Microscopic Colitis: Diagnosis and Management

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# Abstract

Microscopic colitis (MC) is a common cause of chronic, non-bloody, watery diarrhoea in older patients. The diagnosis depends upon characteristic histological findings. Bile acid malabsorption and autoimmune conditions, including coeliac disease, are more frequently found in patients with MC, but colorectal neoplasia and mortality are not increased. Non-steroidal anti-inflammatory drugs, proton-pump inhibitors, selective serotonin reuptake inhibitors and smoking tobacco confer an increased risk of developing microscopic colitis. Although a so-called benign disease, which rarely causes serious complications, it does have an impact on the quality of life. Several treatment options exist, but budesonide is the only treatment proven in randomised-controlled trials to be effective and safe for induction and maintenance of remission. This article provides a practical overview for the gastroenterologist looking after patients with microscopic colitis.

# Introduction/Clinical Features

Microscopic colitis (MC) is a chronic inflammatory disease of the colon, detected in up to 19% of patients presenting for colonoscopy for chronic non-bloody diarrhoea.(1, 2) MC is a collective term for lymphocytic colitis (LC) and collagenous colitis (CC), which have similar clinical features, endoscopic findings, management and response to treatment. For research purposes, and indeed as the understanding of their pathophysiology evolves, they may be treated as distinct entities. For current clinical purposes, however, they are treated simply as MC as demonstrated by the approach in current European and American guidelines.(3, 4) MC is characterised by chronic or intermittent non-bloody diarrhoea, endoscopically normal or near-normal colonic mucosa and characteristic histological findings. LC is defined histologically by an increased number of intraepithelial lymphocytes and CC is distinguished by the presence of a thickened sub-epithelial collagen band.(5) The pathogenesis of MC is not yet clear and is beyond the scope of this article. The cause is likely to be multifactorial, incorporating a dysregulated, adaptive mucosal immune response to luminal antigens in predisposed individuals.

## Epidemiology

The incidence of MC is similar to that of ulcerative colitis and Crohn’s disease. It affects proportionally more elderly and female patients. A population-based study estimated the incidence at 21.0 cases per 100,000 person-years, with a median age at diagnosis of 65.8 years (range 22.8-92.1) and a female to male ratio of 3:1.(6)

Several risk factors and associations have been identified. MC is associated with autoimmune disorders, most frequently coeliac disease. The prevalence of MC in a cohort of 1009 patients with coeliac disease was 4.4%, which is 45-fold greater than in patients without coeliac disease.(7) Bile acid malabsorption (BAM) is also associated and was found in 43% of a cohort of 57 patient with MC.(8) A prospective case-control study identified current smoking (odds ratio [OR], 2.4), a history of polyarthritis (OR, 20.8) and the medications lansoprazole (OR, 6.4), low-dose aspirin (OR, 3.8) and beta-blockers (OR, 3.6) to be associated with an increased risk of CC. Similarly, it identified current smoking (OR, 3.8), autoimmune disease (OR, 8.0), omeprazole (OR, 2.7), low-dose aspirin (OR, 4.7) and sertraline (OR, 17.5) with an increased risk of LC. Certain medications are associated with, or may even induce, MC. Combined causality and chronological criteria and number of published cases have been used to identify higher likelihood medications for triggering MC. Acarbose, aspirin, lansoprazole, non-steroidal anti-inflammatory drugs (NSAID), ranitidine, sertraline and ticlopidine were identified as high likelihood medications. (9) Overall, the most evidence for drug-induced MC implicates NSAIDs, proton-pump inhibitors (PPI) and selective serotonin re-uptake inhibitors (SSRI).

## Quality of Life

Health-related quality of life is reduced in patients with MC compared to matched controls. However, effective treatment can return quality of life indices back to that of ‘normal’ subjects as measured by Short Inflammatory Bowel Disease Questionnaire scores.(10)

Symptoms

The ubiquitous symptom of microscopic colitis is non-bloody, watery diarrhoea. This can have a sudden or insidious onset. Stool frequency varies; commonly patients pass 4-9 stools per day but can often exceed 10 stools per day. Retrospective studies of 199 patients with LC and 163 with CC demonstrated that diarrhoea was present in 96% and 100% of patients respectively. Weight loss and abdominal pain are present in over 40% of cases. Nocturnal diarrhoea and fatigue are also prominent.(11, 12)

## Clinical Course

The clinical course and speed of onset of MC is highly variable within the reported literature. This may be a product of variable study design and evolving treatment approaches over the time frame of the body of work. For a proportion of patients, symptoms will resolve spontaneously or after implicated medications are discontinued, some will have single episodes, some a relapsing-remitting course, the remainder will have continuous symptoms. In CC, one cohort experienced a chronic intermittent course in 85% of cases, a continuous course in 13% and a single symptomatic episode in only 2%. In LC, there may be more isolated or self-resolving episodes with one cohort reporting a chronic intermittent course in 30% of case, continuous in 7% and single episodes 63%.(11, 12)

## Long Term Outcomes and Colorectal Neoplasia Risk

In a 24 patient cohort of CC, aged between 20-82 years old and followed up for 5-16 years post-diagnosis, 42% had chronic or intermittent diarrhoea. 17% were asymptomatic. No patients developed colorectal cancer, ulcerative colitis or Crohn’s disease.(13) When patients with MC have been compared to the general population and matched controls retrospectively after a follow-up period of up to 12 years, or prospectively to patients investigated for chronic non-bloody diarrhoea, the risk of developing colorectal neoplasia is not increased.(2)

# Evaluation and Diagnosis

For a patient’s first presentation with chronic diarrhoea, after a careful history and examination, blood tests including full blood count, urea and electrolytes, C-reactive protein, thyroid function tests and coeliac serology are useful as a matter of routine. Stool culture is indicated if infection is suspected or to be excluded and colonoscopy is indicated if colorectal cancer or an inflammatory bowel disease is suspected. Faecal calprotectin levels are routinely measured during investigation of chronic diarrhoea but are not useful specifically for MC, as detailed below. The British Society of Gastroenterology guidelines provide useful information for the assessment of chronic diarrhoea.

There is clearly overlap between the symptoms of diarrhoea-predominant irritable bowel syndrome and MC. Scoring systems have been proposed to risk stratify patients with respect to MC versus functional diarrhoea, considering the resources, invasiveness and rare, but non-zero, risks associated with colonoscopy.(14) Age >50 years, female gender, weight loss, absence of abdominal pain, current smoking, NSAIDs, PPIs, SSRIs, nocturnal diarrhoea and duration of diarrhoea <6 months are all implicated in these systems. These scoring systems, however, have not yet been validated with prospective studies outside their conceptual publications. They largely mirror the known epidemiological risk factors for MC, the presence of which should already predispose clinicians to pursue colonoscopy with biopsies.

If MC is suspected, colonoscopy with biopsies is mandated.

The current European Microscopic Colitis Group consensus statement recommends excluding coeliac disease, BAM and lactose malabsorption during the evaluation of MC.(3) Malabsorptive symptoms, iron deficiency or significant weight loss should prompt the careful exclusion of coeliac disease. Associated diseases should especially be sought when therapy for MC and or withdrawal of causative drugs does not ameliorate symptoms.

Faecal calprotectin levels can be elevated in MC, but they are not useful in the diagnosis, exclusion or follow-up of MC.(5) Significantly elevated levels, depending on locally determined thresholds, should prompt investigation in patients with otherwise suspected functional bowel disorders, or positive identification of an alternative explanation such as infection or the use of NSAIDs. Analysis of patients with known CC demonstrated that calprotectin was elevated in active CC compared to quiescent CC and controls, but 38% of patients with symptomatically active CC had normal levels, indicating that calprotectin does not have reliable exclusion value when assessing for MC.(15) Prospective analysis of calprotectin in patients presenting for colonoscopy with chronic non-bloody diarrhoea did not show an association between a diagnosis of MC and calprotectin levels.(1) C-reactive protein, erythrocyte sedimentation rate and auto-antibody profiles are not helpful in the evaluation of MC.

## Diagnosis

In patients with a compatible clinical picture, lower gastrointestinal endoscopy with histological analysis of biopsy samples is required to make the diagnosis of MC. Endoscopy typically reveals grossly normal colonic mucosa although erythema or oedema may be observed. Reported endoscopic findings in MC have included alteration of the vascular mucosal pattern, nodularity, and mucosal tears/lacerations (‘cat-scratch colon’) or cicatricial lesions.(16) Figure 1 illustrates such colonoscopic findings.

MC is the diagnosis made in 19% of patients attending for colonoscopy for chronic non-bloody diarrhoea, making it the most frequent diagnosis in such patients.(1, 2) The presence of ulcers at colonoscopy suggests an alternative pathology or may be explained by the concurrent use of NSAIDs.

The diagnostic histological finding in CC is a sub-epithelial collagen band of >10μm thickness (normal collagen band thickness is approximately 3μm). There is an increased predominantly mononuclear inflammatory cell infiltrate in the lamina propria and the surface epithelium can become detached.(5, 17)

The histological diagnosis of LC is defined as >20 intra-epithelial lymphocytes per 100 epithelial cells with an increase in the inflammatory infiltrate in the lamina propria, but without thickening of the sub-epithelial collagen band.(17) Figure 2 shows the typical histology of CC and LC.

One should, ideally, obtain biopsies from the ascending, transverse, descending and sigmoid colon, although there is no consensus about the optimum number of biopsies from each segment.(5) Studies have demonstrated that omitting segments will lead to missed pathology and diagnostic histology is more often found in the right colon. Therefore, flexible sigmoidoscopy is insufficient to confidently exclude MC.(18)

# Management

The goal of treatment is to induce remission from symptoms and, in the frequent cases of a relapsing disease course, to maintain remission sufficiently to improve quality of life. The Hjortswang criteria were devised focusing upon the effect of symptoms on quality of life and define remission as <3 stools/day with <1 watery stool/day.(19) Pragmatically, treatment success will be judged by how satisfied the patient is with their symptomatic response. Proof of histological remission is often described in research literature, but repeat colonoscopy and biopsy is not normally required in clinical practice unless patient progress mandates further evaluation or suggests an alternative diagnosis. Symptomatic and histological remission in MC are usually well correlated.(20-22)

The first step in management is removing exacerbating factors i.e. smoking and medications. PPIs, SSRIs and NSAIDs are to be avoided; more extensive lists of medications with their likelihood of triggering MC have been formulated.(9)

Several pharmacological treatments exist for MC but budesonide is the mainstay for induction and maintenance of remission in MC. Budesonide is recommended as first line therapy in both American Gastroenterological Association guidelines and European Microscopic Colitis Group statements.(3, 4) It is the only treatment studied in randomised-controlled trials (RCT). If symptoms are mild, loperamide, cholestyramine, mesalazine or bismuth may be considered, but these are less effective.

## Budesonide for Induction of Remission

An RCT in CC demonstrated that 9mg oral budesonide once daily for eight weeks, versus mesalazine or placebo, achieved a clinical remission rate of 80% (n=30) on an intention-to-treat basis with a median time to remission of seven days. This was statistically significantly better than mesalazine, which was no better than placebo.(22) Response in LC is similar; a recent RCT in LC of 9mg oral budesonide once daily for eight weeks achieved a clinical remission rate of 79%.(20) This study was stopped early after interim analysis showed that budesonide was superior to placebo. Again, mesalazine was not more effective than placebo. Safety analysis suggested budesonide was safe as well as effective. Serum cortisol levels at baseline and after eight weeks of budesonide treatment were not different.

## Budesonide for Maintenance of Remission After Relapse

Patients can have single episodes of MC, especially in drug-induced MC, but more often will suffer relapse after induction therapy is complete. These will require consideration for maintenance therapy. Long-term outcomes of 33 patients with CC who achieved clinical remission with budesonide were assessed over a median follow-up period of 16 months. 61% clinically relapsed, 88% of these relapses occurred within 3 months after cessation of treatment.(23)

In three RCTs, 4.5-6mg budesonide daily was superior to placebo to maintain clinical remission and associated health-related quality of life over 6-12 months of treatment. Remission was maintained in 61-77% of cases.(10, 24, 25) Relapse after discontinuation of one year of budesonide treatment was frequent, 82.1%, (n=28) suggesting longer term treatment is beneficial.(25)

## Safety of Budesonide

Long-term use of conventional corticosteroids, such as prednisolone, is fraught with side effects and complications. Budesonide appears similarly effective but safe for prolonged use possibly due to its extensive pre-systemic metabolism. One must consider concurrent cytochrome P450 inhibitor use which could potentially increase systemic exposure.(26) Meta-analysis found comparable side effect rates to placebo. Budesonide does not appear to affect endogenous cortisol levels after induction or maintenance therapy for a year and guidelines do not suggest dose tapering is required.(20, 25) A large case-control study of corticosteroids and fracture risk showed there was no increased risk with budesonide use (n=91).(27) One study suggested cumulative budesonide use in MC was associated with lower hip and spine bone mineral density, with a 2500mg cumulative dose over three years predicting osteopenia.(28) Increasing age, female gender and smoking are all associated with MC and osteoporosis. Osteoporosis screening and prevention is recommended in guidelines for any patient with MC requiring maintenance therapy with budesonide. We suggest supplementation of calcium and vitamin D in this cohort and remaining cognizant of side-effects including hypertension and steroid-induced diabetes, even if rare.

Relapse and Refractory Cases

One must always reconsider the diagnosis in the event of persistent symptoms. Medications and smoking status should be carefully reviewed. Coeliac disease, BAM, lactose malabsorption and small intestine bacterial overgrowth should be considered. Loperamide, bismuth, mesalazine can be trialled. Cholestyramine may be especially helpful and can be used concurrently with budesonide. It has been shown to help in MC with co-existing BAM.(8) If symptoms are truly refractory and significantly impactful upon quality of life, immuno-modulating therapy may be required.

## Immuno-modulating Therapy

Data regarding treatment of MC with immuno-modulators such as azathioprine, methotrexate and anti-tumour necrosis factor have been published. One study of budesonide-refractory, -dependent and –intolerant patients reported a 43% complete response rate using azathioprine (n=49), 58% with methotrexate (n=35) and 40% with infliximab or adalimumab (n=10). Notably 35% of patients taking thiopurines had adverse effects resulting in cessation of treatment. Other studies have reported on relative ineffectiveness of azathioprine and methotrexate in MC.(29, 30) Rigorous controlled studies are required to investigate the safety and efficacy of immuno-modulating treatments for MC. Details of surgical intervention such as ileostomy with or without colectomy have been reported, but these are limited to isolated case reports.

# Conclusion and Our Practice:

MC is a common cause for chronic non-bloody, watery diarrhoea, especially in elderly females. Diagnosis depends on high quality colonoscopy and histopathological assessment of biopsies of the left and right colon. Coeliac disease should be excluded at least with anti-tissue transglutaminase levels and BAM always kept in mind. First line treatment is 9mg budesonide once daily for 8 weeks. In the event of relapse, the patient should be re-assessed and re-treated, aiming to taper to the lowest possible budesonide maintenance dose, for example 3mg alternate days. All patients requiring *maintenance* budesonide should be prescribed calcium and vitamin D supplementation and have bone mineral density checked. One should remain vigilant for corticosteroid side effects and, after a year of therapy, assess whether on-going treatment is required.

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Figure 1 – Characteristic Colonoscopic Findings in Microscopic Colitis

a – ‘Cat-scratch colon’, haemorrhagic linear mucosal breaks/tears

b – Cicatricial lesion, fine linear scar-like lesions, possibly the healed remnants of previous cat-scratch type lesions

Figure 2 - Characteristic Histology of Lymphocytic Colitis and Collagenous Colitis

a – Lymphocytic colitis with increased intra-epithelial lymphocytes (haematoxylin-eosin).

b – CD3 immunohistochemistry demonstrates the increased intra-epithelial lymphocytes, stained brown. CD3 antigen is specific to T-lymphocytes.

c- Thickened collagen band and loss of surface epithelium in collagenous colitis (Masson Trichrome). Masson Trichrome staining protocol distinguishes cells from connective tissue, in this example demonstrating the sub-epithelial collagen band stained blue.