Microscopic colitis

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Abstract. *Microscopic colitis is viewed as an umbrella term applicable to both lymphocytic and collagenous colitis. The first case was published in 1976, a new entity with chronic watery diarrhoea with lymphocytic colitis, with or without a subepithelial collagen deposition. Patients are usually middle-aged women. The pathogenesis is unknown. The response to steroids and the female predominance underscores an autoimmune disease. Up to 40 % non-steroidal anti-inflammatory drugs-induced and lansoprazole-induced microscopic colitides are well-known. Biopsies during sigmoideoscopy in unexplained diarrhoea must be standard. Treatment is empirical. The most important step is to ban all non-steroidal anti-inflammatory drugs and other microscopic colitis inducing agents. Immunosuppressive treatment must be considered. However, the disease has a benign course and sometimes is self-limiting.*

Key words: *microscopic colitis, lymphocytic colitis, collagenous colitis*

Microscopic colitis (MC) is viewed as an umbrella term applicable to both lymphocytic colitis (LC) and collagenous colitis (CC) (28,29,38). The first case of CC was published in 1976 by Lindström, who described a new entity in which chronic watery diarrhoea was associated with a thick, subepithelial collagen deposition in biopsy samples of endoscopically normal colonic mucosa (29). The term lymphocytic colitis was proposed in 1989 considering the absence of the collagen band on histological evaluation (28). These entities are now generally recognized and MC has become a common condition of unknown cause especially affecting the large bowel (27). MC features are chronic watery diarrhoea without blood, abdominal pain, normal blood test results, no signs of malabsorption, normal microbiology, radiology and endoscopic findings. Histopathology reveals a thickening of the subepithelial collagen layer beneath the basement membrane throughout the colon with lymphocytic infiltrates in the lamina propria. The pathogenesis and significance of these findings are still unknown.

Therapeutical options are mainly based on case reports. However, in recent literature budesonide and azathioprine seem promising. In some cases, the symptoms are resolved spontaneously.

EPIDEMIOLOGY

Patients with CC are usually middle-aged women, with a female/male ratio from 3 - 20 : 1 (27,44). Most are in the fifth or sixth decade, age range of 10 - 90 years with a mean age of 50 - 60 years (6,36,44). The incidence of CC is estimated between 0.2 - 2.3 / 105 inhabitants (27). In LC there is a less pronounced predominance of women 1.6 - 3 : 1 (36). The peak onset for LC is similarly in the fifth or sixth decade, the same age range as CC, with a mean of 50 - 65 years (36,44). Differences in incidence probably reflect the lack of unification of these entities. Familial clustering of CC has been recognized (25,42,44).

PATHOGENESIS

The pathogenesis of MC is unknown. There are many features, which suggest that MC might be an autoimmune disease. The response to steroids and the female predominance emphasise this hypothesis. Remission has been reported during pregnancy (6). A luminal agent or an immunological reaction against

Table 1 **Reported associations of microscopic colitis and other autoimmune diseases**

Disease	*Association in %*	*Reference*
Coeliac disease	6 - 10 %	36, 39
Thyroid disease	up to 20 %	20, 36
Diabetes mellitus	up to 10 %	36
Rheumatoid arthritis	up to 2.5 %	36

an endogenous antigen produced by enterocytes might trigger the disease (6). Immunoglobulin IgM is increased in CC (40 %) (9). Positive antinuclear antibodies were found in 30 % - 50 % (36,44). P-ANCA was found positive in 10 - 14 % of patients (44). Up to 40 % of patients have one or more associated autoimmune diseases (36). Coeliac disease in 6 - 40 % (36,39), thyroid diseases in up to 20 % (20,36), diabetes mellitus in 10 % and rheumatoid arthritis in 2.5 % of MC patients are reported. Other autoimmune diseases have been reported such as CREST syndrome, Sjögren's syndrome, psoriasis, Raynaud phenomenon, dermatomyositis, polymyalgia rheumatica, Wegener's granulomatosis, Behçet's disease and systemic lupus erythematodes (36). Intraepithelial lymphocytes in patients with CC are increased. These lymphocytes are predominantly CD8+ T-lymphocytes with the α/β heterodimer, whereas the lymphocytes in the lamina propria are dominated by CD4+ T-lymphocytes. However, the distribution of CD8+ T-lymphocytes in the epithelium versus CD4+ T-lymphocytes in the lamina propria is the same as in normal intestinal mucosa.

Luminal agent

The observation that diversion of the faecal stream can normalize or reduce the histopathological changes in CC support the hypothesis of a luminal agent as a possible aetiological factor (24). These presumed agents in the faecal stream presumably cause epithelial leakage and vacuolisation of the enterocytes. They become flattened or cuboidal without a covering mucin layer. This weakens the epithelial barrier resulting in thickening of the subepithelial collagen layer, constructing a new barrier. The predominant abnormalities of MC in the proximal colon support the luminal agent hypothesis. The luminal agent might be phagocytosed by macrophages and then presented to immunocompetent cells stimulating the immune system and initiate a cascade of inflammatory reactions involving fibroblast proliferation possibly responsible for the excessive collagen deposits. Microbiologic studies in MC give no clear explanation. Yersinia enterocolitica has been suggested as a factor in developing MC (7). Resolution of CC after antibiotic treatment for Helicobacter pylori supports the microbiological hypothesis (34). Nitric oxide and plasma nitrate and nitrite levels are increased in CC patients. It is not clear whether nitric oxide is produced by the inflamed mucosa or is of bacterial origin (30,44).

Drugs

Adverse drug effects are implicated to cause microscopic colitis. Best known are non-steroidal anti-inflammatory drugs (NSAIDs)-induced and lansoprazole-induced MC (16,27,49). NSAIDs-induced MC is characterized by histopathological features of CC and hypoproteinaemia. This might be caused by NSAIDs-induced protein-losing enteropathy. The watery stool can even obtain mucus and/or blood. Ulcerations and perforations have been described (49). NSAIDs might be an aetiologic factor in CC. NSAIDs inhibit the synthesis of prostaglandins, especially of PGE2, and give rise to an increased production of collagen (16). Some suggest that colitis caused by NSAIDs should be classified as a different entity, because of differences in clinical features (49). Withdrawal of NSAIDs is usually followed by improvement of the clinical and histological abnormalities. These patients seem to be more prone to use aspirin or other NSAIDs (30 - 60 %) (36). However, withdrawal did not mean a disappearance of complaints in all of them.

Lansoprazole-induced MC shows histopathological abnormalities as seen in CC and LC. The mechanism is unexplained. Toxic or immunological factors may be involved. Symptoms are watery stool and mild abdominal pain. These complaints can occur in up to 5 % of lansoprazole-users (23). Discontinuing the drug resolves the complaints and histology normalizes (43). Similar observations about other PPI have been reported as case-reports, but not confirmed by others (43,48). Other agents causing MC are ticlopidine (LC) (5), cimetidine (22), ranitidine (LC and CC) (3), cyclo 3 fort (LC) (4,44), carbamazepine (LC) (31), simvastatin (17), vinca alkaloid (LC) (19), tardyferon (LC) (14), and a case of acarbose (LC) (37).

Fibroblast dysfunction

A synthesis dysfunction in the fibroblast sheet has been reported. Decreased levels of interstitial collagenase (Matrix Metalloproteinases MMP-1) and increased expression of TIMP-1, a tissue inhibitor of MMP-1, have been found in patients with MC suggesting that reduced matrix degradation and not overactivation of matrix synthesis leads to subepithelial accumulation of matrix proteins like collagen type III and especially type IV and tenascin. These findings indicate that inadequate local fibrinolysis is a major cause of collagen accumulation in CC (33,45). Smoking has been suggested to protect against MC (36,44).

CLINICAL FEATURES

The onset of MC is in 60 % insidious, and in 40 % (sub)acute. The symptoms are watery diarrhoea (4 - 10 stools per day), nocturnal diarrhoea, faecal urgency, bloating, abdominal pain, and meteriorism. Sometimes symptoms are intermittent. Weight loss is quite common. Dehydration is uncommon. When sticky faeces is found one should suspect coeliac disease. Vice versa persistent diarrhoea in treated coeliacs means strong suspicion of MC. The course of MC is relapsing and benign (36). Sometimes, patients become socially disabled caused by frequent diarrhoea. Although the majority of patients are female, the symptoms and progression is similar in men and women. Laboratory findings can show a mild elevated erythrocyte sedimentation rate, a normocytaemic anaemia and occasionally abnormalities in serum levels of IgG, C3 or C4 complement (8). Differences in HLA haplotype between CC and LC have been suggested. In LC there is an increase in HLA A1 and a decrease in HLA A3 haplotype whereas in CC there are no differences between patients and controls (6). However, data are limited. Microbiology remains negative. Steatorrhoea and increased excretion of faecal leukocytes are reported in more than 50 % of patients (44). P-ANCA and other autoimmunologic factors are found positive, implicating a link with auto-immune diseases. Colonoscopy is the preferred diagnostic tool given the possibility for proximal and distal biopsies. Radiology is not helpful in recognizing MC.

DIAGNOSIS AND HISTOPATHOLOGY

Diagnosis is based on classical symptoms of chronic watery diarrhoea without blood, abdominal pain, normal blood test results, no signs of small bowel malabsorption, and normal microbiology, radiology and endoscopy. The pathophysiology of the watery diarrhoea has been investigated, with special interest for the disturbed electrolyte and water transport in CC (15). The mechanisms for diarrhoea in MC include: I) malabsorption of fluid due to hampered transport and to collagenous bands. II) secretory diarrhoea due to anion (chloride) secretion, and III) "leak flux-induced diarrhoea" due to an impaired epithelial barrier secondary to lymphocyte infiltration and thickening of the collagenous band which is comparable with data in Yersinia colitis (15), and to a passive back leak of ions and water into the intestine lumen. This is probably related to decreased function of the tight junctions (15). The definitive diagnosis of MC relies on histologic diagnosis on biopsies taken from the colon, characterized by:

1) A diffuse thickening of the collagen layer beneath the basement membrane in a patchy manner throughout the colon in CC but absent in LC with lymphocytic infiltration in the lamina propria in CC and more pronounced in LC. The presence of more than 10 intraepithelial lymphocytes per 100 epithelial cells seems specific and helpful for diagnosing CC and/or LC (36). The thickness of the subepithelial layer in normal individuals varies from 0 - 3 μm (29). A thickness of 10 μm or more has been accepted to establish the diagnosis CC. A collagen thickness exceeding 45 μm might be an epithelial barrier (20,34). Stool weight correlates with severity of mucosal inflammation and not with collagen thickness (44). The basement membrane consists of collagen type IV. The collagen layer in CC beneath the basement membrane consists of collagen types I, III and IV, and VI. Collagen I and III are thought to be important in tissue repair (6,16). However type VI collagen might be considered to be a pathologic collagen deposition (16).
2) The inflammation in the lamina propria is dominated by lymphocytes and plasma cells. Eosinophils and mast cells can be found but neutrophils are very rarely observed (6). Cryptitis and crypt abcesses do not exclude the diagnosis of MC (26).
3) The epithelial cells appear to be flattened and vacuolized. Intraepithelial lymphocyte infiltration is present but is more prominent in LC. A histopathologic diagnosis can be made with endoscopy. Subtle endoscopic changes in up to 30 % of cases, such as mucosal oedema, erythema or mucosal paleness have been described. Detachment of the surface epithelium can occur. Haemorrhagic mucosal laceration after insufflation in CC patients with a thick collagen layer has been recognized (21). Taking biopsies of macroscopical normal mucosa in cases of diarrhoea is mandatory (27). Considering the patchy distribution of MC in the colon, sigmoideoscopy seems insufficient. Rectal biopsies might be insufficient in up to 75 % because the collagenous layer seems more prominent in the proximal colon. Others could not reproduce any diagnostic accuracy between sigmoideoscopy and colonoscopy (32,40,44). Subepithelial collagen deposits are reported in case reports in duodenum

and ileum mucosa in CC-patients, so-called collagenous enterocolitis or as a primary entity (6). Collagenous gastritis in combination with CC has been reported (16,47). Collagenous and lymphocytic gastritis seems strongly associated with coeliac disease in up to 40 % of the patients (41). Considering the benign course of the disease without any evidence of premalignant potential there seems to be no need for routine follow-up colonoscopy (11,18,44).

MANAGEMENT

Treatment of MC is still empirical. The first and most important step is to ban all NSAIDs and other colitis inducing medications (44). Additional medication is mostly symptomatic such as bismuth subsalicylate, antidiarrhoeals (loperamide, dephenoxylate, atropine) and high fiber diet. Although bismuth is effective and well tolerated its use in Western Europe is limited because it is not regularly available (2). Step two: 5-ASA agents might be helpful (45% response) (13,27). Bonner et al. found a short term response in 17/22 (81%) patients using an average 5-ASA dose of 1500 mg during a-six week period (13). Step three: (topical) corticosteroids, immunosuppressives such as azathioprine, and octreotide and step four, as a last resort, surgery. In our experience step four has never been necessary. In some studies 40 % of the subjects had complete resolution of symptoms without therapy (36). The first group of medication is often well tolerated showing good beneficial effects (36).

If the patient presents with severe watery diarrhoea, step two medication is introduced. If there is no response, corticosteroids are the next step. The response is 80 % - 100 % but relapses occur during tapering. Steroids have many side effects. For most, the usually benign course of MC does not justify prolonged use of steroids. Budesonide is a topical acting steroid with a high lipophilicity leading to both a high receptor-binding affinity and a high first-pass effect in the liver. Clinical efficiency of budesonide in inflammatory bowel disease is not significant different from prednisolone but it leads to significant fewer side effects (45). It has effects on both the inflammatory mucosal changes as well as the thickness of the collagen band (12,33). It is recommended to treat these patients during a course with 9 mg budesonide (2,10,33). Azathioprine and methotrexate should be considered in steroid-dependent and steroid-refractory patients (35,46) or as steroid-sparing agent. Data concerning these therapeutics are limited. Azathioprine seems successful in a dose of 2 mg/kg daily (46). The long term follow-up results are promising with high response rates (13). In a minority of patients the diarrhoea remains severe despite treatment. In these patients, diverting ileostomy with or without colectomy is effective, interestingly showing normal ileostomic volumes postsurgery (44). These data are similar for CC and LC. Abdo et al. (1) investigated several clinical and histological predictors of response in the treatment of CC. They found that the age of onset determining. Older patients were most likely to be controlled with antidiarrhoeal agents or no medication. The younger patients needed more medication. NSAIDs use at time of presentation was associated with greater need for 5-ASA and steroid therapy (1,27). Interestingly, cessation of NSAID in 60 % did not affect the course. Also the degree of inflammation of the lamina propria can be used as a predictor. The more intense the inflammation, the more patients are likely to fail on symptomatic treatment (1).

Table 2 **Reported treatment options for microscopic colitis**

Drug	*Dosage (mg)*	*Response (%)*	*Reference*
5-ASA	1500 mg	up to 80 %	13, 27
prednisone	40 - 60 mg	80 - 100 %	39
budesonide	9 mg		12, 33, 45
azathioprine	2 mg / kg		36, 46

DISCUSSION

MC forms a subclass of inflammatory bowel disease. Some suggest a gradual transition from a LC-like colitis to CC. Wilcox et al. (48) described a patient with histological findings of CC and later LC in reaction to lansoprazole. The thickening of the subepithelial collagen band in CC is believed to be secondary to chronic inflammation. Also the similarity in treatment suggests a common pathologic pathway. The collagen band is the latest microscopic factor to resolve during treatment, stressing the more chronic component. The diagnosis is often only assessed by biopsy. It is recommendable to obtain at least two specimens from transverse colon, descending colon, sigmoid colon, and rectum. This should lead to the diagnosis in the majority of the patients. Colonoscopy should be used in patients with high suspicion for CC or LC. This is because of the declining histopathological changes

from the proximal to the distal colon. The aetiology of MC is unknown. Three major theories are suggested. First, the lymphocytic infiltration is probably based on an adequate immunoresponse to a foreign luminal agent (toxin, microbiological or other substrates). Secondly, the CD4 and CD8 lymphocyte distribution in this form of colitis show similarities with coeliac disease. The latter suggesting a possible autoimmune aetiologic factor. Associations with other autoimmune diseases such as thyroiditis, rheumatoid arthritis, ANA positive diseases, diabetes mellitus and coeliac disease support this theory. Thirdly, the collagen band seems secondary to disorders in collagen matrix and in fibrinolytic factors. The treatment in CC and LC is similar. First of all, NSAIDs and other colitis-inducing medication should be withdrawn. In mild diarrhoea, fibers and antidiarrhoeal agents can be successfully used. In some cases antibiotics such as erythromycin and metronidazole seemed effective. If this is not sufficient, 5-ASA can be added. For more severe manifestations of diarrhoea (stool frequency > 5 times/day) topical steroids such as budesonide are the drug of choice. The symptoms resolve quickly and overall it is well tolerated. If the disease is relapsing or it is refractory, long-term immunosuppressives should be considered. The first results with azathioprine are promising. Usually the disease has a benign course and sometimes is self-limiting.

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