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REVIEW

Towards a new paradigm of microscopic colitis: Incomplete and variant forms

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Abstract

Microscopic colitis (MC) is a chronic inflammatory bowel disease that has emerged in the last three decades as a leading cause of chronic watery diarrhoea. MC classically includes two main subtypes: lymphocytic colitis (LC) and collagenous colitis (CC). Other types of histopathological changes in the colonic mucosa have been described in patients with chronic diarrhoea, without fulfilling the conventional histopathological criteria for MC diagnosis. Whereas those unclassified alterations remained orphan for a long time, the use of the term incomplete MC (MCi) is nowadays universally accepted. However, it is still unresolved whether CC, LC and MCi should be considered as one clinical entity or if they represent three related conditions. In contrast to classical MC, the real epidemiological impact of MCi remains unknown, because only few epidemiological studies and case reports have been described. MCi presents clinical characteristics indistinguishable from complete MC with a good response to budesonide and cholestiramine. Although a number of medical treatments have been assayed in MC patients, currently, there is no causal treatment approach for MC and MCi, and only empirical strategies have been performed. Further studies are needed in order to identify their etiopathogenic mechanisms, and to better classify and treat MC.

Key words: Microscopic colitis; Incomplete microscopic

colitis; Collagenous colitis; Lymphocytic colitis

Core tip: Microscopic colitis (MC) includes two well-defined entities: collagenous colitis and lymphocytic colitis. Similar clinical manifestations, but variable histopathologic features have also been identified and recognized as additional forms of MC, as not all patients suffering from colitis fulfill the criteria for MC diagnosis. Introducing the histological diagnosis for incomplete MC subtypes could reduce the risk of missing patients with a treatable cause of chronic diarrhoea. The importance of developing research studies addressed at describing etiopathogenic mechanisms of MC subtypes is highlighted in this review.

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INTRODUCTION

Microscopic colitis (MC) is a chronic inflammatory bowel disease (IBD) that has emerged in the last three decades as a leading cause of chronic watery diarrhoea significantly affecting the patient health-related quality of life (HRQoL)[1]. The term MC was employed in the early 80's to describe a group of patients with watery diarrhoea and weight loss, exhibiting normal endoscopic findings, but with microscopic inflammation in the colonic mucosa, as identified in biopsy specimens[2]. Later, in 1993, two independent research groups suggested the use of MC as a generic term to cover any type of colitis in which there were specific histological changes without any macroscopic alteration, as evaluated by endoscopic or radiological analysis, including the two main entities known as collagenous colitis (CC) and lymphocytic colitis (LC). Since then, the clinical-histological definition of MC and its classical subtypes have been a matter of debate and nowadays several consensuses classify these patients[1,3,4]. Moreover, other types of histopathological changes in the colonic mucosa have also been described over time in patients with chronic diarrhoea and normal or close to normal endoscopic findings, without fulfilling the classical histopathological criteria for MC diagnosis. Whereas those unclassified alterations remained orphan for a long time, it is nowadays universally accepted the use of the term and concept of incomplete MC (MCi), which proposes those abnormalities as new entities. Furthermore, different variant forms of MC have also been reported under separate names to describe peculiar histopathological infiltrate in the colonic mucosa in patients with clinical manifestations of MC but without the key histological features for LC, CC or MCi[5]. Since it is not appropriate to consider these entities as classical MC, it is crucial to establish a defined and reliable clinical-pathological criterion to confirm the diagnosis of these emerging entities.

This review summarizes current evidence on the definition, epidemiological and clinical significance of MCi and variant forms of MC. We searched the PubMed, Cochrane, MEDLINE, and Scopus libraries using the following individual and combined key words: "borderline lymphocytic colitis", "minimal collagenous colitis", "microscopic colitis undesignated", "microscopic colitis incomplete", "microscopic colitis not otherwise specified", "minimal change colitis", "paucicellular lymphocytic colitis", "cryptal lymphocytic colitis", "lymphocytic colitis with giant cells", "collagenous colitis with giant cells", "pseudomembranous collagenous colitis", "atypical lymphocytic colitis", "atypical microscopic colitis" or "focal active colitis". References cited in the articles obtained were also searched in order to identify other potential sources of information. The results were limited to human studies available in English including all articles published before April 2016.

DEFINITION: EVOLUTION OF A NEW CONCEPT

MC is an umbrella term that includes two main presentations of chronic and relapsing inflammatory disease of the gastrointestinal tract with characteristic histopathological features that allow us distinguish CC from LC[4]. In both entities, there are some common histopathologic features, not pathognomonic of these conditions, such as: surface epithelial injury (mild in LC and marked in CC), elevated and homogeneously distributed mononuclear inflammation in the lamina propria (mainly of lymphocytes and plasma cells), little or no presence of crypt architectural distortion and possible focal IBD-like changes (cryptitis and Paneth cell metaplasia)[5]. LC is particularly defined by large number of surface intraepithelial lymphocytes (IELs: > 20 IELs per 100 surface epithelial cells) with little or no crypt architectural distortion (Figure 1), whereas CC is characterized by irregular thickened collagen band (> 10 μm) under the surface epithelium, independently of IELs infiltration[1,5] (Figure 2). This feature is most evident between the crypts immediately beneath the surface epithelial cells containing entrapped capillaries, red blood cells and mononuclear cells[1,5]. Whereas the histopathological criteria for MC diagnosis seems to be established in its classical forms, many doubts remain in those cases in which the histological aspect of the colonic mucosa is not completely normal but specific findings do not reach the cut-off values considered diagnostic for classical MC.

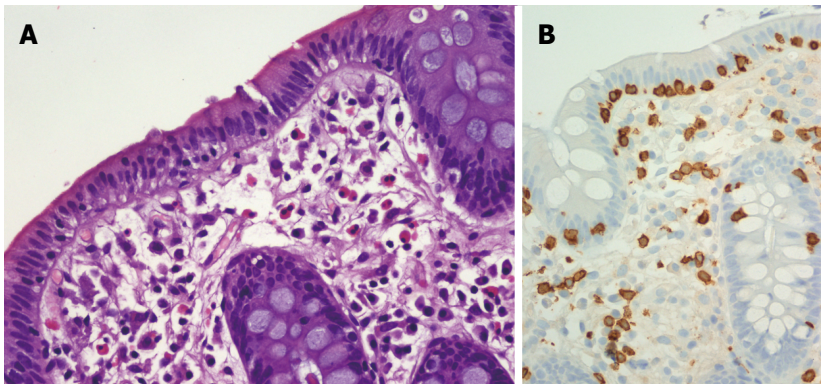

Figure 1 Photomicrographs of a colonic specimen from a lymphocytic colitis patient showing inflammatory hypercellularity in the lamina propria of colonic mucosa and clear presence of a greater number of intraepithelial lymphocyte cells. A: Hematoxylin-eosin staining, magnification × 200; B: More evident with the CD3 staining, magnification × 200.

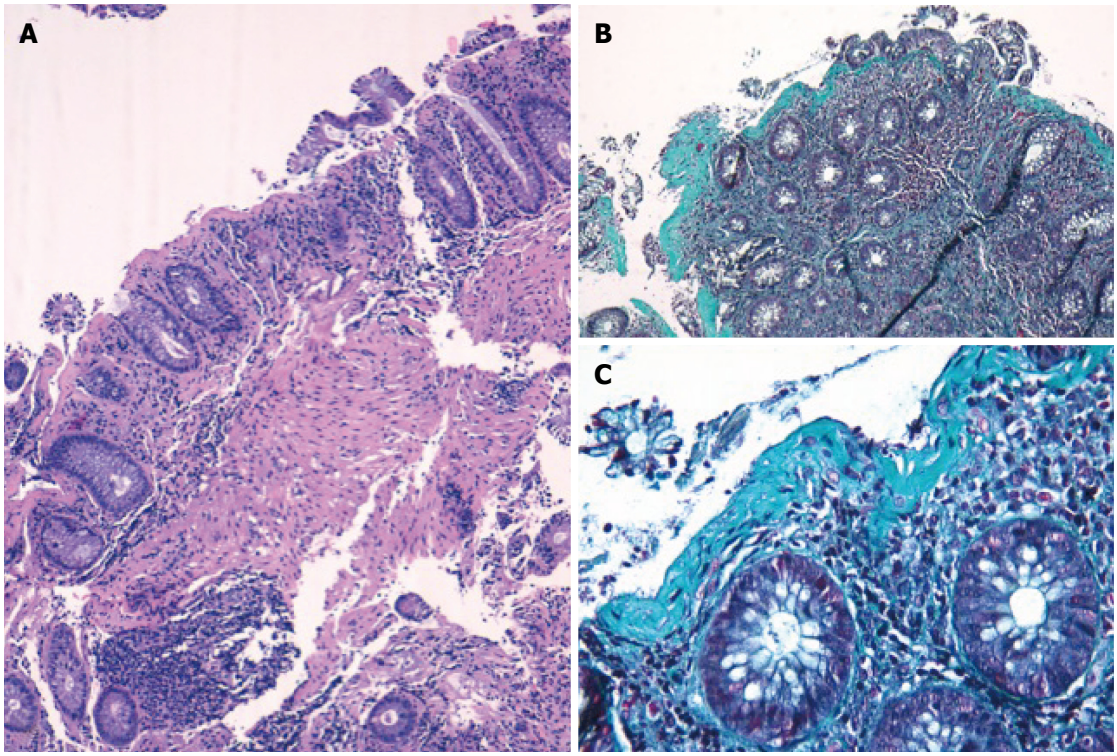

Figure 2 Photomicrographs of a colonic specimen from a collagenous colitis patient showing detachment of superficial epithelium. Hematoxylin-eosin staining, magnification × 100 (A) and thick subepithelial collagen band, Gomori's Trichrome staining (B and C, magnification × 100, × 400, respectively).

Incomplete microscopic colitis

In 2002, the terms "MC not otherwise specified" (MCNOS) as well as "undefined MC" (uMC) and "paucicellular colitis" were equally used to describe a subgroup of patients with chronic diarrhoea and an increased cellular infiltrate in the lamina propria with or without abnormal collagenous layer and/or elevated number of IELs, without completely fulfilling the criteria for MC diagnosis[6-10]. From 2007, some authors proposed classifying MC forms into five subtypes: CC, LC, "minimal change colitis" (crypt architectural abnormality in the form of cryptitis and crypt dilation in the absence of an increase in IELs and larger sub-epithelial collagenous band), MCNOS (increased inflammatory cell infiltrates in the lamina propria in the absence of other abnormalities) and MC with giant cells[11]. Despite the different phenotypes described, not all cases having clinical features of MC fulfill the histological diagnostic criteria for MC diagnosis. Consequently, the term and concept of "incomplete microscopic colitis" (MCi) emerged to recognize this MC subtype, to avoid overdiagnosis as well as underdiagnosis in order to guide therapy decision in the clinical practice[9,10,12] (Table 1).

While the minimum criteria required for MCi diagnosis is still under discussion, > 10 and < 20 IELs per 100 surface epithelial cells and > 5 μm and < 10 μm thickness of the collagen band in colonic biopsies

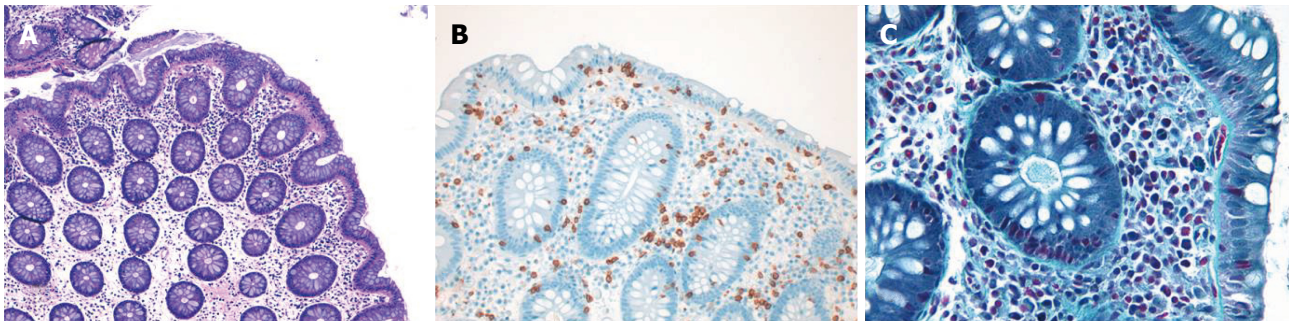

Figure 3 Photomicrographs of a colonic specimen from an incomplete lymphocytic colitis patient. Hematoxylin-eosin staining, magnification × 100 (A) with a mild increase in intraepithelial lymphocytes cells (B, CD3, magnification × 200) and a regular collagen band (C, Gomori's Trichrome staining, magnification × 400).

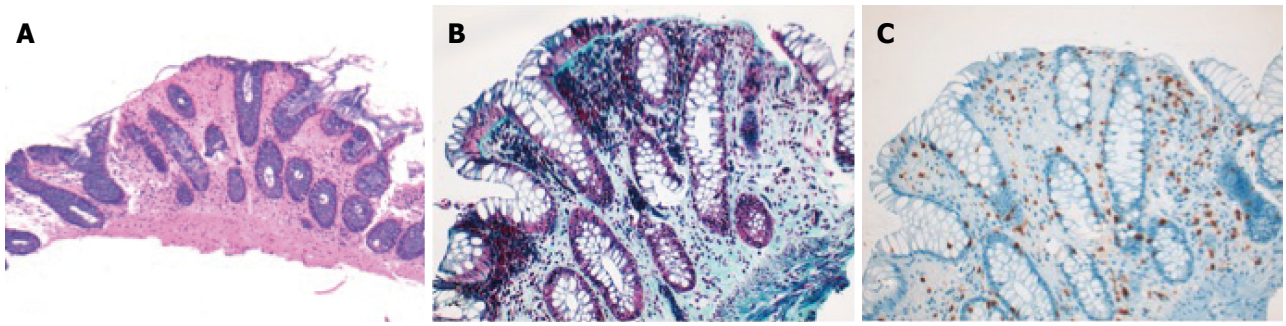

Figure 4 Photomicrographs of a colonic specimen from an incomplete collagenous colitis patient. Hematoxylin-eosin staining, magnification × 100 (A) with slight enhancement of subepithelial collagen band (B, Gomori's Trichrome staining, magnification × 200) without increased intraepithelial lymphocyte cells infiltration (C, CD3 inmunostaining, magnification × 200).

Table 1 Key histological features of classical and incomplete subtypes of microscopic colitis[4,5,25]

Subtype	IELs/100 epithelial cells	Thickness of collagen band
LC	> 20 IELs	< 10 μm
LCi	> 10 and < 20 IELs	< 5 μm
CC	< 20 IELs (sometimes > 20 IELs)	> 10 μm
CCi	< 20 IELs	> 5 and < 10 μm

LC: Lymphocytic colitis; CC: Collagenous colitis; IELs: Intraepithelial lymphocytes cells; LCi: Incomplete lymphocytic colitis; CCi: Incomplete collagenous colitis.

have recently been proposed as cut-off values for the diagnosis of incomplete LC (LCi) and incomplete CC (CCi) subtypes, respectively[5] (Figures 3 and 4). Previously, other terms were used to describe these CMi subtypes, although we can observe a slight difference in the cut-off values employed to define it over time, especially considering the LCi subtype. In fact, the heterogeneous minimal cut-off value for IELs infiltration used in different studies to define LCi reflects the difficulty in establishing an approved value, and reducing the risk of overdiagnosing these entities.

In any case, the differential diagnosis between complete and incomplete forms of MC is not an easy task. Morphological abnormalities in MC may be patchy[13-15], and MCi and fully established MC may coexist at different colonic segments of the same patient, making mandatory the collection of multiple and stepped biopsy samples along the large bowel to establish a correct histopathological diagnosis[4]. In fact, in a retrospective cohort of MC patients, among whom a large proportion of them had a repeated endoscopy after diagnosis, less than 2% had a primary endoscopy without histopathological abnormalities while 76% had chronic inflammation or MCi in their initial biopsies without a specific definition of MC or its subtypes[16]. Furthermore, in the 30% of 115 patients with MC subjected to a second endoscopy after a median of 21 mo no longer fulfilled the histological criteria of MC, and 9% switched MC subtype[16]. In this study, incomplete histological findings in MC were present in a significant number of patients later diagnosed with MC, suggesting that they could represent a different stage of the same disease, however more studies are needed to better determine the clinical-histopathological correlation over time[16,17]. Furthermore, chronic ileal inflammation was described in 15% of patients with MCi compared to 37%-57% with complete MC, observing that generally the colonic inflammation is most pronounced in the right colon adjacent to the terminal ileum. The significance of this nonspecific inflammation defined as the increase in the number of IELs is unknown, but its presence demonstrates that inflammation in MCi and in complete MC could affect the small intestine and is not

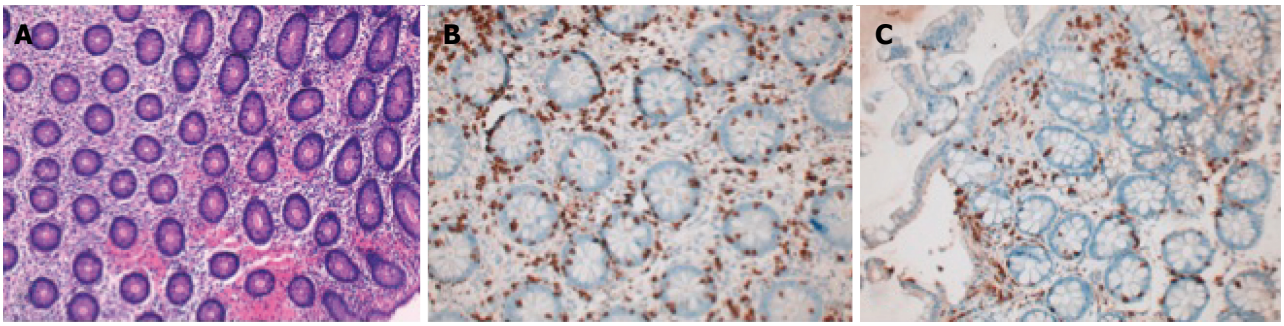

Figure 5 Photomicrographs of a colonic specimen from a cryptal lymphocytic colitis patient. Hematoxylin-eosin staining, magnification × 100 (A) showing only the presence of cryptal lymphocytosis (B, CD3, magnification × 200) and lack of intraepithelial lymphocytosis (C, CD3, magnification × 200).

confined only to the colonic mucosa, as documented in previous reports[18-20].

The difficulty in defining the histopathological diagnosis of all forms of MC is reflected by the intra and inter-observer variability even when applying the currently accepted diagnostic criteria for classical subtypes[21]. However, some authors investigated the ability to discriminate MCi from healthy mucosa and IBD/nonspecific reactive changes and concluded that there was very good intra-observer and inter-observer agreement (κ value varying from 0.88 to 0.96 and from 0.81 to 0.89, respectively) in separating MC/MCi group from non-MC. However, the ability to discriminate MCi from CC and LC was still low with the lowest number of cases agreed in MCi group (κ value ranging from 0.59 to 0.69)[22]. In fact, in a retrospective cohort of 93 patients, 15% of colonic biopsies primarily diagnosed as MCi changed to classical MC diagnosis through the study by two gastrointestinal pathologists[16]. Recently, the use of the CD3 immunohistochemical staining has demonstrated an improvement in the diagnostic agreement among pathologists, with a change in the diagnosis in 34% of cases, especially towards LCi[23]. Moreover, the lack of methodological agreement among pathologists also adds difficulty to MC and MCi diagnosis. For example, the assessment of the thickness of the collagen band by histologic analysis could be measured using an "eyeballed" histologic evaluation, a conventional calibrated micrometer scale or by performing semiautomatic micrometer measurements. Recently, automated image analysis software has been developed to measure the thickness of the subepithelial collagenous band in colonic biopsies of patients with CC and CCi stained with Van Gieson, providing a promising supplementary tool for the diagnosis of CC and CCi[24]. The authors showed that the overall agreement between all pathologists was κ value of 0.69 compared to κ value of 0.71 using the above-described software[24]. Despite the variety of methods, a gold standard for collagen band thickness quantification is still lacking[25]. To identify collagen, the trichrome stain is widely used, but immunohistochemistry with antibodies directed against Tenascin (extracellular matrix glycoprotein) represents a more sensitive method and may be a good alternative, as demonstrated in complete CC. In fact, in normal colon, the basement membrane is composed predominantly of type Ⅳ collagen while in complete CC it mainly consists of type Ⅵ collagen and Tenascin with lower amount of collagen types Ⅰ and Ⅲ[26-29]. Notably, it has been demonstrated that Tenascin immunostaining is also useful to detect minimal deposits of sub-epithelial collagen compared to hematoxylin-eosin, van Gieson's elastin and collagen-Ⅵ stainings (P < 0.001), being useful to discriminate between minimal collagenous colitis and normal mucosa[30,31]. However, more studies are needed in order to determine collagen composition and the pathogenetic mechanisms implicated in its formation, as well as to validate the Tenascin immunostaining use in a larger series of cases of CCi. On the basis of these observations, it would be desirable to establish a consensus on a more stringent panel selection of the best methods to evaluate the histological criterion abnormalities, in order to establish the diagnosis of MCi.

Variant forms of microscopic colitis

Other variant forms of MC have been reported in the literature in patients with clinical history of watery chronic diarrhoea. One study described two patients with a peculiar form of LC called cryptal lymphocytic colitis (Figure 5). It was defined as an increased number of IELs localized within the cryptal epithelium, with a mean number ranging from 39 (range, 33-43) to 46 (range, 32-55) per 100 crypt epithelial cells, while no changes in surface IELs were detected[32]. Immunohistochemistry analysis with anti-$CD3^+$, $CD8^+$ and TIA-1 antibodies showed that the cryptal IELs phenotype was of cytotoxic/suppressor T cells. Moreover, no signs of surface epithelial injury (mucin depletion, epithelial cells with cuboidal configuration, or mucin-depleted flattened epithelial cells) were reported[32]. It is feasible that IELs are attracted by signals derived from antigens present in the lumen of the crypts, as a consequence of the differences between non-adherent mucins in the lumen of the crypts and in the surface epithelium that could influence the selection of antigens in susceptible individuals[32]. However, the causes of selective cryptal

colorectal infiltration by lymphocytes remain unclear.

Other authors described some case reports of pseudomembranous CC as an unusual cause of chronic diarrhoea with a good response to budesonide treatment[33-38]. This variant form was histologically defined as the increased thickening of the sub-epithelial collagen band and pseudomembranes formation characterized by eruptive exudate composed of neuthophil leukocytes, necrotic debris and fibrin at the luminal surface of the colonic mucosa excluding ischemic, toxin-induced or infective aetiologies (*Clostridium difficile* infection)[36,38]. The colonoscopy showed normal colonic appearance in some patients, but inflammation and colonic ulcerations in others. Recently, a case of pseudomembranous CC with superimposed drug damage was reported, describing the presence of cholestyramine crystals on the mucosal surface[39]. However, it is still under debate whether the pseudomembranous formation constitutes part of the spectrum of CC itself or is associated with unknown superimposed infection.

Another variant described is focal active colitis (FAC), although considerable controversy exists regarding the clinical implication of its diagnosis. FAC is characterized by focal crypt damage caused by neutrophils that may be associated with infections, ischemia, Crohn's disease (CD), partially-treated ulcerative colitis or irritable bowel syndrome (IBS)[40]. Some reports showed an association between FAC and oral sodium phosphate ingestion, as it has commonly been used as an oral laxative agent, causing aphtoid ulcers and/or FAC in the colon and rectum[41-44]. Two previous studies described the prevalence of FAC ranging from 3.5% (11/316) to 6.6% (15/226) in IBS patients with normal endoscopic evaluation[41,45]. A follow-up study in 90 patients, showed a positive association of drugs in 24% of them [especially non-steroidal anti-inflammatory drugs (NSAIDs)] and a basal subtype of FAC and infection in 19%[46]. Moreover, in 16% of patients (predominantly women) a diagnosis of IBD was ultimately made (CD in the majority of the patients and ulcerative colitis only in two patients)[46]. The disease duration ranged from 4 mo to 7 years with a mean of 4.2 years and 8 patients (28%) developed CD, especially in pediatric group compared to adult population[47]. In conclusion, it is not currently clear whether FAC should be considered as a variant form of MC or an initial form of IBD.

An additional variant form of MC described by some authors is MC with giant cells, defined as the presence of multinucleated giant cells in an otherwise classic LC and CC, reporting until now 6 cases of LC with giant cells and 12 cases of CC with giant cells[48-50]. The sub-epithelial multinucleated giant cells that are present in the lamina propria are positive for the CD68 marker and seem to arise from merged sub-epithelial macrophages. The presence of giant cells does not appear to confer any additional adverse clinical outcome with doubtful clinical significance.

PATHOPHYSIOLOGICAL RELEVANCE OF LOW-GRADE INTESTINAL MUCOSAL INFLAMMATION

The colonic mucosa daily faces dietary antigens and microbial products present in the intestinal lumen. It is well established that the interactions between the intestinal immune cells and the luminal microorganisms directly regulate the physiological inflammatory state of the intestinal mucosa and that both, overreaction and underreaction have been implicated in the pathogenesis of several chronic gastrointestinal disorders.

Definition of healthy intestinal mucosa

The histological analysis of colonic specimens from healthy donors and non-affected areas from section margins of surgical specimens has allowed a better knowledge of tissue morphology and cell distribution in a non-disease condition. However, factors such as diet, antibiotic consumption, or physiological stress influence mucosal immune cell infiltrate, making it difficult to define reference values, which are especially helpful when diagnosing diseases with mild changes, such as MC and MCi. Despite the lack of histological criterion defining all features of normality, the colon from healthy donors has been described as harbosing about < 5 IELs (mostly $CD8^+$) per 100 surface epithelial cells, being slightly higher in the proximal than in the distal colon[25] (Figure 6). Sometimes a higher number of IELs is present over lymphoid follicles/aggregates, therefore it is not recommended to value lymphocytes counts in these areas[51]. Moreover, a mild increase in IELs numbers without a clear epithelial injury and/or increased lamina propria inflammatory infiltrate may be nonspecific and may be related to different conditions. Consumption of drugs, celiac disease, infectious colitis in remission[52] immunologic conditions (*e.g.*, Hashimoto's thyroiditis, common variable immune deficiency (CVID), autoimmune enteropathy, allergy, immune deficiency), and IBD in remission may lead to an increased number of IELs[12,52,53]. Therefore, knowledge of the clinical presentation, an endoscopic analysis, and anamnestic data will be necessary to differentiate between health and disease[54]. The lamina propria contains B cells (mainly plasma cells, 15%-40% of total mononuclear cells) and a vast majority of T cells (mainly $CD4^+$; 65%), with a few natural killer cells. Moreover, the lamina propria is composed of a not conspicuous number of monocyte-macrophagic cells, especially under the subepithelial collagenous layer, unlike the rectal mucosa, where macrophages are frequently found. The cut-off values for eosinophil normal counts have not been established either, and a proximal-to-distal gradient has been

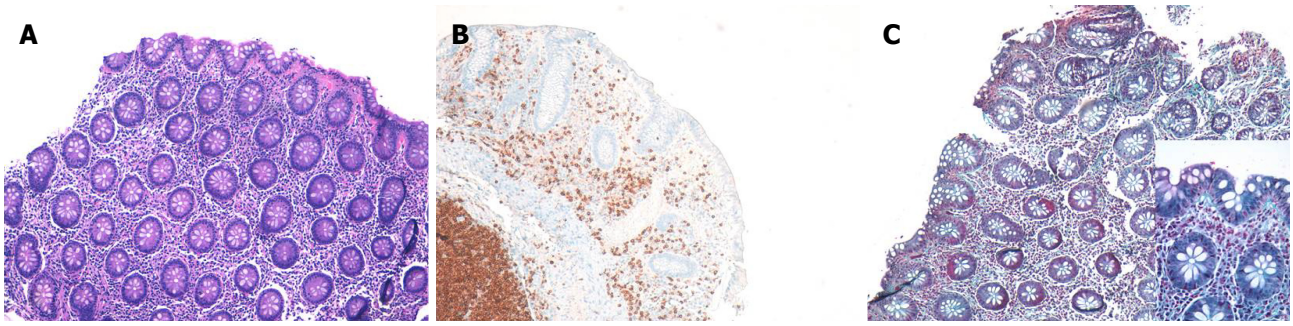

Figure 6 Photomicrographs of a colonic specimen from a healthy donor. Hematoxylin-eosin staining, magnification × 100 (A) showing low number (usually less than 5) of intraepithelial lymphocyte cells, which can be easily identified by CD3 immunohistochemistry marker (B, magnification × 100). The subepithelial collagen band is tiny and regular (C, Gomori's Trichrome staining, magnification × 10 and inset, Gomori's Trichrome staining, magnification × 400).

observed, with 37 to 9 cells per high-powered field in the right and left colon, respectively[55,56]. In the healthy mucosa, the basement membrane is composed of laminins, predominantly collagen Ⅳ, proteoglycans, calcium-binding proteins and other structural and adhesive proteins[56]. Its normal thickness is around 3-4 μm[25], reaching its thickest value in the rectum[56]. When analyzing biopsy specimens, the evaluation of lamina propria cellularity may be very subjective, as different studies have evidenced great inter-observer variability[57]. For this reason, the diagnosis of MC requires a full endoscopy, with collection of two or more biopsies from each segment of the large bowel and a clinical-histopathological correlation[57].

Mucosal immune mechanisms in MC

Variations in number and activation state of mucosal immune cells have been described in physiological and some pathological conditions, in association with intestinal dysfunction. However, the etiopathogenic mechanisms of inflammatory diseases such as MC are not completely known. It is generally accepted that MC is a multifactorial disease, probably secondary to an abnormal immune reaction in predisposed individuals, triggered by different luminal factors[58-60]. Several studies showed that an impaired adaptive immune response through aberrant T-cell responses leads to chronic gut inflammatory conditions in MC patients[58]. In particular, several studies showed a heavy infiltration of $CD8^+$ cytotoxic T-lymphocytes (CTLs) in the colonic mucosa of MC patients due mainly to an increased expansion of resident T-cells[61] with a mixed Th17/Tc17 and Th1/Tc1 mucosal cytokine profile[62-65]. Moreover, other studies showed an impaired epithelial barrier dysfunction in MC that worsened in the case of active disease, which persisted despite effective treatment with the first line budesonide therapy[66]. All these available data derive from studies performed in patients with classical MC without identification of a MCi subgroup, with the exception of paucicellular LC. In fact, one study showed a lack of expression of $CD25^+FOXP3^+$ cells in paucicellular LC compared to higher expression in both LC and CC[9]. Despite recent research, the mechanisms through which mucosal immunity generates colonic dysfunction in MC without the development of significant macroscopic mucosal damage is still unknown. Due to similar histological findings and clinical outcome, a proximity to the pathophysiology of diarrhoea-predominant IBS (IBS-D) has been suggested. In fact, from the clinical point of view, there is significant overlap between MC and IBS. In particular, the pooled prevalence of any type of functional bowel disorders in patients who present diagnostic criteria of MC is 39.1% (95%CI: 22.8-56-6, I^2: 97%), as reported in a recent meta-analysis without any data available in MCi patients[67]. Moreover, from the pathogenetic point of view, low-grade mucosal inflammation has been demonstrated not only in MC but also in IBS-D although to a lesser extent than that in MC[59,68-70]. In particular low-grade inflammation has been demonstrated in association with disease severity in both, IBS and MC[63,71], suggesting immune activation as a key mechanism in both entities. Despite a clear overlap in the pathogenesis and clinical manifestations between IBS and MC, the common pathophysiological pathways between the two conditions remain poorly understood, especially considering the incomplete and variant forms of MC.

EPIDEMIOLOGICAL DATA

MC was initially considered a rare disease with only 446 cases of CC described at the end of 1992[72]. Over time, an increasing number of studies has explored the incidence and prevalence of MC and has evidenced significant geographic variations. To date, the pooled incidence rate of CC was 4.14 (95%CI: 2.89-5-40) per 100000 person-year and 4.85 (95%CI: 3.45-6.25) for LC as shown in a recent meta-analysis, observing a north-south gradient only for CC[73]. An increasing incidence in classical MC has been reported in several studies, whereas other analyses have suggested a more stable incidence in some geographic regions and especially after the year 2000[73]. However, it is unknown whether the increasing incidence is genuine

Table 2 Incidence of incomplete microscopic colitis and paucicellular lymphocytic colitis

Ref.	Study period	Country	MCi subtype	Incidence
Fernández-Bañares *et al*[9]	2006-2009	Spain	Pacicellular LC	3.24 (2-4.48)
Bjornback *et al*[16]	1999-2010	Denmark	MCi	4 (NS)
Rasmussen *et al*[74]	2000-2014	Denmark	MCi	5 (NS)

Incidence per 100000 inhabitants and year. MCi: Incomplete microscopic colitis; Paucicellular LC: Paucicellular lymphocytic colitis; NS: Not specified.

or is the result of greater awareness of the disease.

Incomplete microscopic colitis

In contrast to classical MC, the real epidemiological impact of MCi and variant forms remains unknown, because only a few epidemiological studies and case reports have been described. In fact, as an emerging disease, the definition of MCi and variant forms has evolved over time and it is still under discussion. This has yielded, unfortunately, non-comparable results due to variations in the different cut-off values to define its diagnosis.

The incidence of MCi has been described in only three retrospective population-based studies using a more recently described histological definition for MCi or one of its sub-groups[9,16,74] (Table 2). Firstly, one Spanish study demonstrated the incidence of pauciclellular LC, a subtype that is now considered as synonymous of LCi[5,9]. The mean annual incidence of paucicellular LC was 3.24/100000/year (95%CI: 2-4.48) compared to the mean annual incidence of 2.37/100000/year (95%CI: 1.3-3.43) for CC and LC[9]. However, in the paucicellular LC group the study also included the patients with IELs > 20 IELs per 100 surface epithelial cells but with patchy distribution of epithelial lymphocytosis in more than one biopsy sample, though not in all, possibly generating a slight bias risk in the estimated incidence of this entity[9]. In all, 26 patients with paucicellular LC were identified, showing that they were younger than LC patients with a slightly higher prevalence in female sex (61.5%)[9]. Moreover, 5/26 patients firstly diagnosed as paucicellular LC were finally diagnosed as IBS-D during follow-up, as their condition did not improve after MC conventional therapy[9].

Subsequently, one Danish retrospective population-based cohort study estimated a mean incidence rate of 4/100000/year for MCi compared to 6.7/100000/year for LC and 10.8/100000/year for CC. The incidence of MCi as well as LC increased seven-fold from 1999-2001 to 2008-2010 as compared to a three-fold increase for CC[16]. However, the cut-off values used to establish the MCi diagnosis were not completely equivalent to the more recently accepted ones[5]. In fact, LCi was defined in this study as the existence of an abnormal IELs counts, with a minimal cut-off value of > 5 per 100 epithelial cells compared to the current recommended minimal cut-off value of > 10 per 100 epithelial cells, possibly generating a tendency towards overdiagnosis of LCi in this cohort of patients[16]. Nonetheless, 101 patients with MCi were identified in a consecutive cohort of 539 MC patients, with a mean age at diagnosis of 62 years and with higher prevalence in female sex (82% of women)[16].

Recently, another Danish retrospective consecutive study estimated an incidence of MCi of 5/100000/year compared to 14.5/100000/year for CC and 14.9/100000/year for LC in 2014. However, also in this study, a minimal cut-off value of IELs infiltration was > 5 per 100 epithelial cells compared to the current recommended minimal cut-off value of > 10 per 100 epithelial cells, possibly generating a slight overdiagnosis of LCi in this cohort of patients. This study described 226 cases of MCi in non-selected patients presenting, in the majority of cases, chronic watery diarrhoea, with a median age of 61 years-old and a 69% of women prevalence[74]. Discrepancy between histopathology in the right and left colon was rare and only in one patient MCi was found in the right colon and LC in the left colon. The diagnostic sensitivity of biopsies from the right and left colon did not differ among MC subgroups including MCi, the latter having a sensibility of 91% (95%CI: 84-96) for the right colon and of 97% (95%CI: 91-99) for the left colon[74]. MCi persisted histologically for up to one year in 45% of patients compared to 77% of CC patients and 64% of LC patients. While these differences did not reach statistical significance, these data showed that the pathological changes in CC and LC were more persistent than those in MCi[74].

Moreover, other studies described the prevalence of CMi in patients with chronic diarrhoea, although heterogeneous definitions are used to defining them, using several unspecific names [nonspecific microscopic colitis (NSMC) or NOSMC or uMC]. In particular, in one study the authors described NSMC prevalence of 46.7% (28/60) in patients with IBS-D defined using the Rome Ⅱ criteria[75]. However, the term NSMC was used to define IELs infiltration of < 20 per 100 epithelial cells without defining the minimal cut-off value. This group of patients could be considered as having an incomplete form of LC because the mean reported number of IELs per 100 epithelial cells was 11.71 (± 1.83)[75]. Another study used the term NOSMC to define the presence of an increased number of IELs > 7/100 but < 20/100 per epithelial cells with the absence of both a thickened sub-epithelial collagen layer and flattening of epithelial cells, epithelial loss and detachment[76]. Of 613 patients with watery chronic diarrhoea and normal finding at colonoscopy, 64 cases (10%) of NOSMC were diagnosed without describing any clinical characteristics of these patients sub-group in the article[76]. Another recent multicenter prospective case-control study used

the term undetermined MC to define the abnormal IELs infiltration and/or sub-epithelial collagen thickening without reaching the diagnostic thresholds for CC and LC but without specifying the cut-off values used to define these entities[77]. They described 8 undetermined MC cases of 433 (1.8%) patients with watery chronic diarrhoea with normal colonoscopy[77]. Finally, in a nationwide population-based cohort from The Netherlands, the authors classified MC patients in CC, LC and undefined MC (uMC), the latter was used to define the cases in which no information for further sub classification was available[78]. The authors showed a relatively high frequency of uMC (10%) with general and sex specific mean annual incidence rates between 2000 and 2012 ranging around 0.4 (95%CI: 0.3-0.5) per 100000 inhabitants and year and which changed only marginally over time[78]. Although the term uMC was chosen to avoid any confusion with the term MCi, the same authors proposed that it was plausible that the majority of the uMC cases identified were either LC or cases not fully meeting the criteria for either CC or LC, stressing the need to improve the knowledge on MC variant and incomplete forms in both gastroenterologists and pathologists[78].

CLINICAL FINDINGS

All three entities LC, CC and MCi present indistinguishable clinical findings, with some differential features associated with chronic watery diarrhoea[16]. In MC the chronic diarrhoea seems to be associated with nightly defecation in 25%-50% of cases, high frequency of defecation urgency (70%) and fecal incontinence (40%) that particularly affect patient's quality of life[4]. Moreover, MC can be associated with other additional symptoms such as abdominal pain, abdominal bloating, fatigue and weight loss (described in up to 50% of cases). However, in a retrospective cohort MCi patients were less likely to report nightly defecation (31% *vs* 39% of LC and 57% of CC), watery stools (68% *vs* 88% in LC and 92% of CC) and fecal incontinence (22% *vs* 34% of LC and 43% of CC)[16]. In contrast to that, the frequency of other associated symptoms was similar in the three groups included[16]. Regarding paucicellular LC patients, a study evidenced less likely reported significant weight loss compared to MC patients[9]. Moreover, routine laboratory parameters were generally normal in all MC subtypes except for a slightly increased C reactive protein (CRP), respect to reference values[16]. Unfortunately, serological or fecal markers are not available yet, so neither diagnosis nor monitoring can be performed in any MC subtypes without biopsies collection. In view of the few data available, we can assume that MCi patients expressed a milder clinical activity with less alarm symptoms (such as weight loss and nocturnal diarrhoea) compared to classical MC. Since a subtle clinical expression of the disease reflects a possible more benign evolution course, in the absence of correct awareness of this mild clinical expression there could be increased risk of misdiagnosis or delayed diagnosis.

Risk factors

Several risk factors have been identified in MC patients such as the use of certain drugs and the association with autoimmune diseases. In particular, the use of NSAIDs, including low-dose of aspirin, proton pump inhibitors (PPIs), selective serotonin reuptake inhibitors (SSRIs) and other drugs, has been associated to an increased risk of developing MC[4]. However, only a few studies evaluated drug consumption as a risk factor in MCi. In particular, the consistent ingestion of NSAIDs showed a similar risk for complete LC and paucicellular LC, but lower than CC[9,10]. In MCi the use of NSAID, salicylic acid and PPI was similar compared to CC and LC patients, except for a slightly higher use of statin in MCi compared to CC and LC groups (24% *vs* 19% *vs* 18%, respectively)[16]. However, it is important to highlight that no universally accepted methods are available for assessing cause-effect relationships in adverse drug reactions[79]. In fact, the association between drugs intake and MC or MCi derived primarily from case control studies and drug prescription registry data, and only a few drugs show causal relationship in MC but not in MCi.

Other associated diseases

The presence of autoimmune diseases has been described to be associated with MC in over 30%-50% of cases, with OR 11 (95%CI: 5.1-23.8) for CC ($P < 0.001$) and OR 16.6 (95%CI: 6.4-43.1) for LC ($P < 0.001$), especially for celiac disease, type 1 diabetes, autoimmune thyroiditis, seropositive/seronegative rheumatoid arthritis and others[4,80]. There are few data available about the association between autoimmune disease and MCi. In particular, in paucicellular LC less association with autoimmune diseases was observed showing a prevalence of 15.4% compared to 38.6% in LC and 32.4% in CC. Moreover, a lower frequency of HLA-DQ2 genotype was observed in paucicellular LC compared to LC (30.4% *vs* 48%)[9]. Only a few cases of CMi were described to be associated with concomitant celiac disease in one Danish cohort (2/176 cases) but not in another study (0/101 cases). However, the new association between MC and Takayasu's arteritis (TAK) has been recently reported with especially higher frequency in MCi than in complete MC cases (20% *vs* 10%)[81]. Moreover MC (complete and incomplete forms) was found to be significantly higher in active TAK patients than in the active group (67% *vs* 14%, $P \leqslant 0.03$, OR 7.9)[81]. TAK is a chronic granulomatous vasculitis, mainly affecting the aorta and its branches especially in middle-aged females. It has been found as the most common subtype in vasculitis patients with IBD[82]. Its etiopathogenesis is still unknown, but upregulated innate and adaptive immune response

has been observed in this disease[81].

Moreover, MC has been associated with bile acid malabsorption (BAM; 44%) in both CC and LC patients as shown using the tauroselcholic (selenium-75) acid technique (SeHCAT)[4]. Whereas bile acid chelating agents have shown effectiveness in CC, these data come from only noncontrolled studies and do not show any significant improvement of the colon histology. Also in the MCi Danish cohort, BAM was very common with higher prevalence (48%) compared to CC and LC (26% and 18%, respectively)[16]. However, in paucicellular LC this association was less frequent[9]. Although these data suggest the possible implication of bile acids in the pathogenetic mechanisms of MC, its influence is not completely understood.

Finally, MCi patients presented a higher rate of lactose malabsorption (9% *vs* 3% in CC and 1% in LC), as diagnosed by oral testing and later by C/C genotype by the lactase-phlorizin hydrolase 13910 polymorphism gene analysis, suggesting a possible involvement of the small bowel to induce a secondary lactose malabsorption, especially in MCi[16]. Although about two thirds of the World's population undergoes a genetically programmed decrease in lactase synthesis after weaning[83], symptoms of lactose intolerance generally do not occur until there is less than 50% of lactase activity. However, IBS patients show an increased risk of developing symptoms especially for IBS-D subtype[84]. In fact, visceral hypersensitivity and anxiety are associated with symptoms after ingestion of only a modest dose of lactose. Moreover, IBS patients with lactose intolerance also show heightened activity of the innate mucosal immune system with increased counts of mast cells, IELs and enterochromaffin cells in the terminal ileum and right colon[85]. We can speculate that other mechanisms such as visceral hypersensitivity could be implicated in symptoms development in MC and MCi, similarly to IBS, however studies designed to test this hypothesis are needed.

THERAPY

Several therapeutic interventions have been developed to achieve clinical and histological remission of MC and, in recent years, a number of randomized-controlled trials have provided a more evidence-based approach to treating this disease. Oral budesonide is currently the first line of treatment for the induction of clinical relief in moderate-severe MC, with a 76%-88% clinical response in CC and LC patients[4]. However, few drug efficacy data coming from retrospective cohorts of MCi patients are available. Noteworthy, there is a phase Ⅲ randomized trial to test the efficacy and safety of budesonide in MCi. This study is already registered and is in the process of subject recruitment (www.clinicaltrials.gov, Identifier NCT02142634). In one retrospective cohort budesonide was prescribed as short-term therapy of 2-4 mo, leading to normalization of stool consistency and frequency in 84% (95%CI: 66%-95%) for MCi, 84% (95%CI: 77%-89%) for CC and 88% (95%CI: 80%-98%) for LC, respectively[16]. Moreover, another retrospective study showed the effectiveness of budesonide treatment in MCi, while only a minor number of patients were treated with colestyramine and mesalazine[74]. The response to budesonide was independent of the SeHCAT results. However, in only three patients with paucicellular LC budesonide therapy did not achieve clinical response[9]. Therefore, the effect of budesonide in the MCi-group seems to be similar to that of the other MC sub-groups. These findings further support the hypothesis that inflammed lamina propria may well be more important for the diarrhoea than specific IELs infiltration in all MC subtype entities. In fact, a recent study has evaluated the contribution of inflammatory mediators to water secretion in the sigmoid colon of patients with LC. The key effector cytokines TNFα, IFNγ and IL-15 inhibited γ-ENaC upregulation in response to aldosterone through a MEK ½-mediated pathway, preventing ENaC from reaching its maximum transport capacity, leading to Na malabsorption, which directly contributes to diarrhoea[86]. Other treatments were also used in MCi patients and its sub-groups. The efficacy of cholestyramine was 100% (95%CI: 75%-100%) in MCi associated with BAM, compared to 56% (95%CI: 35%-75%) in CC patients and 82% (95%CI: 48%-98%) in LC patients. Paucicellular LC seems to respond well to loperamide or cholestyramine treatment, and 6/10 patients achieved clinical remission with mesalazine treatment[9]. It is important to stress that in MCi, some cases of spontaneous remission such as those observed in the classical subtypes of MC have also been reported, however this was particularly evident for patients with MCi[74].

Although a number of medical treatments have been evaluated in MC patients, currently there is no casual intervention for MC and MCi, and current therapy for MC and MCi mainly follows an empirical approach. Further studies are needed in order to better understand the molecular mechanisms behind the origin of the disease and to develop specific therapies for each MC subtype.

CONCLUSIONS AND FUTURE PERSPECTIVES

MCi has clinical and histological features that support its classification as a form of MC. In fact, MCi presents clinical characteristics indistinguishable from complete MC and it shows a good response to budesonide and cholestiramine treatment. Therefore, introducing the histological diagnosis of MCi could reduce the risk of missing patients with a treatable cause of chronic diarrhoea. Of note, variant forms of MC are extremely rare disorders with still unclear clinical significance and which probably do not represent real specific entities[13]. Further investigations on the prevalence of

MCi and its sub-groups and detailed studies that can better define its natural history and etiopathological characteristics are warranted.

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