

Microscopic Colitis: A Challenging Disorder

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Abstract

Background: The clinical importance of microscopic colitis (MC) is increasing. This is explained by both the increasing incidence and the challenges posed by the disease. However, recent MC data also reveal a number of doubts and uncertainties. **Summary:** This review focuses on current knowledge of MC and highlights the various controversies and criticisms regarding the clinical data about definitions, subtypes, pathogenesis, diagnosis, and treatment of this condition. **Key Messages:** The diagnosis of MC is based on histology, which distinguishes 2 subtypes. However, transitional forms often cause misclassification, which calls into question the reality (specificity, meaning) of the distinction between the 2 forms. The location of the colon biopsy is not defined by international consensus. There is no credible, clear explanation for the incidence increase. The pathogenesis is unknown, probably multifactorial, but the importance of the immunological background is increasing. The natural history of the disease and the underlying cause of relapses are unclear. It is suggested that MC would be the prelude of IBD. Further data collection is needed to clarify these issues.

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Microscopic colitis (MC) has come to the forefront of gastroenterologists' interest in the last decade. Increased attention is warranted by a number of factors, including the increasing incidence of the disease and the contradictions in knowledge.

Definition, Epidemiology

MC refers to the presence of usually intact colon mucosa during endoscopic examination and can only be diagnosed by histological examination. There are 2 forms of MC which can be distinguished by histological differences. In lymphocytic colitis (LC), there is chronic inflammatory infiltration in the lamina propria with lymphocyte and plasma cell proliferation, and in the epithelium lymphocyte count of >20/100 epithelial cells are observed. In collagen colitis (CC), subepithelial collagen is thickened (>10 µm). The normal upper limit of the collagen layer width is 7 µm; the thickness of 15 µm is already indicative.

In addition to the 2 histological subtypes, in the so-called incomplete MC despite the clinical symptoms suggestive for the disease, the histological features picture does not meet the criteria for any form [1]. In this form, histological abnormalities are only partially observed.

The number of lymphocytes and plasma cells is $<10/100$ cells, and subepithelial collagen is $<10\ \mu\text{m}$. The incomplete MC also raises the suspicion that the 2 classical forms may not represent 2 distinct entities, but rather a different stage of development of a single disease [2].

In the background of 8–16% of chronic nonbloody diarrhea, if the colonoscopy shows a regular macroscopic picture, MC is most likely [3]. It is predominantly seen in persons over 60 years of age and more frequently in women. CC is 9 times more common in women than in men [4]. The gender ratio in LC is lower. The incidence of MC is increasing worldwide [5]. The incidence is 4.1/100 per person years in CC and 4.9 in LC [6].

The incidence of MC has reached IBD levels in some populations and has even exceeded the incidence of Crohn's disease [7, 8]. Improved access to colonoscopy and increased awareness and knowledge of gastroenterologists and pathologists of the disease may be the reason for the more frequent recognition of MC. There are also ethnic differences in the prevalence of MC. It is more common in white populations and Jews than in non-white inhabitants, East Asians, and Hispanics [9]. To date, MC does not increase the risk of colon carcinoma [2].

Pathophysiology

The biological mechanism for the development of MC is unclear and is likely to be heterogeneous. Histological abnormalities in MC may also translate into clinical manifestations of different effects [10]. MC can be considered as an immune-mediated disorder with a critical involvement of adaptive immune system and cytotoxic responses. Uncontrolled immune responses to various luminal and mucosal effects may occur in genetically predisposed individuals. Bacteria and exogenous toxins from the intestinal lumen affect the mucosa and may trigger immunological responses. This is facilitated by increased intestinal permeability and reduced expression of tight-junction proteins. Variable cytokine profile leads to overexpression of tumor necrosis factor alpha and various interleukins. The role of gut microbiota in MC pathogenesis has also been raised, primarily because of a decrease in the concentration of Akkermansia species in some cases. However, this is not proven to be a primary pathogenetic factor and may be a secondary consequence.

Concerning the genetic background, data on the association with human leukocyte antigen are controversial [2]. Although data on interleukin -6-174 gene polymorphism and MC correlation have been reported

Table 1. Possible causes of watery diarrhea if colonoscopy shows a regular pattern

MC
Celiac disease
Infectious colitis (e.g., cryptosporidiosis)
SIBO
Giardiasis
Bile acid malabsorption
Bile acid exposure after removal of the gallbladder
Neuroendocrine tumors
Laxative abuse
Crohn's disease located in the Ileum
Gastrocolic fistula
Carbohydrate malabsorption disorder (e.g., lactose, sorbitol)
Irritable bowel syndrome

SIBO, small intestine bacterial overgrowth; MC, microscopic colitis.

[10]. This polymorphism leads to increased production of interleukin-6, an effective proinflammatory and pro-fibrogenic cytokine. However, the data available so far only suggest an initial evidence of the relationship and are not sufficient to prove the overall genetic risk [10].

Among the risk factors that trigger MC, drugs side effect are the most significant. Nonsteroidal anti-inflammatory drugs, proton pump inhibitors, selective serotonin reuptake inhibitors are known to induce MC [6]. However, planned clinical data, drug withdrawal, and challenge effects have not yet been verified. Other risk factors include smoking and alcohol exposure.

Clinical Presentation, Natural History, and Diagnosis

The clinical sign of MC is chronic, watery diarrhea that may be associated with cramping abdominal pain. Diarrhea may return after years of temporary remission of the symptoms.

The natural course of MC is characterized by the alternation of asymptomatic and diarrheal phases. Symptoms can disappear for years without treatment (spontaneous remission). However, according to randomized controlled trials, the symptoms reoccur in 80% of patients within 3 months of stopping budesonide treatment. Despite the recurrent symptoms, the disease does not worsen, does not represent an increased risk of death or malignant colon cancer.

The diagnosis of MC is based on histological examination. The clinical symptoms and regular macroscopic picture may be the feature of a number of disorders that must be considered in the differential diagnosis (Table 1).

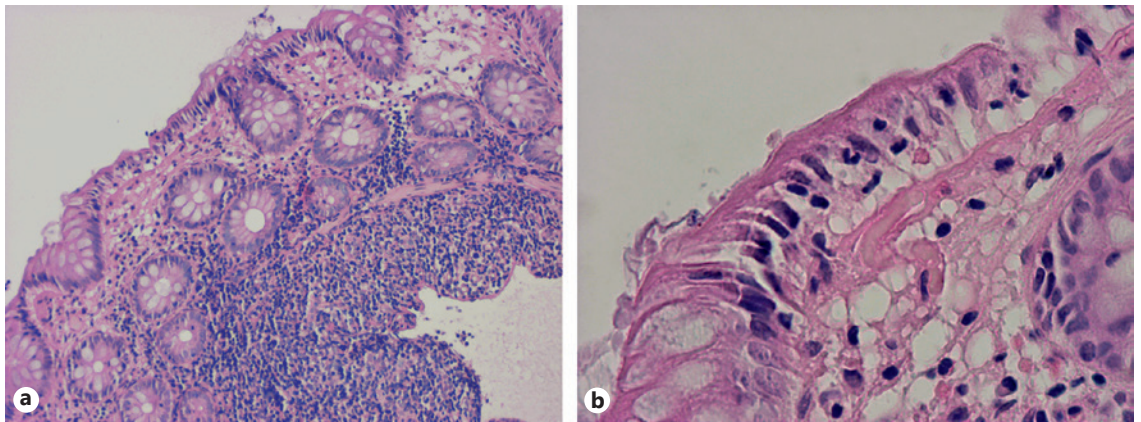


Fig. 1. Histology of lymphocytic colitis (hematoxylin-eosin staining), **a** 100 \times , **b** 400 \times magnification. There is a large number of lymphocytes among surface epithelial cells, with an IEL number of approx. 40/100 epithelial cells.

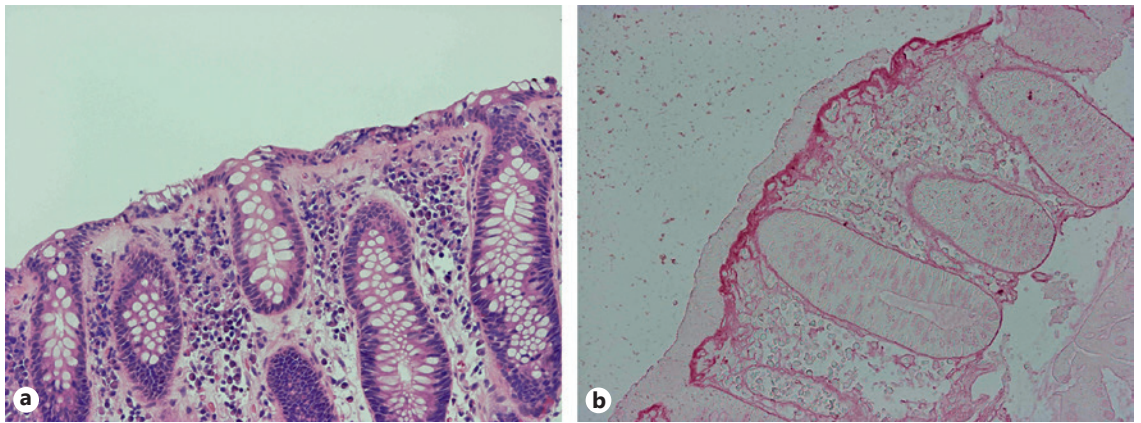


Fig. 2. Histological image of collagen colitis (hematoxylin-eosin staining) **a** 100 \times , **b** picosirius red 100 \times magnification. A thick eosinophilic collagen layer beneath the surface epithelium with haematoxylin-eosin staining, which is a vivid red color due to picro-

sirius staining, with a thickness of 15–30 micrometers. Surface epithelial cells are disordered and focal IEL numbers are increased. Plasma cell lymphocytic infiltration is visible near the surface of the stroma.

Neither laboratory abnormalities nor biomarkers (including fecal biomarkers) are diagnostic. Taking into account various risk factors and symptoms, a scoring system has also been developed to identify and predict the MC [11, 12]. However, the diagnosis cannot be made on this basis.

Colonoscopy is usually normal, although nonspecific alterations (hyperemia, edema, loss of vascular pattern, patchy erythema) may occur.

The histological feature of LC is intraepithelial lymphocytosis, which is primarily associated with an increase in the number of surface intraepithelial lymphocytes (IELs) [6]. The criterion is that at least 20 IELs of 100 surface epithelial cells are stained with hematoxylin-eosin (Fig. 1a, b). Normal value does not exceed 5. The surface epithelium may be slightly damaged, and a small degree

of collagen deposition may be observed in the subepithelium. If IELs are at threshold, immunohistochemistry is recommended to detect intraepithelial T cells. However, immunohistochemistry is a more sensitive method, with more stained IELs than with haematoxylin eosin, and is recommended in borderline cases when it is difficult to diagnose the disease [13].

The diagnostic criterion for CC is the thickened collagen band beneath the surface epithelium, which must exceed 10 μm for diagnosis (Fig. 2a, b). The surface epithelium may also be damaged, and the number of IELs cells may increase, but below the LC-specific value. In most cases, hematoxylin-eosin staining is of diagnostic value, but in borderline cases, connective tissue staining is also required.

In incomplete MC, the diagnostic criteria for LC and CC are not fully met. Although the number of IELs cells and the collagen band width increase, they do not reach the diagnostic threshold [14–16].

Choosing the location and number of biopsies is essential for diagnosis. MCs appear in patches and cell proliferation and collagen thickening may vary at different sites in the colon [2].

Because histological abnormalities may also be located regionally, biopsy from a nonaffected section may also be misleading. In the different colon segments, there is no dominant area for diagnosis [17]. Therefore, a total of at least 8 biopsies from all colon segments are required for diagnosis.

Treatment

The first-line therapy for MC is budesonide, with a dose of 9 mg/day 80% of patients can become symptom free within 6–8 weeks. In addition to resolution of symptoms, histological abnormalities may improve. Budesonide, a second-generation corticosteroid, exerts its action at the site of inflammation and binds with high affinity to intracellular glucocorticoid receptors. Budesonide cessation can lead to relapse of the disease and occurs primarily in 60–80% of CC. Therefore, maintenance therapy of 6 mg daily budesonide is necessary [18]. There is insufficient data on the need for long-term therapy in LC. Other anti-inflammatory and antisecretory drugs (prednisolone, mesalazine, cholestyramine, bismuth subsalicylate, loperamide) are less effective than budesonide.

Immunomodulatory therapy (thiopurin, azathioprine, methorexate) has been attempted in a relatively small number of patients, but the results are not encouraging (22–43% complete or partial response rate) [19]. There is limited experience with MC biological therapy. Moderate data on the use of antitumor necrosis factor agents and vedolizumab in some 10 patients are known. Biological treatment is considered primarily for budesonide-refractory patients, as a second-line therapy.

Challenges of Microscopic Colitis

Despite increasing professional interest in MC knowledge, there are more and more contradictions and challenges.

The definition of the disease is based on histological criteria; furthermore, the morphological features are

quantified (e.g., number of surface IELs, width of collagen band in μm). In many cases, quantitative data can only be validated by immunohistology, which makes routine histology uncertain.

It is not certain whether the 2 histological forms are really different entities or whether they could be different stages of a single pathological process. The incomplete MC can be integrated into this concept.

Borderline cases can only be defined by special histological techniques. How can borderline cases be interpreted? Are we observing a subset of a pathological process, a phase of the process, or an individual response to different triggers?

There are contradictory data on the dominance of the 2 subtypes [20]. Some data confirm the predominance of the LC subtype, while others contradict it. The question is whether this contradiction is the result of different histological judgments or inappropriate diagnostic work.

In many cases, uncertainty in quantitative data can lead to misclassification.

The causes of the increasing incidence of MC are unknown. Easier access to colonoscopy does not seem to be an adequate explanation, as incidences vary across countries with the same availability and levels of development.

There is also a lot of uncertainty about etiopathogenesis. Although the immunological origin is most likely, the gender differences, the older age predominance, and relative benign natural history do not support this assumption.

The relationship between different drug molecules and MC formation cannot be explained.

Pathologists do not know enough about the disease. The gastroenterologist should be advised that MC is a presumption (suspicion) otherwise the pathologist will not look for pathological features.

The location and number of biopsy sampling are not well defined. MC can undoubtedly affect the colon mucosa in a patchy manner, but it should be clarified which area of the colon and how many biopsies should be performed to minimize diagnostic error.

The natural history of the disease is not well known. The question is, in case of relapse, the histological picture is identical to the previous one? It is not known whether there is a transition between histological forms.

In the acute phase, the topical steroid is effective in most cases. However, budesonide-refractory MC is an important clinical challenge. Immunomodulators and biological treatments can be considered as second-line therapy.

After the acute phase, the duration of maintenance treatment is not known.

Theoretically, there is also the possibility that MC may be a form of IBD that has not yet been classified. In any event, similar or partially identical elements of putative pathogenesis and a partially identical mode of treatment are not against the possibility. However, no clear date is published on the relation between MC and other IBD.

Conclusion

Many elements of MC are contradictory. Despite growing interest and incidence, many questions remain unanswered. These questions concern many aspects of the disease that require further investigation.

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