New insights and challenges in microscopic colitis

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***Abstract*:** Microscopic colitis (MC) is described as an inflammatory bowel disease characterized by chronic, bloodless diarrhea with normal or close to normal endoscopic findings. Histopathological examination reveals two subtypes: collagenous colitis (CC) and lymphocytic colitis (LC), which are indistinguishable clinically. The disease debuts typically in middle-aged patients, but can occur at all ages, including children. A female predominance is found in both CC and LC, but is not confirmed by others in LC. The etiology is unclear, but the disease has been assumed to be of autoimmune origin. However, several etiologies may render a microscopic inflammation in the mucosa; this is a common, universal reaction to a variety of irritants in contact with the intestinal lumen. Furthermore, some patients with a microscopic inflammation in their colonic mucosa have no symptoms, or are suffering from constipation or abdominal pain, rather than diarrhea. Recently, a discussion was initiated calling into question the overdiagnosing of symptoms and pointing out the danger of exacerbating people's perception of their ailments, of weakening their eligibility in health insurance, of overprescription of drugs, and thus the increasing cost to the society of health care. In the light of this discussion, this review will highlight histopathological and clinical features of MC, and discuss the diagnosis and management of this disease. Perhaps, the intestinal mucosa has no other mode by which to react than an inflammatory response, irrespective of the presence or absence of autoimmunity. Thus, to better identify and classify subgroups of MC, and to clarify and correctly handle the inflammatory changes, this field of research stands to benefit from a review of the results and experience gained to date.

Keywords: ageing, irritable bowel syndrome, lifestyle factors, microscopic colitis, smoking

Background

Introduction

Chronic diarrhea is reported in 4–5% of individuals and makes up a considerable proportion of the consultations in gastroenterology [Thomas *et al.* 2003]. Diarrhea has for a long time been considered as functional after exclusion of celiac disease, inflammatory bowel disease (IBD), malignancy and so on [Drossman *et al.* 2006]. Over recent decades, microscopic colitis (MC) has emerged as a common cause of diarrhea, especially in middle-aged or older women, and the disease is regarded as a subgroup within IBD [Münch *et al.* 2012]. The disease is characterized by chronic, watery diarrhea and normal or close to normal findings by endoscopic examination. Intestinal, mucosal biopsies show characteristic histopathological changes [Robert, 2004; Thijs *et al.* 2005; Temmerman and Baert, 2009]. Although as many as 63% of patients only have a single attack of the disease [Olesen *et al.* 2004a], the patients who have received the diagnosis are considered to be suffering from a chronic disease. MC can be considered a primary lymphocytic disorder of the gut, whereas many other disorders may be associated with lymphocytic infiltration or collagenous deposition, in which cases MC could be considered a secondary disorder [Carmack *et al.* 2009].

Histopathology

In 1976, Lindström described microscopic inflammatory changes in colon with a remarkable subepithelial collagen band and called the condition *collagenous colitis* (CC) [Lindström, 1976]. Read

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and colleagues introduced the term *microscopic colitis* [Read *et al.* 1980]. In 1989, Lanzeby and colleagues showed that an increased number of colonic intraepithelial lymphocytes (IELs) was the most characteristic feature of MC and suggested the term *lymphocytic colitis* (LC) [Lazenby *et al.* 1989]. The diagnosis of MC is based on histopathological examination of mucosal biopsies from the colon, obtained through endoscopy [Robert, 2004; Thijs *et al.* 2005; Temmerman and Baert, 2009], in combination with nonbloody diarrhea [Olesen *et al.* 2004a; Pardi and Kelly, 2011]. The histopathological criteria for CC are a thickened subepithelial collagen layer of at least 10 μm (reference value: 2–7 μm); inflammation in the lamina propria with increased numbers of lymphocytes and plasma cells; epithelial damage; and increased numbers of IELs may be present. The histopathological criteria for LC are a density of at least 20 IELs per 100 surface epithelial cells; chronic inflammatory infiltrate of mononuclear cells in the lamina propria; epithelial damage; and a subepithelial collagen layer of less than 10 μm. The normal basement membrane in the bowel consists mainly of collagen type IV, laminin, and fibronectin. The increased collagen band observed in MC consists basically of collagen type I and III [Flejou *et al.* 1984], which are the subtypes produced by repair functions, indicating a reactive origin [Braskén, 1991]. The biopsies should preferably be taken from the ascending colon, since the pathological hallmarks may be absent in the descending colon, and in the normally occurring thicker collagen layer in the rectosigmoid region [Jessurun *et al.* 1987; Wang *et al.* 1988; Carpenter *et al.* 1992; Fernandez-Banares *et al.* 1999].

Recently, Carmack and colleagues have introduced the terms *primary* and *secondary* lymphocytic disorders of the gastrointestinal tract [Carmack *et al.* 2009]. Infiltration of lymphocytes in the lamina propria is unspecific and can be observed in all segments of the gastrointestinal tract. A common cause of lymphocyte infiltration in the stomach is infection by *Helicobacter pylori*, whereas celiac disease may cause MC throughout the gastrointestinal tract [Carmack *et al.* 2009]. Autoimmune diseases, bacterial and viral enteritis, and drugs are other etiologies of secondary LC [Carmack *et al.* 2009]. Seasonal fluctuations in the histopathology have been identified and suggest an allergic origin of MC in some circumstances [LaSala *et al.* 2005]. Surgical traction *per se* may lead to invasion of lymphocytes into the tissue [Lee *et al.* 2009].

CC-like findings have been reported in patients suffering from colon cancer, carcinoid lesions, adenomas and hyperplastic polyps, bacterial infections, lactose intolerance, and constipation [Flejou *et al.* 1984; Teglbjaerg *et al.* 1984; Nussinson *et al.* 1988; Wang *et al.* 1988; Gubbins *et al.* 1991; Leigh *et al.* 1993]. Both CC and LC are described in ulcerative colitis and Crohn's disease, together with the characteristics of these diseases [Goldblum and Wang, 2000]. MC in this context should be considered as a part of the original IBD disease, and not as a separate entity [Jegadeesan *et al.* 2013]. Furthermore, these changes can also be found in persons without any signs of gastrointestinal symptoms or diseases [Wang *et al.* 1988; Thörn *et al.* 2013]. Altogether, there is no histopathological hallmark that differentiates primary, idiopathic MC from a MC evolved secondary to another syndrome or its treatment, or that differentiate MC in healthy subjects from patients with symptoms.

Epidemiology

Population studies have shown an increasing incidence of MC over recent decades, with a mean incidence rate of 1.1–7.0/100,000 inhabitants for CC and an incidence rate of 3.1–5.5/100,000 inhabitants for LC [Fernandez-Banares *et al.* 1999; Olesen *et al.* 2004b; Pardi *et al.* 2007; Vigren *et al.* 2012; Thörn *et al.* 2013]. The increased incidence has stabilized over the past years, and the incidence is associated with female gender and increasing age [Gentile *et al.* 2014]. Reports indicate that MC is more frequent in colder, northern countries than in southern countries [Pardi *et al.* 2007; Fernandez-Banares *et al.* 2011; Gentile *et al.* 2014]. This north–south gradient has led to speculations that vitamin D is involved in the pathogenesis, but this has not been confirmed [Sjöberg *et al.* 2013]. The female-to-male ratio ranges from 2.8:1 to 7.5:1 for CC and from 2.1:1 to 2.7:1 for LC [Fernandez-Banares *et al.* 1999; Olesen *et al.* 2004b; Vigren *et al.* 2012], whereas in a later review, the ratio was 3.0–9.0:1 for CC and 6.0:1 to no difference in LC [Pardi and Kelly, 2011]. The average age at diagnosis is approximately 65 years [Münch *et al.* 2012].

Etiology and pathophysiology in MC

The etiology is in most cases unknown, and is probably multifactorial, also when only primary MC is included, as the terminology constitutes a

morphological, descriptive term, representing many different entities, presenting with an inflammation in the mucosa.

Genetic predisposition

Only a limited number of familial MC cases have been reported [Abdo *et al.* 2001; Järnerot *et al.* 2001], but as many as 12% of patients with MC have a family history of IBD [Olesen *et al.* 2004a]. There is an association between the expression of MC and HLA-DQ, and patients with MC have a high prevalence of tumor necrosis factor α and metalloproteinase-9 gene polymorphisms [Fernandez-Banares *et al.* 2005; Koskela *et al.* 2008; Madisch *et al.* 2011].

Hormonal factors

Endocrine factors have been discussed since most studies report a female predominance of MC [Fernandez-Banares *et al.* 1999; Olesen *et al.* 2004b; Vigren *et al.* 2012]. The intestinal epithelium provides a protective barrier for the internal milieu against luminal factors, which is dependent on intercellular, epithelial tight junctions [Turner, 2006]. Increased paracellular permeability has been implicated in the pathogenesis of chronic, mucosal inflammation [Meddings, 1997; Teshima *et al.* 2012]. Estrogens and progesterone have been shown to exhibit anti-inflammatory and epithelial barrier-enhancing properties in experimentally induced colitis in rats [Günal *et al.* 2003; Karatepe *et al.* 2012; Moussa *et al.* 2012], and the fall in hormone levels at menopause could theoretically explain the peak age of debut of MC in middle-aged women [Pardi and Kelly, 2011]. However, no differences in reproductive factors between CC and LC, or between patients with MC or healthy controls, could be identified [Roth *et al.* 2013c].

Autoimmunity and comorbidity

The association of MC with various autoimmune diseases such as celiac disease, thyroid disease, rheumatoid arthritis, and diabetes mellitus has given rise to the hypothesis that MC is an autoimmune disease [Pardi *et al.* 2002; Olesen *et al.* 2004a]. The predominance of middle-aged female patients further strengthens the autoimmune hypothesis, although no specific autoantibody has been identified [Pardi and Kelly, 2011]. Several small studies have proposed an increased prevalence of antinuclear antibody, antigliadin IgA, and anti-*Saccharomyces cerevisiae* antibodies in serum in patients with MC [Holstein *et al.* 2006]. Scrutinizing a greater cohort of patients with MC with 11 different autoantibodies did not show any increased prevalence of autoantibodies in patients with MC compared with healthy controls [Roth and Ohlsson, 2013; Roth *et al.* 2013b; Gustafsson *et al.* 2013]. Recent research suggests an increased morbidity in a wide range of chronic diseases in patients with MC, irrespective of autoimmunity, including ischemic cardiovascular diseases, hypertension, asthma, and allergy [Roth *et al.* 2013d].

Smoking and alcohol habits

Smoking has been confirmed to be associated with MC [Yen *et al.* 2012; Vigren *et al.* 2011], and smokers contract MC 10 years earlier than nonsmokers [Vigren *et al.* 2011]. Accordingly, lung cancer is associated with MC [Chan *et al.* 1999]. Current MC and MC in combination with abdominal pain were associated with smoking, whereas transient MC was associated with past smoking, and pure MC without abdominal pain was not associated with smoking [Roth *et al.* 2013a, 2014].

In one study, alcohol consumption was higher in patients with MC compared with healthy controls [Yen *et al.* 2012]. Nevertheless, wine drinking did not tend to increase the risk of developing MC. Rather, wine drinking seemed to provide protection against the development of MC in smokers [Roth *et al.* 2014].

Luminal factors

The histological changes in MC are resolved by diverting the fecal stream by ileostomy, supporting the hypothesis of the role of luminal factors [Jarnerot *et al.* 1995], but the effect of food has been only rudimentarily studied.

Several drugs have been associated with the development of MC as causative or triggering agents [Olesen *et al.* 2004a]; the most common being nonsteroidal anti-inflammatory drugs (NSAIDs), proton-pump inhibitors (PPIs), and antidepressant or antipsychotic drugs [Chassany *et al.* 2000; Beaugerie and Pardi, 2005; Fernandez-Banarnes *et al.* 2007]. The pathophysiology can be explained by altered intestinal flora, a direct pharmacological effect on the colon, or an idiosyncratic hypersensitivity reaction [Münch *et al.* 2012]. A chronological connection must be established between the

introduction of the drug and the histopathological changes in combination with symptoms, and improvement or disappearance of the diarrhea and restored histological picture when the treatment is ceased [Beaugerie and Pardi, 2005].

There is growing evidence for involvement of gut microbiota in the development of IBD [Wagner, 2008; Shim, 2013], but its effect on the development of MC has not been adequately studied. Bacterial and viral gastroenteritis may induce MC [Makinen *et al.* 1998; Perk *et al.* 1999; Erim *et al.* 2003]. Bile acid malabsorption has been shown to coexist in 60% of patients with LC and in 44% of patients with CC [Ung *et al.* 2000; Fernandez-Banares *et al.* 2001]. It remains to be determined whether bile acid malabsorption is causative or secondary.

Clinical presentation

The clinical features of MC are described and defined as chronic, relapsing, nonbloody, watery diarrhea [Olesen *et al.* 2004a; Pardi and Kelly, 2011]. The diarrhea may be mild, but severe, frequent diarrhea with urgency is common [Bohr *et al.* 1996]. Nevertheless, some patients with histopathological features of MC are asymptomatic [Wang *et al.* 1988; Gubbins *et al.* 1991; Thörn *et al.* 2013]. About 50% of patients with diagnosed MC fulfill the criteria for irritable bowel syndrome (IBS) [Roth and Ohlsson, 2013]. These patients have abdominal pain, and some patients also have constipation. In fact, all gastrointestinal symptoms are accentuated in patients with MC compared with healthy controls [Roth and Ohlsson, 2013]. The clinical aspects of CC and LC are indistinguishable [Rasmussen and Munck, 2012; Roth and Ohlsson, 2013]. The onset is often insidious, but 25–40% of the patients have a sudden onset [Bohr *et al.* 1996; Olesen *et al.* 2004a]. The majority of patients have only a single attack of the disease with spontaneous remission in about 10% [Gubbins *et al.* 1991; Olesen *et al.* 2004a; Roth *et al.* 2013a; Thörn *et al.* 2013], and the patients are in symptomatic remission after 3–4 years [Bonner *et al.* 2000]. Thirty percent of patients with MC have a chronic intermittent disease, and only 7% have a chronic, continuous course which may be refractory to treatment [Järnerot *et al.* 1995; Olesen *et al.* 2004a].

Diagnosis and treatment

First, it is mandatory to exclude inflammation secondary to another gastrointestinal disease, drug treatment or infection [Carmack *et al.* 2009]. When secondary MC is the case, the MC must be regarded as a part of the original disease, and the original disease or condition must be treated. Withdrawal of toxic agents and drugs is mandatory when MC was evolved after such administration [Fernandez-Banares *et al.* 2007]. As many of these patients are past or current smokers, and older, intestinal ischemia must be considered [Roth *et al.* 2014]. Smoking abstinence should be encouraged, as past smoking is associated with transient, and not persistent, MC [Roth *et al.* 2014]. After exclusion of secondary MC, the diagnosis of true, primary MC can be set [Pardi and Kelly, 2011].

The primary aim in the treatment of MC is to achieve clinical remission and improve the patient's quality of life [Hjortswang *et al.* 2009]. The secondary aim is maintenance of clinical remission [Ianiro *et al.* 2012].

As most patients complain of diarrhea, traditional antidiarrheal agents such as loperamide are frequently used as first-line therapy [Pardi *et al.* 2002; Olesen *et al.* 2004a]. Budesonide is the only drug which has been proved to be efficient by randomized, placebo-controlled trials, and it is to date the standard treatment for moderate to severe MC [Münch *et al.* 2012; Storr, 2013]. Budesonide therapy resulted in a significant improvement in both clinical symptoms and histological inflammatory changes, but the relapse frequency is about 61–80% [Baert *et al.* 2002; Bonderup *et al.* 2003; Bonderup et al. 2009; Mielke et al. 2005; Miehlke *et al.* 2009]. The relapse frequency is reduced by sustained treatment at low dosage [Stewart *et al.* 2011]. Budesonide has the advantage over corticosteroids due to the high, hepatic first-pass elimination, thus avoiding the side effects of steroids [Stewart *et al.* 2011], and the efficacy of budesonide is superior to prednisolone, although no comparative studies are available [Munck *et al.* 2003].

Treatment with bile acid bindings is efficient to diminish the symptoms, but has no effect on the histopathological changes [Ung *et al.* 2001]. Bismuth subsalicylate was effective in MC in a small, randomized, placebo-controlled trial [Fine and Lee, 1998]. Aminosalicylates have, in uncontrolled or retrospective studies, had a moderate to good effect in MC [Pardi *et al.* 2002; Chande *et al.* 2008]. The experience of other immunosuppressive therapies are gathered in some systematic reviews, based on retrospective studies and case

reports [Riddell *et al.* 2007; Münch *et al.* 2012]. In severe, refractory cases, these therapies or surgical intervention may be appropriate to test [Järnerot *et al.* 1995].

Treatment strategy of MC

(1) Cessation of possible offending irritants or medications.
(2) Antidiarrheal drugs.
(3) Budesonide.
(4) Cholestyramine, immunomodulating drugs, or ileostomy and colectomy.

Discussion

Over the past century, the population, especially women, have changed their life habits and lifestyle substantially. A microscopic inflammation in the colonic mucosa may hypothetically be the reaction to all the irritants the colon is exposed to in daily life. The barrier function of the gut epithelium may be diminished in the course of a lifetime, due to fall in estrogen levels around the menopause and changes in microbiota diversity [Günal *et al.* 2003; Karatepe *et al.* 2012; Moussa *et al.* 2012; Patten and Collett, 2013; Kamada *et al.* 2013], facilitating the penetration of irritants into the mucosa. The greater prevalence of MC findings in the ascending than descending colon suggests an important role for luminal factors [Jessurun *et al.* 1987; Carpenter *et al.* 1992]. Thus, the increased incidence of MC with increasing age could represent a normal ageing process [Gentile *et al.* 2014].

Surgical traction of the tissue is enough for lymphocyte invasion [Lee *et al.* 2009]. During colonoscopy, the bowel is cleaned by laxatives and biopsies are taken at the end of the examination, after traction of the bowel. Biopsy-taking at the start of the examination should perhaps be more appropriate and reduce the incidence of LC. The nature of the collagen layer in CC has only been studied sparsely, but the few studies performed suggest the collagen layer is a secondary reaction to prior damage, and thus not causal [Braskén, 1991].

Younger people with abdominal pain and altered bowel habits are often diagnosed as having IBS and colonoscopy is avoided not to aggravate the condition further [Drossman *et al.* 2006]. Older people with gastrointestinal complaints are often prescribed a colonoscopy to rule out malignancy. Thus, younger people are less frequently examined by colonoscopy than older patients, which may affect the age at incidence peak of MC. During the past two decades, colonoscopy has almost completely replaced X-ray examination of the colon, an examination which could never yield the diagnosis MC. Awareness by pathologists may also increase the incidence figures. CC was observed in the biopsies only at re-examination, not initially [Wang *et al.* 1988; Olesen *et al.* 2004b]. All these scenarios influence the diagnosis setting, the peak age at diagnosis, and whether the diagnosis IBS or MC is set. Thus, the true incidence figures over time and peak age at diagnosis setting must be recognized in the light of these aspects. A recent population-based study shows a stability in incidence figures, which may reflect the truth when all factors stated above have been settled [Gentile *et al.* 2014].

Smoking has been described as a risk factor for developing postinfectious, functional gastrointestinal disorders (FGIDs) [Parry *et al.* 2005], for overlapping syndromes of reflux diseases and FGID [Fujiwara *et al.* 2011], and for functional dyspepsia, but not for IBS [Boekema *et al.* 2001]. Another study has shown that both visceral and peripheral pain are increased by smoking [Pisinger *et al.* 2011]. Smoking was associated with patients fulfilling both the criteria for IBS-like symptoms and MC, and not with pure MC [Roth *et al.* 2013a, 2014]. It remains to be determined whether smoking causes IBS, with the ensuing need of a colonoscopy whereby microscopic inflammation can occasionally be found, or whether smoking induces true MC. Another hypothesis is that smokers with MC also experience abdominal pain. Furthermore, the atherosclerosis evolved in smokers may cause intestinal ischemia with signs of lymphocyte infiltration [O'Neill and Yalamarthi, 2012]. Associations between MC and smoking may reflect confounders and do not prove any causality. Further studies should attempt to elucidate whether there is a protective effect against the consequences of smoking when combined with alcohol, in analogy with the protective effect of alcohol against the induction of rheumatoid arthritis [Maxwell *et al.* 2010].

The reported connection between MC and autoimmune diseases [Pardi *et al.* 2002; Olesen *et al.* 2004a] may be explained by the fact that a patient already in hospital care due to another chronic disease is more often referred to a specialist in gastroenterology and for a colonoscopy when presenting with gastrointestinal complaints than a healthy person in primary care. Thus, many cohorts presented in the literature, also epidemiological

studies, constitute selected cases of the disease [Fernandez-Banares *et al.* 1999; Olesen *et al.* 2004a, 2004b; Pardi *et al.* 2007]. Diabetes mellitus and MC is one of the connections reported [Pardi *et al.* 2002; Olesen *et al.* 2004a]. When analyzed further, this connection was seen between MC and diabetes mellitus type 2, and not type 1 [Roth *et al.* 2013d]. Thus, the connection may rather reflect mechanisms other than autoimmunity, for example, cardiovascular changes and metabolic dysfunction. A microscopic inflammation is sometimes seen throughout the gastrointestinal mucosa in celiac disease, and therefore, the connection between celiac disease and MC may in some cases represent one entity instead of two different entities [Carmack *et al.* 2009]. As the villi are absent in the colon, the only possible reaction to gluten in the colon is infiltration of lymphocytes and other inflammatory cells into the lamina propria. This is further underlined by healing of the MC after introduction of a gluten-free diet [Olesen *et al.* 2004a]. Both the MC and the villus atrophy are sometimes resistant to diet [Olesen *et al.* 2004a; Carmack *et al.* 2009]. All patients with both MC and any type of thyroid disorder were found to be under treatment with levothyroxine, and in most cases, the drug was introduced prior to the debut of MC [Gustafsson *et al.* 2013]. Furthermore, patients with MC had a lower prevalence of antithyroid peroxidase antibodies than healthy controls [Gustafsson *et al.* 2013]. It is not surprising that a disease like MC, which is prevalent among middle-aged or older people, is associated with other chronic diseases. It is of great importance to examine patients from a whole region, and not only from tertiary centers, and to use appropriate control groups to estimate true associations [Gustafsson *et al.* 2013; Roth *et al.* 2013d].

All drugs used in the treatment of autoimmune diseases have been suspected to induce MC [Pardi *et al.* 2002; Beaugerie and Pardi, 2005; Fernandez-Banares *et al.* 2007; Carmack *et al.* 2009; Münch *et al.* 2012]. Thus, the finding of MC in patients with autoimmune diseases may reflect the treatment with NSAIDs, PPIs, and other drugs. If not taking into consideration secondary forms of MC, underlying, treatable diseases may be overlooked, while only the gastrointestinal symptoms are treated symptomatically or with budesonide. Some scientists are more prone to exclude secondary forms of MC than others [Gentile *et al.* 2014]. In recent decades, the treatment of cardiovascular diseases and diabetes mellitus has been more aggressive, and patients live longer under treatment with several different vasoactive drugs, of which some are associated with MC [Fernandez-Banares *et al.* 2007; O'Neill S and Yalamarthi, 2012]. Vascular changes in the bowel are a frequently underestimated condition, and the characteristics for ischemic colitis are similar to those described for the MC population [Bohr *et al.* 1996; Olesen *et al.* 2004a; Pardi and Kelly, 2011; O'Neil and Yalamarthi, 2012]. Corticosteroids are used in the treatment of MC, with a better response than other anti-inflammatory drugs [Münch *et al.* 2012]. However, corticosteroids and budesonide have a broad, nonspecific, anti-inflammatory effect and can also be useful in the treatment of ischemic, radiatic, and toxic colitis [Kochhar *et al.* 1991; Onishi *et al.* 2008; O'Neil and Yalamarthi, 2012]. The reduced effect by other anti-inflammatory drugs [Riddell *et al.* 2007; Münch *et al.* 2012] may reflect a noninflammatory etiology of MC. The concomitant existence of many, severe diseases and the intake of several drugs may have a synergistic, harmful effect on the colonic mucosa [Roth *et al.* 2013d]. It is not reasonable to believe that patients in the age range of 80–90 years, with cardiovascular damage, several diseases, and drug treatments have an additional autoimmune disease as the explanation for their lymphocyte infiltration in the lamina propria.

The growing, worldwide opinion is that at least two attacks of gastrointestinal inflammation and symptoms are necessary before the diagnosis of IBD is set [Henriksen *et al.* 2006], as a single attack of diarrhea is impossible to differentiate from an infectious gastroenteritis. When scrutinizing all medical records in several districts of Sweden, it was found that the majority of patients had had only a single attack of MC [Olesen *et al.* 2004a; Roth *et al.* 2013a; Thörn *et al.* 2013]. The same rule as for IBD should be introduced with respect to MC. Accordingly, one single attack of lymphocyte infiltration may not be judged as a lifelong disease. Furthermore, we must have a new classification to differentiate primary from secondary MC, and a pure histopathological description from a clinical syndrome. This would be more useful than the classification of CC and LC, which are indistinguishable from each other in daily practice [Rasmussen and Munck, 2012; Roth and Ohlsson, 2013]. In secondary MC, treatment should focus on the original disease, and cessation of drugs must be considered before the diagnosis MC is set. The risk of overdiagnosing the disease is to stigmatize harmless conditions and weaken

the person's eligibility for health insurance. An overprescription of budesonide to older women, already sick from, or at risk of developing osteoporosis, must be avoided.

Summary

Since 1976 when the first case of MC was reported, many studies have been conducted and new knowledge has been confirmed. MC is a nonspecific, histopathological picture which may be the result of a variety of different etiologic and pathologic processes, as well as being a normal variant in healthy subjects. The incidence of MC is associated with increased age, suggesting that MC may be a normal ageing process along with a diminished epithelial barrier, possibly due to ischemia and reduced estrogen levels, while at the same time the mucosa is exposed to many drugs.

A new classification is necessary to get more homogenous cohorts, before further research in this field can be performed to try to identify possible etiologies of primary, idiopathic MC. The importance of classification and division of MC into CC and LC must be called into question, at least in the clinical setting and in the handling of the diseases. A description of the normal ageing of the gastrointestinal mucosa should be performed, especially regarding the natural expression of inflammatory cells and thickness of the collagenous layer, related to different age groups.

A new terminology is suggested in this field.

(1) The term MC should be reserved for a description solely of the histopathology.
(2) A primary, idiopathic, histopathological finding, in combination with gastrointestinal symptoms, should be called primary MC. Examinations of at least two colonic biopsies at an interval of some months should be performed, and the clinical gastrointestinal symptoms, not only restricted to diarrhea, should be of a chronic, relapsing or continuous nature.
(3) Secondary causes of the histopathological findings should be referred to as secondary MC.
(4) One single attack of histopathological findings and gastrointestinal symptoms should be considered a transient MC and not classified under the same terminology as relapsing or chronic symptoms.

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Conflict of interest statement

The author declares that there is no conflict of interest.

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