, USA 1990-1993	1.6	1.0
Olmsted County, USA 1994-1997	3.9	6.4
Olmsted County, USA 1997-2001	6.2	12.9
Lothian, UK 1998-2003	0.8	
Tayside, UK 1999-2004	1.1	0.6
Calgary, Canada 2002-2004	4.6	5.4

watery diarrhea[5].

CC mainly affects middle-aged women with a peak incidence around 65 years of age, and the female:male ratio is about 7:1 (Figure 1)[6,18]. However, the disease can occur in all ages, including children[19]. In LC, the peak incidence is in the same age group as CC, but the female predominance is less pronounced with a female:male ratio of 2-3:1 (Figure 1)[20].

CLINICAL PRESENTATION

The clinical symptoms of CC and LC are similar and the diseases cannot be differentiated on clinical grounds. Both disorders cause chronic or recurrent non-bloody, watery diarrhea, often associated with nocturnal diarrhea, diffuse abdominal pain, and weight loss, which may be substantial[18,20,21]. Although some patients may suffer from severe diarrhea, serious dehydration is rare. Fatigue, nausea and fecal incontinence are other associated symptoms and the disease may significantly impair quality of life in the affected patient[22,23].

The onset of disease can be sudden and mimic infectious diarrhea[18,20]. The clinical course is often chronic relapsing and benign. Severe complications are rare, although there are reports of colonic perforation in CC[24-26]. No increased risk of colorectal cancer has been reported in CC[27]. A few cases with concomitant lymphoproliferative disorders and CC have been presented but further studies are required to assess if there is an increased risk[28].

Some patients may have mild symptoms that may be misinterpreted as irritable bowel syndrome[29]. Morphological findings of LC have been reported even in constipated or asymptomatic patients[30]. The natural history of the condition in these patients is unknown.

Patients with MC often have concomitant autoimmune diseases[18,20,21]. The most common are thyroid disorders, celiac disease, diabetes mellitus and rheumatoid arthritis. The occurrence of such associations, reported in up to 40%-50% of patients in some cases, is variable depending on the study, and differences between LC and CC with respect to

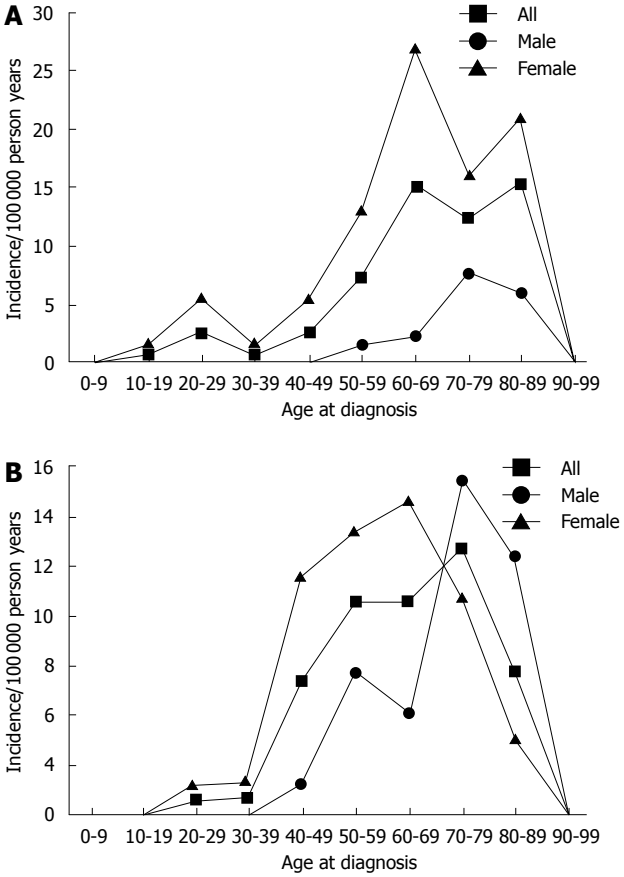

Figure 1 Age- and sex-specific incidence of CC (A) and LC (B). Reprinted with permission from *Gut* 2004; 53: 346-350[5].

associated conditions have been described[18,20,21,31]. Bile acid malabsorption can often co-exist with MC and lead to worsening of symptoms[32]. An interchange between ulcerative colitis or Crohn's disease and MC has been reported occasionally[33,34]. Whether this merely is a chance association of two fairly common disorders occurring in the same individual, or results from a common genetic predisposition or shared immunological pathways remains unknown.

ETIOLOGY AND PATHOGENESIS OF MUCOSAL INFLAMMATION

The cause of MC is multifactorial and largely unknown. CC and LC are presently considered to represent specific mucosal responses in predisposed individuals to various noxious luminal agents. As CC and LC have many clinical similarities and share histopathological features, except for the subepithelial collagen layer found in CC, it has been discussed whether LC and CC are in fact the same disease seen in different stages of development. Conversion of LC to CC or *vice versa* has been reported. However, conversion is seen infrequently and this fact, together with the observed difference in sex ratio, makes it more likely to consider CC and LC as two separate but related entities.

Data on the mucosal inflammation in MC are limited. In the epithelium, mainly CD8+ T lymphocytes are

found that carry the α/β form of the T-cell receptor, and in the lamina propria there are mainly CD4+ T lymphocytes[35]. By means of segmental colorectal perfusion, increased luminal levels of eosinophilic cationic protein (ECP), basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) have been found in CC[36-38]. By immunohistochemistry, others have verified increased mucosal levels of VEGF that are not affected following therapy with budesonide[39]. A study of cytokines in MC found a TH1 mucosal cytokine profile with interferon γ, tumor necrosis factor (TNF)α and interleukin-15 as the predominantly up-regulated cytokines[40]. Using Ussing chamber technology, transcellular and paracellular mucosal permeability has been found to be increased in patients with CC[41,42]. The excess subepithelial collagen in CC may be caused by an imbalance of collagen turnover. An increased collagen synthesis is supported by the finding of an increase in the number or the activity of myofibroblasts[43]. Among degrading enzymes, matrix-metalloproteinases (MMPs) have a central role that is regulated by tissue endogenous inhibitors of metalloproteinases (TIMPs)[44]. Impaired collagen degradation in CC is supported by the finding of restricted MMP-1 RNA expression and increased TIMP expression[45].

GENETICS

A familial occurrence of MC has been reported, but the role of genetic factors still remains largely unknown[46-49]. Human leukocyte antigen (HLA) studies have shown an association between MC and HLA-DQ2 or DQ1/3, and recently an association has reported between MC and HLA-DR3-DQ2 haplotype and with TNF2 allele carriage, irrespective of the presence of concomitant celiac disease[50,51]. Variants of the MMP-9 gene have been reported to be associated with CC[52]. No association with NOD2/CARD15 polymorphisms and susceptibility to CC has been found[53].

LUMINAL FACTORS

The mucosal inflammation with an increased number of intraepithelial T lymphocytes has suggested that MC may be caused by an immunological response to a luminal agent in predisposed individuals. This theory is supported by the observation that diversion of the fecal stream by an ileostomy normalizes or reduces the characteristic histopathological changes in CC[54]. After closure of the ileostomy, recurrence of symptoms and histopathological changes occur.

Drug-induced MC

There are several reports on drug-induced MC and a strong likelihood of association has been found with acarbose, aspirin, Cyclo3 Fort, non-steroidal anti-inflammatory drugs, lansoprazole, ranitidine, sertraline and ticlopidine[55]. Assessment of concomitant drug use in patients with MC is therefore important to identify and consider withdrawal of drugs that might cause or worsen the condition.

Infection

An infectious cause has been suspected, especially in patients with a sudden onset of disease. An association with MC and *Campylobacter jejuni, Yersinia enterocolitica* or *Clostridium difficile* has been reported occasionally[56-59]. LC shares many features with "Brainerd diarrhea", which refers to outbreaks of acute watery diarrhea with long duration, first reported among 122 residents of Brainerd, Minnesota, USA[60]. Colonic biopsies of these patients show epithelial lymphocytosis similar to LC, but no crypt distortion or epithelial destruction[61]. Investigations of several outbreaks of Brainerd diarrhea have established an incubation period of 10-30 d and median duration of illness of 16 mo[62]. Although an infectious agent is thought to be the cause of Brainerd diarrhea, no microorganism has yet been identified. Furthermore, a seasonal pattern of onset of LC[20,63] may support an infectious cause. However, in most cases of MC with a sudden onset, stool cultures remain negative.

Bile acids

Bile acid malabsorption can coexist with MC, which leads to worsening of symptoms. Concurrent bile acid malabsorption was found in 27%-44% of patients with CC and in 9%-60% of patients with LC[32,64,65]. These observations are the rationale for recommendations on bile acid binding treatment in MC. The treatment is especially effective in patients with concomitant bile acid malabsorption, but improvement has also been shown in patients without bile acid malabsorption.

Autoimmunity

The association with other autoimmune diseases such as thyroid disease, celiac disease, diabetes mellitus or arthritis has suggested an autoimmune process. However, no specific autoantibody or marker has been identified.

Nitric oxide (NO)

Colonic NO production is greatly increased in active MC caused by upregulation of inducible nitric oxide synthase (iNOS) in the colonic epithelium[66-69]. A major transcriptional inducer of iNOS gene expression is the transcription factor nuclear factor-κB (NF-κB). In active CC, colonic mucosal NF-κB has been found to be activated in epithelial cells but not in lamina propria macrophages, in contrast to ulcerative colitis[70]. The levels of NO are correlated to clinical and histological disease activity[67]. NO has been suggested to be involved in the pathophysiology of diarrhea in CC, as infusion in the colon of N^G-monomethyl-L-arginine, an inhibitor of NOS, reduced colonic net secretion by 70% and the addition of L-arginine, a precursor of NO synthesis, increased colonic net secretion by 50%[68]. Further

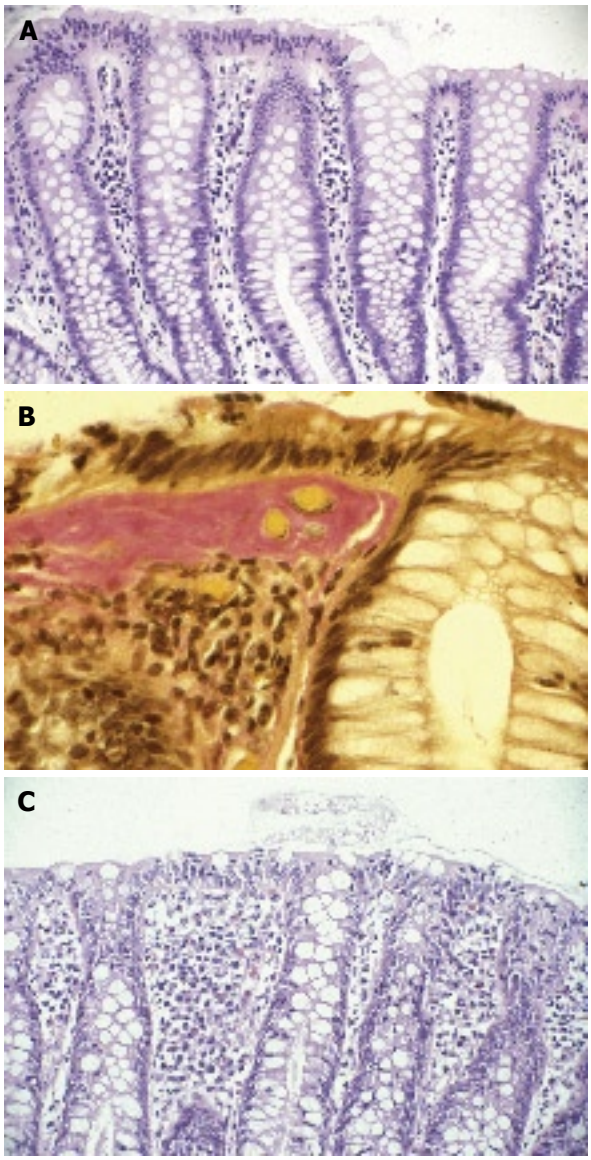

Figure 2 Biopsy from colon. A: normal colonic mucosa (H&E stain); B: typical findings of CC-increased subepithelial collagen layer, inflammation of lamina propria and epithelial cell damage with intraepithelial lymphocytes (Van Gieson's stain); C: typical findings of LC-epithelial cell damage with intraepithelial lymphocytes and inflammation in the lamina propria (H&E stain).

support for NO being involved in the pathogenesis of CC comes from therapeutic studies. Treatment with budesonide, in contrast to placebo, has resulted in a significant reduction of iNOS mRNA that is correlated with clinical and histopathological improvement[71].

Secretory or osmotic diarrhea

The exact mechanism of diarrhea in MC has not been clarified fully. In CC, diarrhea has been regarded as secretory and caused by reduced net absorption of Na^+ and Cl^- ions caused by epithelial cell lesions, and the thickened collagenous layer as a co-factor that causes a diffusion barrier, and by additional active Cl^- secretion[72]. Fasting, on the other hand, seems to reduce diarrhea, which indicates an osmotic component in some patients as well[73].

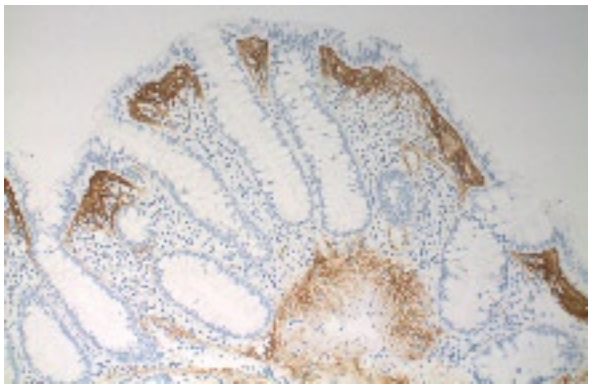

Figure 3 Tenascin immunostaining in CC.

DIAGNOSIS

Diagnosis of MC relies solely on typical microscopic changes seen in colonic mucosal biopsies[74]. In CC, a thickening of the subepithelial collagen layer is seen together with a chronic mononuclear inflammation in the lamina propria, and epithelial cell damage, with an occasionally increased number of intraepithelial lymphocytes (Figure 2). The thickened subepithelial collagen layer in CC is $\geqslant$ 10 μm in well-orientated sections, in contrast to a normal basal membrane of $<$ 3 μm. The thickening of the collagen layer may be variable and is most prominent in the ascending or transverse colon, and may be absent in biopsies from the sigmoid colon or rectum, which emphasizes the importance of obtaining biopsies from the proximal colon when diagnosing CC[75]. Generally, the histopathological changes are restricted to the large bowel, but a thickened collagen layer has infrequently been found in the stomach, duodenum or terminal ileum. In addition to conventional histological staining, the use of tenascin immunostaining has been suggested in uncertain cases of CC (Figure 3)[43,76].

The diagnostic features of LC (Figure 2) are an increased number of intraepithelial lymphocytes ($\geqslant$ 20/100 surface epithelial cells), in conjunction with surface epithelial cell damage and infiltration of lymphocytes and plasma cells into the lamina propria, but the collagen layer is normal, in contrast to CC[74]. In uncertain cases, immunostaining of CD3+ T lymphocytes facilitates the assessment of intraepithelial lymphocyte count (Figure 4).

Barium enema and colonoscopy are usually normal, although subtle mucosal changes can be seen such as edema, erythema and abnormal vascular pattern[18,20]. Tears of colonic mucosa have occasionally been seen during colonoscopy, which might be a sign of increased risk of colonic perforation during the procedure[26,77-79]. In the future, the use of confocal laser microscopy may enable *in vivo* diagnosis of MC[80-82].

Laboratory tests are non-diagnostic and only non-specific abnormalities such as moderately elevated C-reactive protein, erythrocyte sedimentation rate, or mild anemia are found. Stool tests reveal no pathological microorganisms, but fecal calprotectin can be slightly elevated[83].

Table 2 Data from four randomized, placebo-controlled trials of oral budesonide in CC and LC

Author year	Number of cases	Dosage	Clinical response budesonide *vs* placebo	Histological response budesonide *vs* placebo	Adverse events
Collagenous colitis					
Baert *et al*[91] 2002	28	9 mg/d Budenofalk 8 wk	Improvement: 8/14 *vs* 3/14 ($P = 0.05$)	Reduction of lamina propria inflammation in 9/13 *vs* 4/12 ($P < 0.001$) No difference in collagen layer	Mild No difference between treatment groups
Miehlke *et al*[93] 2002	45	9 mg/d Entocort 6 wk	Remission: 15/23 *vs* 0/22 ($P < 0.0001$)	Improvement in 17/23 *vs* 5/22 ($P < 0.01$) No difference in collagen layer	Mild 38% *vs* 12% $P = 0.052$
Bonderup *et al*[92] 2003	20	9 mg/d Entocort 8 wk	Response: 10/10 *vs* 2/10 ($P < 0.001$)	Reduction of overall inflammation ($P < 0.01$) and of collagen layer in sigmoid colon ($P < 0.02$)	None
Lymphocytic colitis					
Miehlke *et al*[95] 2007	41	9 mg/d Budenofalk 6 wk	Remission: 18/21 *vs* 8/20 ($P = 0.004$)	Response in 11/15 *vs* 4/12 ($P = 0.04$)	Mild No difference between treatment groups

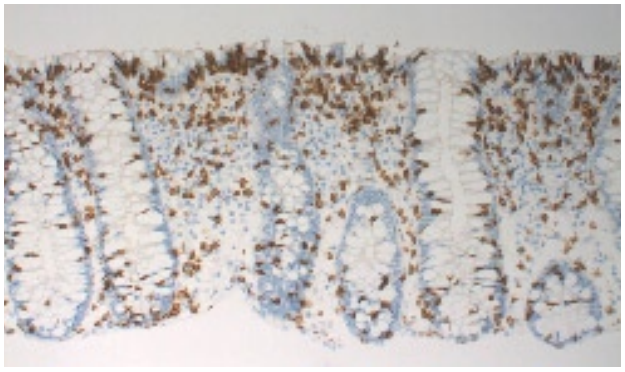

Figure 4 Immunostaining of CD3+ T lymphocytes in LC.

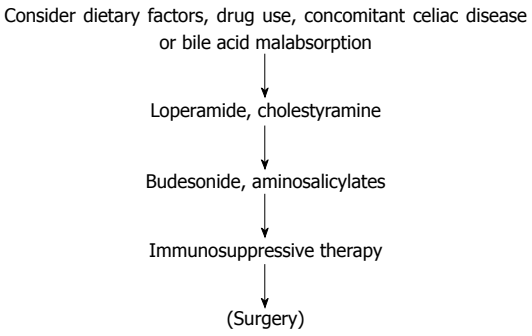

Figure 5 Treatment algorithm for MC.

ATYPICAL MC

In addition to CC and LC, other rare subtypes of MC have been described including MC with giant cells[84,85], paucicellular LC[86], cryptal LC[87], pseudomembranous CC[88], MC with granulomatous inflammation[89], and MC not otherwise specified[74]. The clinical features of these conditions are similar to those of classical MC, but histopathological appearance differs. Further studies are required to address the relationship and clinical significance of these atypical forms of MC[90].

THERAPY AND PROGNOSIS

A careful assessment of concomitant drug use and dietary factors such as excess use of caffeine, alcohol and dairy products that might worsen the condition is important. Concomitant bile acid malabsorption or celiac disease should be considered. In the patient with mild symptoms, loperamide or cholestyramine are recommended as the first step of treatment (Figure 5).

Budesonide is the best-documented treatment and significantly improves the clinical symptoms and the patient's quality of life. Three short-term, randomized controlled trials in CC have consistently shown that budesonide 9 mg daily for 6-8 wk is superior to placebo (Table 2)[91-93]. About 80% of patients responded to budesonide and had a decrease in the number of loose stools after 2-4 wk of therapy. In a Cochrane meta-analysis, the pooled odds ratio for clinical response with budesonide compared to placebo was 12.32 (95% CI 5.53-27.46), and the number needed to treat was two patients[94]. In a placebo-controlled trial including 41 patients, budesonide treatment was effective also in LC[95]. After 6 wk treatment, 18 of 21 patients (86%; 95% CI 65%-96%) in the budesonide group achieved a clinical response compared to eight of 20 patients (40%; 95% CI 22%-61%) in the placebo group, which yielded an odds ratio of 9.00 (95% CI 1.98-40.93; $P = 0.004$)[96]. The number needed to treat to achieve a clinical response with budesonide was three patients.

The relapse rate is high after cessation of successful short-term budesonide therapy in CC and 61%-80% of treated patients will have a recurrence of symptoms[91-93]. In clinical practice, tapering doses of budesonide to 3-6 mg/d have been used as maintenance therapy and may well control clinical symptoms. There is now evidence for such a strategy in CC, and two studies have proven maintenance therapy with budesonide 6 mg/d for 6 mo is well-tolerated and superior to placebo[97,98]. A total of 80 patients, who had responded to open-label budesonide, were randomized to budesonide 6 mg/d or placebo for 6 mo. Clinical response was maintained in 33/40 (83%) patients who received budesonide compared to 11/40 (28%) patients who

received placebo ($P = 0.0002$). Pooled odds ratio was 8.40 (95% CI, 2.73-25.81) with a number needed to treat of two patients for maintenance of clinical response with budesonide. Histological response was seen in 48% of patients who received budesonide compared to 15% of patients who received placebo ($P = 0.002$)[94]. However, 6 mo maintenance therapy did not alter the subsequent course, as the relapse risk after withdrawal of 24 wk maintenance treatment was similar to that observed after 6 wk induction therapy, and the median time to relapse was equal in the two groups (39 d *versus* 38 d)[97].

Other oral corticosteroids, such as prednisolone, are associated with more frequent side-effects, and the efficacy seems inferior to budesonide, although no formal comparative studies are available[99].

Bismuth subsalicylate has been shown to be effective in a small placebo-controlled study including nine patients with CC and five with LC[100]. This drug is not available in a number of countries because of concerns regarding drug toxicity.

Sulfasalazine or mesalazine have been extensively used in MC but not strictly evaluated in randomized placebo-controlled trials. In a recent trial, 64 patients with MC were randomized to mesalazine 2.4 g/d or mesalazine 2.4 g/d + cholestyramine 4 g/d for 6 mo. A high remission rate was seen in both treatment arms, and 85% of patients with LC and 91% of those with CC were in remission at study end. Combined therapy was superior in CC and induced an earlier clinical response in both diseases[101]. The benefit of mesalazine with or without cholestyramine needs to be confirmed in a placebo-controlled trial.

Antibiotics such as metronidazole or erythromycin have been used but not in a controlled fashion. Probiotic treatment shows uncertain results and need further evaluation[102]. *Boswelia serrata* extract has been tried in a placebo-controlled trial showing a non-significant trend in favor of active treatment[103].

In patients with unresponsive or steroid-resistant disease, immunosuppressive therapy may be considered, although the evidence is limited. An open study with azathioprine gave partial or complete remission in eight of nine patients with MC[104]. The efficacy of methotrexate has been assessed in a retrospective study[105]. Out of 19 patients with CC, a good response, generally seen within 2-3 wk of treatment, was seen in 16 and a partial response in two patients. The dose of methotrexate ranged from 5-25 mg/wk (median 7.5-10 mg/wk).

Surgical therapy may be considered for patients with severe unresponsive MC. Both split ileostomy and subtotal colectomy have been performed and reported as successful[54,106]. The indications for surgical therapy today are limited, considering the improvement of medical therapy.

The long-term prognosis of MC is generally good. In a follow-up study of CC, 63% of the patients had a lasting remission after 3.5 years, and in another cohort study, all 25 patients were improved 47 mo after diagnosis, and only 29% of them required ongoing medication[107,108]. A benign course was reported in 27 cases with LC, with resolution of diarrhea and normalization of histology in > 80% of patients within 38 mo[109]. Others have reported that 63% of patients with LC had a single attack, with a median duration from onset of symptoms to remission of 6 mo[20].

CONCLUSION

MC is a fairly common cause of chronic diarrhea, especially in elderly women, and may considerably impair the patient's quality of life. The correct diagnosis depends on the awareness of the condition by the clinician (referring the patient with chronic diarrhea to colonoscopy and not to barium enema), by the endoscopist (obtaining mucosal biopsies although the colonic mucosa is endoscopically normal) and by the pathologist (recognizing the histopathological features of MC). Treatment with budesonide is effective in the short term and improves the patient's symptoms and quality of life, but the optimal long-term therapy needs further study. The long-term prognosis is good and the risk of complications including colonic cancer is low.

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