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CLINICAL REVIEW

Diagnosis and treatment of microscopic colitis

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Abstract Microscopic colitis (MC) designates two types of chronic diarrhea diseases, which are lymphocytic colitis and collagenous colitis. The prevalence of microscopic colitis is increasing in both Western and Eastern countries, possibly due to the high incidence of colonoscopic survey in chronic diarrhea patients. Although the overall prognosis of MC patients is mostly good, it should be noted that appropriate diagnosis and choice of treatment is required to assure a good clinical outcome for MC patients. Also, a certain population of MC patients may take a severe and refractory clinical course, and thus require advanced clinical care using medications supported by less evidence. In this review, we would like to feature the essential points regarding the diagnosis of MC, and also describe the current standard of treatments for MC patients. In addition, we would like to add some findings from the national survey and research carried out in Japan, to compare those data with the western countries.

Keywords Microscopic colitis · Collagenous colitis · Lymphocytic Colitis · Budesonide

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Introduction

Microscopic colitis (MC) is a category of intestinal disorder that includes two sub-types of diseases such as collagenous colitis (CC) and lymphocytic colitis (LC). The concept of the disease was first described by Lindstrom [1], through the finding of a subepithelial collagenous deposit in the biopsy of a chronic watery (non-bloody) diarrhea patient. The term "microscopic colitis" was established by Read et al. in 1980, to describe a certain category of disease characterized by chronic, non-bloody diarrhea [2]. Since then, the concept has grown to constitute a certain category of gastrointestinal disease, and several statements or guidelines have been published from the leading international societies or study groups [3–6]. However, the disease is still not sufficiently recognized by physicians or even among gastroenterologists, and thus patients may receive an alternative inappropriate diagnosis such as irritable bowel syndrome (IBS). Thus, in this review, we would like to describe the essential points for the proper diagnosis of MC, and guide the standard treatments for those MC patients. Also, we would like to introduce some of our findings based on the national survey and research carried out in Japan, and compare those with data from Western countries.

Epidemiology and prevalence of MC

The general trend of the diagnosis of MC is increasing in Western as well as in Eastern countries. However, recent reports demonstrate that the number of MC patients is reaching a plateau in the USA and Sweden [7, 8]. The trend and the details of the epidemiologic data have been described elsewhere [4, 5]. However, the number of MC

patients is also increasing in Asian countries such as Japan and Korea. The most recent multi-center study in Korea showed that up to 22 % of chronic diarrhea patients can be diagnosed with MC [9]. A national survey in Japan identified a total of 140 MC patients [10]. A single-center survey of 82 chronic diarrhea patients in Nagano, Japan, showed that up to 28 % of those patients may meet the criteria of MC [11]. Thus, a certain population of chronic diarrhea patients can be diagnosed as MC, both in Western and in Eastern countries. One of the reason as to why diagnosis of MC is increasing may be the increased frequency of diagnostic colonoscopy during the workup for the evaluation of chronic diarrhea patients [12]. However, a study showed that the susceptibility to MC may differ among different ethnic groups [13]. In the study, MC was less common in Indian, Hispanic, and East Asian groups.

Pathophysiology and risk factors of MC

The majority of the pathophysiology of MC is not fully understood. However, several studies have suggested the involvement of an impaired or dysregulated immune response, possibly to a yet-to-be-identified luminal antigen [14, 15]. Recent studies suggest the involvement of Th17 cells [16], or those of the microbiome [17]. Genetic factors or the involvement of miRNAs have been suggested, but they remain largely controversial [18]. Additionally, epithelial cells may also play a certain role in the pathogenesis of MC, as they have been implicated in the development of intestinal inflammation [19]. LC and CC may arise from a different immunopathologic basis [20], but the clinical manifestation is mostly common, and therefore it is usually difficult to distinguish one from the other [21].

There are several risk factors that predispose patients to develop MC. Certain categories of drugs can cause drug-induced MC. The most well-known drug may be the proton-pump inhibitors [22, 23]. The addition of non-steroidal anti-inflammatory drugs (NSAIDs) may further increase the risk of developing MC [24]. A study has ranked the relative risk of each drug, based on the scoring of developing MC [25, 26]. In the study, 10 drugs including PPIs, NSAIDs, and SSRIs were ranked as high-risk drugs for developing MC. In Japan, lansoprazole has been identified as carrying one of the highest risks for developing MC [27]. However, it is not known why a specific population of patients who are exposed to these drugs develop MC, while it never happens in other patients. A possible explanation may be genetic susceptibility determined by polymorphism of the drug target-related gene [28].

Another risk factor is smoking. Smoking may be associated with the persistence of MC [29], or otherwise enhance the risk of developing MC at a younger age [30]. Also, autoimmune diseases including celiac disease, type 1 diabetes, autoimmune thyroiditis, or Takayasu's arteritis may be associated with MC [31–33], and therefore it is important to note that these patients may develop MC at a relatively higher incidence.

Diagnosis of MC

Diagnosis of MC should begin from the onset of clinical symptoms. The key symptom may be the persistent non-bloody diarrhea. The chronic nature of the diarrhea is often defined as those persisting for over 4 weeks. If such a symptom appears in a woman over the age of 50, diagnosis of MC should be highly suspected. Also, the existence of a newly started drug, or an accompanying autoimmune disease will support the possible diagnosis of MC. When a diagnosis of MC is suspected from the symptoms, background disease, or drug consumption history, the next workup should be a colonoscopy [34].

As the original definition of MC is a colitis that shows endoscopically normal colonic mucosa, it is unsurprising that colonoscopy is positioned as a key modality in the diagnostic process of MC in many guidelines or statements [4, 5, 35]. The importance of colonoscopy in the diagnosis of MC should be noted at least in the following two aspects: detection of MC-related mucosal lesions and careful collection of biopsies from every colonic segment.

Endoscopic appearance of the colon of MC patients may vary between patients, and may not always appear as a macroscopically normal mucosa. Recent advances in diagnostic endoscopy have suggested that several MC-related mucosal lesions may exist, and should be considered as a supportive finding in the diagnostic process of MC [21, 36–38]. Consistently, in a survey of Japanese CC patients, endoscopic findings were observed in up to 80 % of those patients [39]. Representative endoscopic findings that have been observed in MC patients are as follows: hyper-vascularity, indistinct vascular pattern, linear ulcers, and cat scratch sign (Table 1). Linear mucosal defects may be related to lansoprazole-associated collagenous colitis in Japanese cases [40], but it still remains controversial as to whether it can be commonly applied to cases of other areas. In a case of CC, severe mucosal fractures and even a perforation have been reported [41]. A caveat for these finding is that they may also appear in non-MC cases, and therefore the disease sensitivity is not guaranteed. Using advanced endoscopic imaging techniques such as narrow-band imaging (NBI) or Fujinon Intelligence Color Enhancement (FICE) may further reveal MC-related or MC-specific endoscopic findings.

The importance of endoscopic survey in the diagnosis of MC is also emphasized in taking biopsies from each part of

Table 1 Endoscopic findings reported in microscopic colitis patients

Endoscopic findings	References
Hypervascularity	[33, 36]
Indistinct vascular pattern	[33–36]
Patchy erythema	[34, 35]
Mucosal fragility	[33, 34]
Linear ulcer/scar	[33, 34, 36–38]
Granular mucosa	[36]
Cat scratch sign	[34, 36]
Crack-like appearance	[36]

the colonic segment. It is highly recommended to take at least two biopsies per segment, to assure a high likelihood of detecting any present MC-specific pathological findings [5]. There may be differences among the colonic segments in the appearance rate of MC-specific pathologic changes [42], but so far it appears to be sufficiently relevant to take biopsies from all the segments, rather than taking biopsies from a specific segment.

The pathologic evaluation of the biopsy specimens is the most important part of the diagnosis of MC. Whether a patient may be diagnosed as CC or LC completely depends on the existence of the specific pathological findings in the biopsy specimens. Definite criteria for the diagnosis of LC or CC is not fully established, but the key components may be defined as follows: subepithelial collagenous band (>10 μm in thickness) for CC (Fig. 1), and increase of intraepithelial lymphocytes (>10–20 IELs per 100 epithelial cells) for LC (Fig. 2) [4]. Tanaka et al. has suggested a pathological criteria for the diagnosis of Japanese MC patients (Table 2) [43]. In the criteria, it is suggested that the pathologic diagnosis should be considered from five components: thickening of the subepithelial collagen band, increase in number of the intraepithelial lymphocytes, infiltration of the lymphocytes and the plasma cells in the lamina propria, damage of the surface epithelium, and the existence of crypt distortion. However, a definite pathological decision may be difficult in some cases, and therefore those cases may be assigned as incomplete MC (MCi). In those cases, adding the immunohistochemical staining of CD3 or tenascin may aid in the diagnosis (Fig. 2) [44, 45].

Other supportive tools for the diagnosis of MC may be the fecal markers. The use of calprotectin in MC is controversial and currently not recommended [5]. However, it has been suggested that calprotectin may be useful to discriminate between MC and irritable bowel syndrome (IBS) [46]. Other markers such as chromogranin A, chromogranin B, or secretoneruin are suggested to be a candidate fecal marker for CC [47].

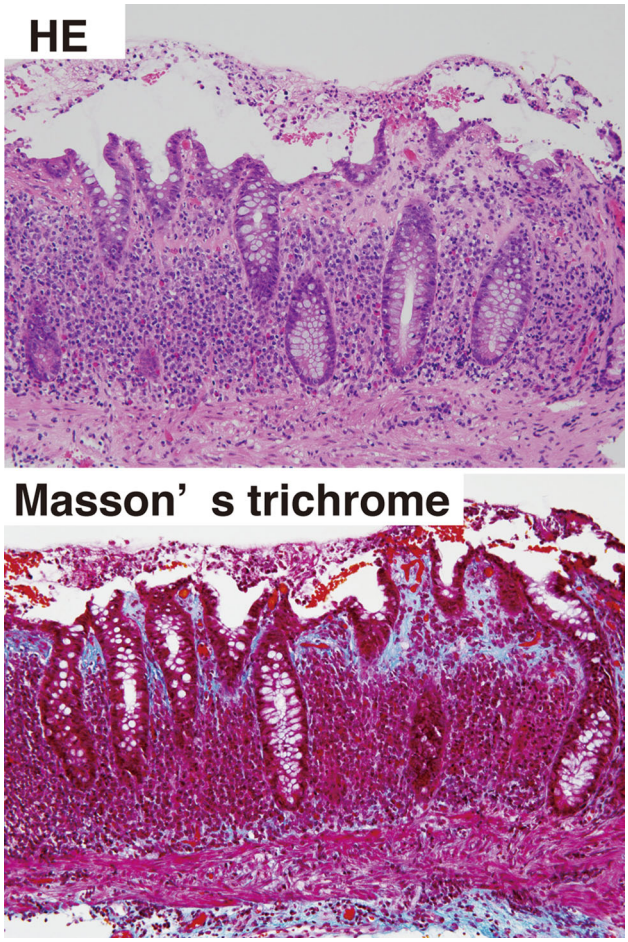

Fig. 1 Subepithelial collagen band in collagenous colitis. H&E staining (*upper panel*) and Masson's trichrome staining (*lower panel*) of the colonic tissue obtained from a collagenous colitis patient are shown. Note that thickening of the collagenous layer is clearly observed at the subepithelial area

MC frequently overlaps with related diseases such as IBS or celiac disease, which makes it sometimes difficult to confirm the diagnosis of MC [43, 44]. For those cases that are difficult to define, a scoring system has been suggested [45]. The system exhibited 90.5 % sensitivity and 45.3 % specificity in the diagnosis of MC. However, as only six items are considered in the scoring system, it is still considered controversial as to whether the system has the sufficient level of sensitivity and specificity [46].

In close relation to the treatment evaluation, judging the disease activity is also important. In this regard, the European study group has suggested a clinical disease activity scale, and defined that clinical remission should be judged when an MC patient has stool frequency of less than three times a day, and bowel movements are completely absent of watery stool [4].

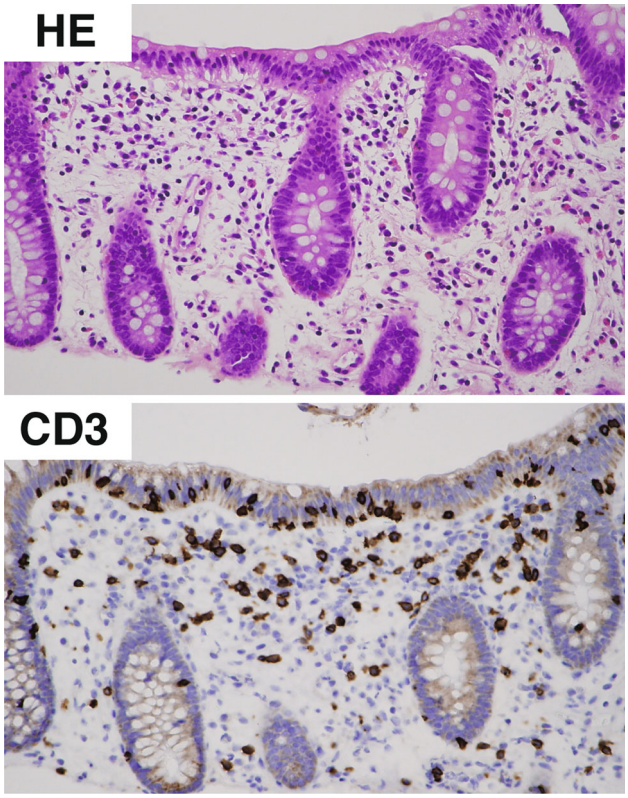

Fig. 2 Increase of intraepithelial lymphocytes in lymphocytic colitis. H&E staining (*upper panel*) and CD3 immunostaining (*lower panel*) of the colonic tissue obtained from a lymphocytic colitis patient are shown. Note that immunostaining of CD3 clearly demonstrates the increase of CD3-positive cells in the surface epithelial layer

Standard treatment of MC

The first line of treatment recommended to an MC patient is to avoid possible risk factors such as smoking or high-risk drugs. Spontaneous resolution of the disease activity is frequently observed in mild cases by simply avoiding suspected risk factors [47–49].

The second line, and the only medication that has an established evidence, is oral budesonide [4, 5, 35]. Oral budesonide at 9 mg per day for up to 8 weeks is the most established induction therapy to achieve remission of MC. The overall response may be expected for up to 81 % of MC patients [50]. In contrast, use of mesalazine is less successful to treat MC patients [51]. Other choices may be bismuth salicylate or mesalazine plus cholestylamine, but less possibility of successful treatment is expected, compared to budesonide. The high therapeutic potential of budesonide has been proved in recurrent cases of MC [52], and also in low-dose maintenance therapy [53]. Oral budesonide has been approved in more than 40 countries, but there still remain areas, such as Japan, where oral budesonide is not available as an approved drug. In those areas, oral prednisolone may be used as a substitute for budesonide. However, use of prednisolone cannot completely substitute budesonide, as it has a significantly high recurrence rate compared to budesonide [52]. No significant difference in the response to available therapies, including budesonide, was observed between CC and LC [54].

In more refractory cases, immune-modulators or biologic agents may represent a candidate treatment, but none of them have an established clinical evidence of their benefit [48]. For most refractory cases, continuous supportive nutrition, colectomy, or ileostomy may be an optional choice, but restoration of intestinal continuity may lead to the relapse of the disease [55].

Although there are only a limited number of drugs proven to be effective for MC, the overall prognosis is generally optimistic. A recent population-based study showed that up to 75 % of patients achieve long-term clinical remission [49]. However, a small percentage of patients are completely refractory to the standard treatments, and can be defined as severe refractory cases that may require surgical treatment [48]. Such an observation is

Table 2 Suggested criteria for the pathologic diagnosis of microscopic colitis (Adapted from reference 40 of Dr. Masanori Tanaka, Department of Pathology and Laboratory Medicine, Hirosaki City Hospital)

	Collagenous colitis	Lymphocytic colitis
Thickening of the sub-epithelial collagen band (SECB)	Present (SECB $\geqq$ 10 μm)	Absent (SECB $<$ 10 μm)
Increase in number of intraepithelial lymphocytes (IEL)	Present in most cases, but not necessarily required	IEL $\geqq$ 20 per 100 surface epithelial cells
Infiltration of lymphocytes and plasma cells in the lamina propria	Mild $\sim$ moderate (rarely severe)	
Damage of the surface epithelium (e.g., flattening or exfoliation)	Present in most cases, but not necessarily required	
Distortion of the crypt	Absent $\sim$ mild	

Biopsies should be taken from every segment of the colon

Avoid judging the thickening of the SECB and crypt distortion by inappropriately oriented tissue sections

also experienced in Japan, as three cases of severe refractory cases were reported in the last national survey [10]. Among them, two cases were young women, the diagnosis was not a drug-induced type of MC, and their disease onset was before 40 years of age. Thus, it might be better to note that a spontaneous MC of young disease onset might carry a risk of severe and refractory clinical phenotype.

Closing remarks

One of the problems in managing MC is the low attention paid to its diagnosis and treatment from the general community. The disease should receive much greater recognition in order to guide chronic diarrhea patients to the most appropriate diagnosis and treatment. Also, the disease concept is expanding to include analogous diseases not only in the colon, but also in the stomach or small intestine [50, 51]. Thus, we should be aware that "microscopic" gastrointestinal disease may possibly appear in any part of the gastrointestinal tract.

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Compliance with Ethical Standards

Conflict of interest Ryuichi Okamoto, Mariko Negi, Syohei Tomii, Yoshinobu Eishi, and Mamoru Watanabe declare that they have no conflicts of interest to declare.

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