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TITLE PAGE

Title: Macroscopic Findings, Incidence, and Characteristics of Microscopic Colitis in a Large Cohort of Patients from the United Kingdom.

Short "running" title: Macroscopic Findings in MC in a UK cohort.

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ABSTRACT

Objective: Microscopic colitis (MC) is classically associated with normal or near-normal endoscopic appearances. However, non-specific macroscopic findings have been described, the importance of biopsy location for confirming a diagnosis of MC is unclear, and reported incidence data from the United Kingdom are limited. This study was designed to assess macroscopic features, incidence, demographics, and location and positivity of biopsy samples in MC.

Materials and Methods: Retrospective, cross-sectional study of individuals with newly diagnosed MC.

Results: From 2010 to 2015, 540 cases of MC were reported. Macroscopic findings occurred in 16.5% (n = 89) cases, with trends towards increased frequency of ulceration or linear scarring in collagenous colitis (CC). The mean incidence of MC was 11.3 per 100,000 population/year, including 291 (53.9%) with CC (incidence 6.1 per 100,000/year), 203 (37.6%) with lymphocytic colitis (incidence 4.2 per 100,000/year), and 46 (8.5%) with MC, not otherwise specified. Most individuals were female (70.2%). Common features in patients with MC included symptom duration <6 months, weight loss, abdominal pain, and use of proton pump inhibitors, statins, or non-steroidal anti-inflammatory drugs. In individuals with right- and left-sided biopsies taken, 98.2% had diagnostic features in both. However, rectal biopsies were only positive in 88.7%.

Conclusions: One-in-six patients with MC demonstrated distinct macroscopic findings at colonoscopy. Our data confirm a female preponderance in MC, a relatively short symptom duration, and use of certain drugs as common features. Both right- and left-sided biopsies were frequently positive, suggesting flexible sigmoidoscopy and biopsy could confirm a diagnosis in certain individuals.

Keywords: Microscopic colitis

Inflammatory bowel disease

Epidemiology

Endoscopy

Pathology

Abbreviations:

ANOVA	analysis of variance
CC	collagenous colitis
IBD	inflammatory bowel disease
LC	lymphocytic colitis
MC	microscopic colitis
MC-NOS	microscopic colitis, not otherwise specified
NSAID	non-steroidal anti-inflammatory drug
PPI	proton pump inhibitor
SSRI	selective serotonin re-uptake inhibitor
SD	standard deviation
UK	United Kingdom

Introduction

Microscopic colitis (MC) is an important but potentially overlooked cause of chronic diarrhoea associated with a significant impact on health related quality of life [1, 2]. Two main histological subtypes are described: collagenous (CC) and lymphocytic colitis (LC), although cases not meeting diagnostic criteria are often defined as MC, not otherwise specified or incomplete MC [3, 4]. The presentation and subsequent management of patients is similar, regardless of histological subtype [5]. Analyses of large pathology databases have shown that MC occurs in approximately 10% of all individuals presenting with diarrhoea [6, 7], with a reported incidence of up to 21 per 100,000 person-years [8]. However, incidence data from the United Kingdom (UK) are scarce [9, 10].

The aetiology, pathophysiology, and optimum treatments for MC are unknown, and there are controversies regarding the nomenclature of the condition. Specific macroscopic features have been described in case reports, including linear streaks and mucosal tears, mucosal ulceration, or other non-specific features [11, 12, 13, 14, 15, 16, 17, 18, 19]. More recently, several larger cohorts have described subtle macroscopic findings in up to 30% of individuals with MC, occurring with greater frequency in collagenous colitis [20]. There have also been case reports describing macroscopic changes sufficient to raise a clinical suspicion of classical inflammatory bowel disease (IBD) at the time of colonoscopy [19, 21]. Given these findings, the adequacy of the term 'microscopic' colitis has been questioned [22, 23, 24].

Regardless of the presence of macroscopic features, the recommendation for making a diagnosis of MC has been to take multiple random colonic biopsies in any individual presenting with persistent watery diarrhoea [25, 26, 27]. Some authors recommend taking biopsies from all anatomical segments of the colon [28], but more recently a UK consensus statement concluded that all individuals with chronic diarrhoea undergoing colonoscopy

should have right-sided, left-sided, and rectal biopsies [29], because of concerns that cases of MC with features seen only in the right colon will otherwise be missed [28, 30]. This is in contrast to the results from some studies, which suggest that flexible sigmoidoscopy and left-sided biopsies alone would be sufficient to make a diagnosis in >95% of individuals [20, 31, 32].

We have therefore examined all of these issues in a large cohort of patients with MC from the UK. Our first aim was to assess the frequency of any subtle or gross macroscopic changes, including differences between histological subtypes, and to identify cases with findings more in keeping with classical IBD, such as ulceration or bleeding. The second aim was to estimate the incidence of MC, and common features, including presenting symptoms, co-morbidities, and prescribed medications. Finally, the third aim was to examine the site, location, and diagnostic yield of colonic biopsies in individuals with confirmed MC, to help inform future guidelines in terms of the optimal diagnostic strategy for the condition.

Methods

Participants and Setting

We identified all patients newly diagnosed with MC from histology reports generated in the histopathology department at the Leeds Teaching Hospitals Trust, West Yorkshire during a 6-year period (January 2010 –December 2015). The hospitals are the sole provider of secondary care services to the entire population of almost 800,000 people in the city of Leeds in the North of England. Individuals with a diagnosis of CC, LC, or MC, not otherwise specified were included. We excluded patients who had a diagnosis of MC documented previously, and those patients who were tertiary referrals from another hospital in a different city. The relevant local research ethics committee in Leeds was approached, and confirmed that ethics approval was not required for a study such as this, which was a retrospective review of routinely collected clinical information.

Data Collection and Synthesis

The medical records for each individual were accessed in order to obtain patient demographics, presenting features, details of relevant medication use (as described by previous investigators)[33], relevant co-morbidities, and type of procedure undertaken. Reports from either the index colonoscopy or flexible sigmoidoscopy were available via the ADAM endoscopy reporting system (Fujifilm Europe GmbH, Dusseldorf, Germany). We reviewed the index endoscopy reports for the presence of any documented macroscopic findings and, where recorded, the number and location of biopsies taken.

The histology reports from the biopsies taken at the index colonoscopy for each individual were then accessed, in order to determine the subtype of MC. We grouped cases by subtype based on the diagnosis recorded by the reporting histopathologist. At our institution, the following reference standards are used: collagenous colitis is defined as the presence of a subepithelial collagen band of ≥10μm in thickness, in association with diffuse chronic inflammation, and lymphocytic colitis defined using a threshold of >20 intra-epithelial lymphocytes per 100 epithelial cells, with associated diffuse chronic inflammation, but no thickening of the subepithelial collagen band. Other investigators have demonstrated that there is little inter-observer variability in the diagnosis of MC [34]. In this study we also included cases in which the final recorded diagnosis did not specify the subtype of MC and classified these as MC, not otherwise specified as, at our centre, the reported diagnostic criteria for incomplete collagenous or lymphocytic colitis are not yet used [35].

Biopsy results were grouped into right-sided (proximal to the splenic flexure), left-sided (including descending or sigmoid colon), or rectal, and recorded as positive or negative for MC, or exhibiting non-specific changes, if there was inflammation that was non-diagnostic for MC, or a mild increase in intra-epithelial lymphocytes. Furthermore, we documented if the recorded diagnosis was definite or probable for MC as has previously been reported [36].

Statistical Analysis

To assess for differences in demographic characteristics, presenting features, current prescribed medications, co-morbidities, and macroscopic findings between MC subtypes, continuous variables were expressed as means and standard deviations (SD), and compared using a one-way analysis of variance (ANOVA). Categorical variables were compared

between groups using a χ^2 test. We also compared demographic characteristics, presenting features, current prescribed medications, and co-morbidities, according to presence or absence of macroscopic findings. Due to multiple comparisons, statistical significance was defined as a P value of <0.01 for all these analyses, which were performed using SPSS for Windows version 21.0 (SPSS Inc., Chicago, IL, USA).

Results

There were 568 patients with a diagnosis of MC over the 6-year period. After excluding 28 patients who had a previous diagnosis evident from existing histology reports or clinic letters, there were 540 new cases of MC identified. Most individuals underwent full colonoscopy, but there were 81 (15.0%) individuals who underwent flexible sigmoidoscopy only.

Macroscopic Findings at Endoscopy in MC

Overall macroscopic changes were reported in 89 (16.5%) patients, and an endoscopic diagnosis of 'colitis' was recorded in 26 (4.8%) individuals (Table 1). The latter was usually labelled as indeterminate colitis by the endoscopist, but there was one case where a diagnosis of suspected Crohn's colitis was made, based on patchy inflammation and frank ulceration. Macroscopic changes occurred most frequently in CC, although this difference was not statistically significant ($P = 0.07$). There were trends towards ulceration and linear scarring occurring more frequently in CC, compared with LC or MC, not otherwise specified ($P = 0.04$ and $P = 0.02$, respectively).

We compared the demographic characteristics, presenting features, current prescribed medications, and co-morbidities, between those with, and those without macroscopic findings. These analyses revealed no differences in terms of demographic features or co-morbidities (Supplementary Table 1). However, there were significant differences in presenting features and medication use according to whether or not any macroscopic findings were present. Patients with abdominal pain were significantly more likely to have an endoscopic diagnosis of colitis or ulceration, while patients taking NSAIDs or aspirin were

more likely to have any macroscopic finding, and those taking NSAIDs were more likely to have ulceration.

Epidemiology of MC

Overall, between 82 and 99 new cases were identified per year among the 800,000 population of Leeds, corresponding to an incidence of MC of 10.3 to 12.4 per 100,000 population per year. The most frequent subtype was CC occurring in 291 patients (53.9%), followed by LC in 203 (37.6%), giving incidence rates by subtype of 6.1 per 100,000/year for CC and 4.2 per 100,000/year for LC. There were also 46 (8.5%) individuals with a recorded diagnosis of MC, not otherwise specified, giving an incidence of 0.96 per 100,000/year. In terms of the histological diagnoses made, a definite diagnosis was made in 503 (93.1%) and a diagnosis of probable MC made in 37 (6.9%) cases.

Table 2 outlines the demographics, presenting features, co-morbidities, and current prescribed medications of all individuals with MC, and according to subtype. The mean age of included individuals was 64.9 years, and 379 (70.2%) were female. A duration of diarrhoea <6 months was the commonest presenting feature, followed by weight loss, and abdominal pain, although the latter was not present in almost 80% of patients. The most commonly prescribed medications were proton pump inhibitors (PPIs), followed by statins, and then non-steroidal anti-inflammatory drugs (NSAIDs). Thyroid disease was present in 32 (5.9%) patients, and a documented diagnosis of coeliac disease in 24 (4.4%). Individuals with CC were more likely to be female, more likely to report weight loss, more likely to be taking NSAIDs, and there were trends towards them being older ($P = 0.01$), and more likely to be taking PPIs ($P = 0.02$), while those with LC were significantly more likely to have co-existent coeliac disease.

Diagnostic Yield of Biopsies in MC

Table 3 summarises the number of patients with biopsies taken from each segment, as well as the diagnostic yield from these. For both right- and left-sided biopsies the yield for MC was very high. Right-sided biopsies were diagnostic in 98.7% of patients, compared with 98.9% for left-sided biopsies. In comparison, rectal biopsies had a lower yield for a diagnosis of MC, with biopsies confirmatory in 88.7% of patients. There were no cases of MC diagnosed with positive rectal biopsies without changes in either right- or left-sided colonic biopsies. Seven (14.0%) of 50 patients in whom terminal ileal biopsies were obtained had features described as considered compatible with a diagnosis of MC, and in another nine (18.0%) patients non-specific changes, including raised intra-epithelial lymphocytes, were documented.

In total, 451 individuals had both right- and left-sided biopsies taken. This included five individuals undergoing flexible sigmoidoscopy, but in whom biopsies from the transverse colon were obtained. Both right- and left-sided biopsies were diagnostic in 442 (98.2%) of these patients (Table 4). A diagnosis of MC would have been missed in four individuals if only left-sided biopsies were taken. Three of these patients had documented normal histology on left-sided biopsy and the fourth had non-specific features. In two of these cases rectal biopsies were taken, which were also non-specific. There were four patients who had features of MC only in the left-sided biopsies, with right-sided biopsies showing non-specific changes in three patients and normal histology in the fourth.

Discussion

In this single centre, retrospective study, MC occurred in 540 individuals. Macroscopic findings at lower gastrointestinal (GI) endoscopy occurred in one in six individuals with MC, with non-specific features such as erythema or petechiae the most frequent findings, although almost 5% of individuals had an endoscopic diagnosis of colitis recorded. Overall, macroscopic findings were more common in CC, but this difference was not statistically significant. They were also significantly more prevalent in patients with abdominal pain, and those taking NSAIDs or aspirin. The average age of patients with MC was 64.9 years and 70% were female, and the incidence was from 10.3 to 12.4 per 100,000 population per year. The commonest subtype was CC, occurring in 53.9%, and these individuals were more likely to be female, more likely to be taking NSAIDs, and more likely to present with weight loss than those with LC. Patients with LC were more likely to have a pre-existing diagnosis of coeliac disease. Finally, either right- or left-sided colonic biopsies were diagnostic for MC in more than 98% of patients with MC, but taking only rectal biopsies would have led to a missed diagnosis in >10% of cases.

This study included a large cohort of individuals with MC referred from primary care centres in the UK, all of whom had lower GI endoscopy findings recorded using standardised endoscopy software. However, there are some limitations. As this was a retrospective study, we were limited by the quality of clinical documentation by the responsible physician, meaning that data for presenting features, co-morbidities, and medications may be inaccurate or missing in some patients. In addition, although lower GI endoscopy reporting was standardised, decisions regarding the site of biopsy, and number of samples obtained, were at the discretion of the endoscopist. Furthermore, we did not review the original histological specimens, but recorded the reporting histopathologist's diagnosis, potentially leading to misclassification of patients as having, or not having, MC. However, both the recognition of

low inter-observer variability in diagnosing CC and LC [34], and the observed high proportion of cases with a definite recorded diagnosis, especially compared with a previous Canadian study [36], is reassuring. More recently histological diagnoses of incomplete collagenous or lymphocytic colitis have been proposed, which may be relevant in cases of MC, not otherwise specified, such as those seen in our study, but it should be noted that criteria for these diagnoses are not yet widely accepted and the ultimate clinical course and treatment is not thought to differ [37]. Finally, we did not collect stool markers of inflammation and assess whether these varied by subtype, or according to presence of macroscopic findings. Faecal calprotectin testing was not used consistently or routinely within our department during the time this study was conducted and, in any case, in a recent study faecal calprotectin levels, although higher than among individuals with functional bowel disease, were still within the normal range[38].

Of note, the overall incidence of MC appears high compared with other reported data from the UK. A previous study in the UK reported an incidence of only 0.27% per 100,000 population per year, but included only 90 cases over a 7-year period, and was conducted between 1990 and 1996. In comparison, a previous meta-analysis, which included two small UK studies published in abstract form [39, 40], calculated pooled incidence rates of 4.14 per 100,000/year for CC and 4.85 per 100,000/year for LC [9]. These incidence rates are more in keeping with our data, and the analysis incorporated data from studies with similar methodology to our study; with investigators reviewing all pathology reports, but not necessarily all histology specimens [8, 41]. More recent studies have confirmed higher incidence rates, with Bonderup et al. reporting rates as high as 14.9 per 100,000/year for CC and 9.8 per 100,000/year for LC in Denmark [42]. More modest incidence rates of 5.3 per 100,000/year and 2.6 per 100,000/year for CC and LC respectively were reported in a French study published more recently, but it should be noted that this only included individuals

diagnosed between 2005 and 2007 [43]. Although the reasons for these regional variations in incidence are not clear, increasing awareness of MC as a potential cause of chronic diarrhoea, and improved recognition of the importance of taking colonic biopsies are likely to have increased the incidence rates, compared with the previous UK data, which were reported almost 20 years ago [10].

In keeping with data from other prospective cohorts we observed a clear female preponderance in patients with MC, and an average age of greater than 60 years of age [44, 45]. We also observed a higher proportion of those with CC were female, which is in keeping with other studies [6]. The finding that CC was more likely to be associated with certain drugs, and LC more likely to be associated with coeliac disease, may implicate different factors in the aetiology and pathogenesis of these two MC subtypes. We observed a lower prevalence of coeliac disease than in a recent Danish study (4.4% versus 6%) [20], and diagnoses consistent with co-existent autoimmune diseases were recorded less frequently than in other prospective studies [44]. This may relate, in part, to our retrospective study design, which could be limited by incomplete documentation of relevant co-morbidities, or failure to screen individuals with MC for coeliac disease, due to a lack of awareness of an association between the two conditions.

The prevalence of macroscopic findings of 16.5% in individuals with MC observed in our study was lower than in a recent Swedish cohort study reporting subtle endoscopic findings such as erythema, oedema, or abnormal vessel pattern in 37% of individuals with CC and 25% with LC [20]. However, other studies have reported macroscopic findings in 20-30% of individuals with all subtypes of MC [46, 47, 48], and it may be that endoscopist-related factors, such as degree of experience and training, affects the detection of subtle macroscopic signs [36]. Although our results were not statistically significant, there was a trend towards macroscopic features being more likely in CC, which is consistent with

previous published data [20]. This may relate to the higher rates of NSAID use we observed among those with CC. Regarding specific macroscopic findings, we observed linear scarring in only 9 individuals with CC, but this is in keeping with previous case reports [15, 17, 49]. We also found that almost 5% of individuals with MC had endoscopic features suggesting or mimicking ulcerative colitis or Crohn's disease, most of whom were subsequently found to have CC on histology, again in keeping with several case reports [19, 50]. Unfortunately, in our study the location of macroscopic features within the colon was not clear in the majority of cases so we were unable to comment on whether these were more likely to be seen in the right colon, as in one previous case report [51].

The high yield of both right- and left-sided colonic biopsies for diagnosing MC seen in our cohort is similar to data reported by Bjornbak et al., in which >95% of individuals had positive biopsies from either the right or left side of the colon [37] and in a recent study using data from France [52]. These findings support previous suggestions that flexible sigmoidoscopy with left-sided biopsies could be a reasonable diagnostic test for MC in some individuals [30, 53]. In contrast, without performing a full colonoscopy, there is the potential to miss other concerning pathology including colonic cancer or Crohn's disease. However, it is not uncommon for patients with chronic diarrhoea to have a full colonoscopy without random colonic biopsies being obtained [54]. Our data suggest that in this situation, if the original colonoscopy was macroscopically normal, a flexible sigmoidoscopy could be undertaken subsequently to obtain left-sided biopsies, rather than the patient having to undergo a repeat colonoscopy. This approach could also be used in patients who have had a recent normal colonoscopy for other reasons, or in those deemed unfit for colonoscopy.

In summary, this study has highlighted differences in the associated features across MC subtypes, suggesting potentially different aetiologies. It is also clear that macroscopic features are not uncommon in MC, and the diagnosis should be considered even in

individuals with features that may fit with ulcerative colitis or Crohn's disease. This suggests that it may be more appropriate to refer to these colitides by their histologic subtype, rather than by the term MC. A key priority remains to improve the awareness of these conditions, ensuring that patients with chronic diarrhoea with features suggestive of MC, and who may therefore be at risk of this condition, have an appropriate endoscopic evaluation with biopsies taken. However, the overall yield of colonic biopsies for MC in individuals with chronic diarrhoea, but a macroscopically normal colonoscopy, remains low. Clinical tools to stratify individuals, reducing the costs of obtaining and interpreting potentially unnecessary biopsies from low-risk individuals, and identifying those at higher risk of MC may also have a role [55, 56, 57].

Disclosures of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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Guarantor of the Article

JSK is guarantor

Specific Author Contributions

JSK and ACF devised the study. OR provided access to the histopathology database and reviewed any unclear cases. JSK, ACF and OR drafted the paper.

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Table 1. Macroscopic Findings at Colonoscopy in 540 Patients with Microscopic Colitis, and According to Subtype.

	All Patients (n = 540)	Collagenous Colitis (n = 291)	Lymphocytic Colitis (n = 203)	MC, not Otherwise Specified (n = 46)	P value*
Any macroscopic findings (%)	89 (16.5)	56 (19.2)	30 (14.8)	3 (6.5)	0.07
Erythema (%)	40 (7.4)	25 (8.6)	15 (7.4)	0 (0)	0.12
Petechiae (%)	27 (5.0)	12 (4.1)	12 (5.9)	3 (6.5)	0.59
Endoscopic diagnosis of colitis (%)	26 (4.8)	21 (7.2)	4 (2.0)	1 (2.2)	0.02
Oedema or congestion (%)	24 (4.4)	12 (4.1)	12 (5.9)	0 (0)	0.20
Reduced vascularity (%)	19 (3.5)	14 (4.8)	5 (2.5)	0 (0)	0.15
Ulceration (%)	11 (2.0)	10 (3.4)	1 (0.5)	0 (0)	0.04
Linear scars (%)	9 (1.7)	9 (3.1)	0 (0)	0 (0)	0.02
Contact or point bleeding (%)	9 (1.7)	7 (2.4)	2 (1.0)	0 (0)	0.31

*P value for Pearson χ^2.

Table 2. Demographics, Presenting Features, Current Prescribed Medications, and Co-morbidities in 540 Patients with Microscopic Colitis, and According to Subtype.

	All Patients (n = 540)	**Collagenous Colitis (n = 291)**	**Lymphocytic Colitis (n = 203)**	**MC, not Otherwise Specified (n = 46)**	**P value***
Mean age (SD)	64.9 (12.5)	67.2 (11.5)	63.8 (13.5)	66.5 (13.8)	0.01
Female (%)	379 (70.2)	223 (76.6)	126 (62.1)	30 (65.2)	0.002
Presenting features (%)					
Duration of diarrhoea <6 months	286 (53.0)	165 (56.7)	98 (48.3)	23 (50.0)	0.59
Weight loss	152 (28.1)	95 (32.6)	51 (25.1)	6 (13.0)	0.003
Abdominal pain	120 (22.2)	68 (23.4)	44 (21.7)	8 (17.4)	0.37
Nocturnal stools	69 (12.8)	43 (14.8)	22 (10.8)	4 (8.7)	0.13

Prescribed medications (%)					
PPIs	197 (36.5)	120 (41.2)	58 (28.6)	19 (41.3)	0.02
Statins	83 (15.4)	48 (16.5)	28 (13.8)	7 (15.2)	0.54
NSAIDs	71 (13.1)	54 (18.6)	11 (5.4)	6 (13.0)	<0.001
Aspirin	57 (10.6)	35 (12.0)	16 (7.9)	6 (13.0)	
Selective serotonin	47 (8.7)	22 (7.6)	21 (10.3)	4 (8.7)	0.29
re-uptake inhibitors (SSRIs)					0.43
Co-morbidities (%)					
Thyroid disease	32 (5.9)	19 (6.5)	9 (4.4)	4 (8.7)	0.89
Coeliac disease	24 (4.4)	7 (2.4)	16 (7.9)	1 (2.2)	0.008
Inflammatory arthritis	7 (1.3)	7 (2.4)	0 (0)	0 (0)	0.02
Other inflammatory	22 (4.1)	14 (4.8)	7 (3.4)	1 (2.2)	0.31
Disease					

*P value for one-way ANOVA for continuous data and Pearson χ^2 for comparison of categorical data.

Table 3. Location and Diagnostic Yield of Colonic Biopsies in 540 Patients with Microscopic Colitis.

Site	Total Number of Patients with Biopsies	Median Number of Biopsies (range)	Positive for Microscopic Findings (%)	Negative Microscopic Findings (%)	Non-specific Changes (%)
Terminal ileum	50	2 (1 – 6)	7 (14.0)	34 (68.0)	9 (18.0)
Right colon (proximal to splenic flexure)	457	3 (1 – 12)	451 (98.7)	1 (0.2)	5 (1.1)
Left colon (distal to splenic flexure)*	530	3 (1 – 12)	524 (98.9)	3 (0.6)	3 (0.6)
Rectum	292	2 (1 – 6)	259 (88.7)	14 (4.8)	19 (6.5)

*Includes patients who had a flexible sigmoidoscopy only.

Table 4. Yield of Right-sided Versus Left-sided Biopsies in 451 Patients with Microscopic Colitis.

	All Patients (n = 451)	Collagenous Colitis (n = 237)	Lymphocytic Colitis (n = 177)	MC, not Otherwise Specified (n = 37)
Both left-sided and right-sided biopsies diagnostic (%)	443 (98.2)	234 (98.7)	170 (96.0)	37 (100)
Only left-sided biopsies diagnostic (%)	4 (0.9)	3 (1.3)	1 (0.6)	0 (0)
Only right-sided biopsies diagnostic (%)	4 (0.9)	0 (0)	4 (2.3)	0 (0)