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ORIGINAL ARTICLE

Distribution of histopathological features along the colon in microscopic colitis

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Abstract

Purpose The diagnosis microscopic colitis (MC) consisting of collagenous colitis (CC) and lymphocytic colitis (LC) relies on histological assessment of mucosal biopsies from the colon. The optimal biopsy strategy for reliable diagnosis of MC is controversial. The aim of this study was to evaluate the distribution of histopathological features of MC throughout the colon.

Methods Mucosal biopsies from multiple colonic segments of patients with MC who participated in one of the three prospective European multicenter trials were analyzed. Histological slides were stained with hematoxylin-and-eosin, a connective tissue stain, and CD3 in selected cases.

Results In total, 255 patients were included, 199 and 56 patients with CC and LC, respectively. Both groups exhibited a gradient with more pronounced inflammation in the lamina propria in the proximal colon compared with the distal colon. Similarly, the thickness of the subepithelial collagenous band in CC showed a gradient with higher values in the proximal colon. The mean number of intraepithelial lymphocytes was > 20 in all colonic segments in patients within both subgroups. Biopsies from 86 to 94% of individual segments were diagnostic, rectum excluded. Biopsies from non-diagnostic segments often showed features of another subgroup of MC.

Conclusion Conclusively, although the severity of the histological changes in MC differed in the colonic mucosa, the minimum criteria required for the diagnosis were present in the random biopsies from the majority of segments. Thus, our findings show MC to be a pancolitis, rectum excluded, questioning previously proclaimed patchiness throughout the colon.

Keywords Colonic biopsies · Histopathology · Histology · Diagnosis · Chronic diarrhea · Inflammatory bowel disease · Microscopic colitis

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Introduction

Microscopic colitis (MC) is an increasingly recognized inflammatory bowel disease of the colon that has emerged as a common cause of chronic watery diarrhea. Symptoms include nocturnal diarrhea, urgency, fecal incontinence, and abdominal pain causing poor quality of life [1, 2]. Epidemiological studies have shown an increasing incidence of MC approaching figures comparable with Crohn's disease and ulcerative colitis in some populations [3]. Usually the endoscopic appearance of MC is normal or with nonspecific edema although more extensive changes may be seen [4]. The diagnosis rests on specific histological changes in colonic biopsies. The two major histological subtypes are collagenous colitis (CC) and lymphocytic colitis (LC) [5, 6]. In addition, variant or incomplete forms of microscopic colitis (MCi) have been described [6]. The incidence of MC in colonic biopsies from patients with chronic diarrhea varies from 1.3 to 19% depending on the selection of patients [7, 8]. Considering the high overall symptom burden and the severely affected quality of life, the major challenge in medical care of MC is to set a proper diagnosis and to differentiate these patients from other disease entities including irritable bowel syndrome [9].

According to the literature, the histological changes, especially in CC, may be patchy and not continuously distributed throughout the colon [6, 10–12], and current guidelines recommend obtaining mucosal biopsies from multiple colonic segments [2, 13–15]. However, data to support these recommendations are controversial. Some retrospective studies suggest that partial colonoscopy with only left-sided colonic biopsies may be sufficient for reliable diagnosis of MC [16, 17].

The aim of this study was to examine the distribution and severity of histopathological features in biopsies from the colonic mucosa in a large cohort of patients with CC or LC who participated in prospective clinical trials and with biopsies histologically assessed in a standardized fashion.

Materials and methods

Included patients

This is a post hoc histopathological analysis of pre-treatment mucosal biopsies obtained from patients diagnosed with MC and who participated in one of the three prospective European multicenter clinical trials, namely BUC-60/COC [18], BUC-63/COC [19], and BUG-1/LMC [20]. Overall, patients were enrolled in the studies between May 2007 and November 2016 with the last clinical follow-up in January 2017. The first two studies included patients diagnosed with CC while the third included patients diagnosed with LC. Patients were recruited from hospital departments and private practices from 31, 20, and 23 centers in the BUC-60/COC, BUC-63/COC, and BUG-1/LMC trials, respectively. Germany, Denmark, Sweden, Belgium, Czech Republic, Lithuania, Spain, Hungary, the Netherlands, and UK were among the participating countries. Exclusion criteria were infectious diarrhea, celiac disease, chronic inflammatory bowel disease (IBD), ischemic colitis, polyps > 2 cm, or tumors. Patients treated with budesonide, salicylates, steroids, antibiotics, cholestyramine, *Boswellia serrata* extract, and nonsteroidal anti-inflammatory or other immunosuppressant drugs within 4 weeks prior to colonoscopy were also excluded. Furthermore, all patients with suspicion of drug-induced MC (mainly PPI, NSAID, and SSRI) were not eligible to continue in the studies. According to the respective study protocols, a full colonoscopy should be performed at baseline and two mucosal biopsies obtained from the cecum/ascending, transverse, descending, and sigmoid colon, and the rectum. Biopsies from the cecum/ascending and transverse colon were defined as right sided, and descending, sigmoid, and rectum were defined as left sided.

Histopathological assessment

All biopsy specimens were formalin-fixed and paraffin-embedded. Established criteria for the histological diagnosis were used by the local pathologists. Major criteria included an inflammatory infiltrate in the lamina propria combined with a subepithelial collagen band > 10 μm in thickness for CC and > 20 intraepithelial lymphocytes (IELs)/100 epithelial cells, but a collagenous band < 10 μm for LC. Minor criteria included damage to and detachment of the surface epithelium which has especially been reported in CC, while mucin depletion and flattening were more commonly seen in LC. The inflammatory infiltrate in the lamina propria consists mainly of lymphocytes and plasma cells, but may include less extensive amounts of eosinophils and neutrophils [6, 10, 11]. Figure 1 a–d show examples of CC and LC.

Next, all biopsies were evaluated by one central pathologist in each of the three trials. One section with a thickness of 2–4 μm and 5 μm stained with hematoxylin-and-eosin (H&E) was available from patients with LC and CC, respectively. Van Gieson or Goldner stained slides were used to assist exact measurement of the thickness in micrometer of the collagenous band in well-oriented areas of the biopsies with at least three adjacent crypts cut in their vertical plane performed by use of an eyepiece measurement [18–20]. Counting of IELs was performed in hot spots consisting of at least three adjacent crypts. In borderline cases, CD3 immunohistochemically (IHC) stained slides were used to facilitate counting the exact number of IELs in the BUG-1 trial [20]. CD3 stained slides were not available in the BUC-63 trial [19]. Counting of IELs was not performed in the BUC-60 trial [18]. The inflammatory infiltrate of the lamina propria was assessed in a semiquantitative way and assigned to one of the following categories: 0

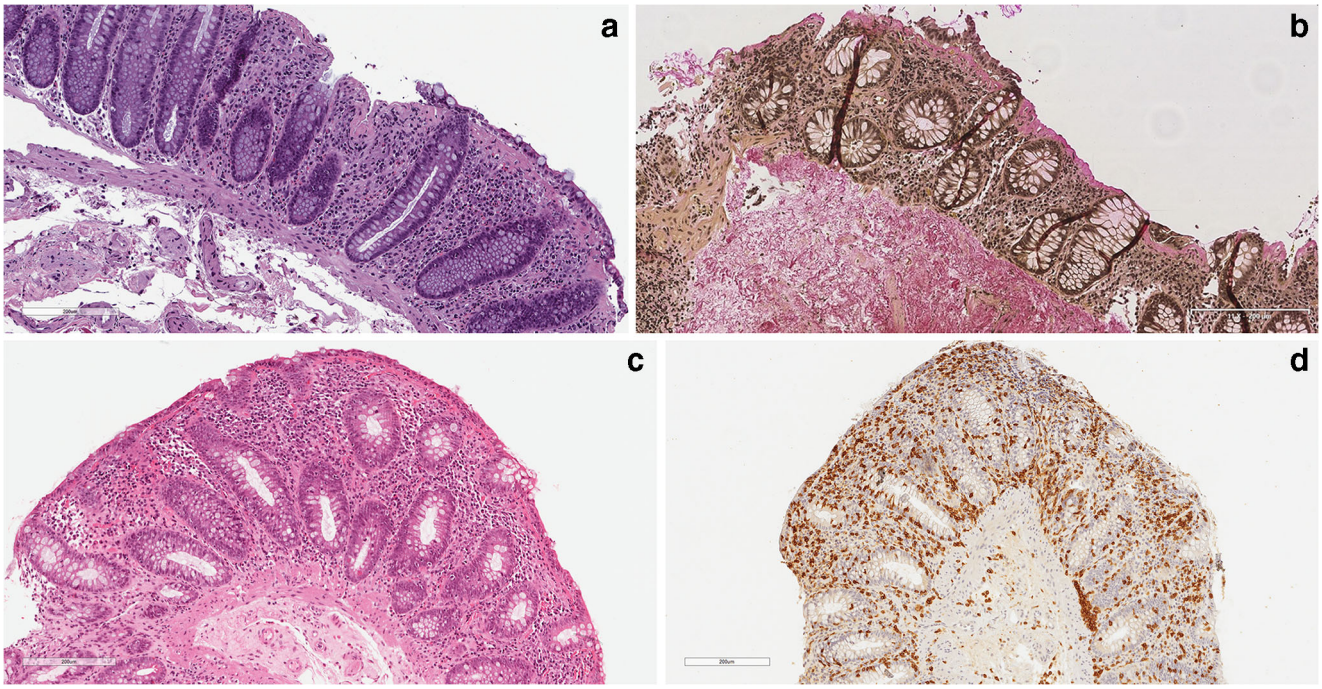

Fig. 1 **a** Collagenous colitis - HE stained slide. The surface epithelium is detached, and mucin depleted. The subepithelial collagenous band is markedly thickened and a mixed inflammatory infiltrate is present in the lamina propria. **b** Collagenous colitis -Van Gieson stained slide. **c** Lymphocytic colitis - HE stained slide. The surface epithelium is mucin depleted and flattened with an increased number of intraepithelial lymphocytes. A mixed inflammatory infiltrate is present in the lamina propria. **d** Lymphocytic colitis - CD3 stained slide

= none (normal cellularity), 1 = mild (slightly increased cellularity), 2 = moderate (increased cellularity), or 3 = severe inflammation (tightly packed inflammatory cells) [18–20]. If more than one biopsy was available per segment, the one with most pronounced changes was considered. Each segment was evaluated separately.

No patients with a final diagnosis of incomplete CC (CCi) or incomplete LC (LCi) were included in any of the trials. However, the changes in biopsies from some segments might not be sufficient for MC while fulfilling the criteria for the incomplete forms. As the clinical characteristics of MC and MCi are indistinguishable, clinicians can apply the same treatment algorithm and therefore these forms are included in the "Results" section. Accepted cutoff values for the incomplete forms were a collagenous band > 5 μm for CCi and > 10 IELs/100 epithelial cells for LCi combined with inflammation in the lamina propria [6]. For each segment, a diagnosis of CC overruled LC and a diagnosis of MC overruled MCi.

Statistics

All calculations were performed with the software package SAS, version 9.4 (SAS Institute Inc., Cary, NC 27513, USA). For statistical comparisons between two colonic segments, only patients with available data for both segments were included.

A McNemar test for paired samples was considered appropriate for segment-wise comparison of no inflammation vs. inflammation (consisting of the merged groups mild, moderate, and severe) as well as no/mild inflammation vs. moderate/severe inflammation in the lamina propria for patients with CC and LC, respectively. For comparison of the severity of the inflammation in the lamina propria between CC and LC in matched colonic segments, a two-sided Fisher's exact test was used.

The proportion of patients with a collagenous band > 10 μm as well as 95% confidence intervals (CI) is provided for each segment. Furthermore, the proportion of patients with > 20 IELs/100 epithelial cells as well as 95% CI is provided for each segment. For segment-wise comparison of the proportion of patients with a collagenous band > 10 μm and the proportion of patients with > 20 IELs, a McNemar test for paired samples was used. Segment-wise comparison of the number of IELs in patients with CC and LC, respectively, was performed using a Wilcoxon signed-rank test. A Wilcoxon-Mann-Whitney test was used for comparing the thickness of the collagen band and the number of IELs between CC and LC in matched segments.

All evaluations were understood in the exploratory sense. Hence, multiplicity issues were ignored. p values < 0.05 were considered statistically significant.

Ethics

Ethical committee's in the participating countries approved the studies. All patients provided written informed consent.

Results

Characteristics of included patients

In all, 255 patients were included in the present pathology study, 199 patients with CC and 56 patients with LC. The demographic characteristics of the study cohort are shown in Table 1. Overall, biopsies from a total of 906 colonic segments were assessed including 707 segments from patients with CC and 199 segments from patients with LC (Table 2 and Table 3). The mean number of sampled segments was 3.6 in both CC and LC. Biopsies from all five colonic segments were available from 102 patients (40%), 80 patients with CC, and 22 patients with LC.

Inflammation in the lamina propria according to localization and subgroup of MC

In patients diagnosed with CC, inflammation in the lamina propria was seen in the majority of biopsies from the entire colon. Cases with no inflammation were almost exclusively limited to the rectum with $p < 0.05$ for the rectum compared with all other segments. There was a gradient with more pronounced inflammation (moderate and severe) in the proximal colon compared with the distal colon (Table 2). This was not as evident in patients diagnosed with LC although a significantly higher number of patients were categorized with no or mild inflammation in the rectum compared with all other segments (Table 3). For all segments, more pronounced inflammation (moderate and severe) was reported in patients with LC compared with CC with significance reached in the rectum and sigmoid colon.

Thickness of the collagenous band according to localization and subgroup of MC

The thickness of the subepithelial collagenous band in patients with CC showed a gradient with higher values in the proximal colon (Table 2). Furthermore, the proportion of patients with a collagen band thickness of > 10 μm was significantly lower in the rectum compared with all other segments and in sigmoid compared with the descending and cecum/ascending colon, respectively (Table 2).

The mean thickness of the collagenous band in patients with LC varied from 3.6 μm in the cecum/ascending colon to 3.9 μm in the transverse and descending colon (Table 3).

Number of IELs according to localization and subgroup of MC

In patients with LC, the number of IELs/100 epithelial cells was increased in all parts of the colon ranging from a mean of 30.8 IELs in the rectum up to the descending colon to 36.3 IELs in the transverse colon (Table 3).

The number of IELs was only reported in one of the two original studies including patients with CC, the BUC-63 study. The mean number of IELs/100 epithelial cells varied from 28.6 IELs in the cecum/ascending colon to 33.5 IELs in the transverse colon (Table 2).

The proportion of patients with > 20 IELs/100 epithelial cells was significantly higher in the cecum/ascending and descending colon in LC compared with patients with a final diagnose of CC.

Patients fulfilling the diagnostic criteria of MC or MCi according to localization and subgroup of MC

Tables 4 and 5 show the percentage of patients fulfilling the criteria of CC, CCi, LC, and LCi in individual segments from patients with a final diagnosis of CC or LC, respectively.

For CC, a gradient was seen with a higher diagnostic rate in the right side of the colon with an additional number of segments fulfilling the criteria of CCi. Furthermore, a huge overlap with LC was observed as > 2/3 of biopsies from all segments fulfilled the criteria and of LC close to 90% of all segments fulfilled the criteria of LCi.

Table 1 Demographic characteristics of the study cohort

	Collagenous colitis ($N = 199$)[1]	Lymphocytic colitis ($N = 56$)[2]
Mean age (years)	58.7	57.7
Female gender, n (%)	156 (83.4)	35 (71.4)
New diagnosis, n (%)	70 (37.4)	19 (38.8)
Current smoker, n (%)	67 (35.8)	17 (34.7)
Former smoker, n (%)	54 (28.9)	11 (22.4)
Stool frequency/day, n (mean)	5.6	5.2

[1] Data missing for 12 patients for age, gender, new diagnosis, and smoking status and for 15 patients for stool frequency

[2] Data missing for 7 patients for age, gender, new diagnosis, and smoking status and for 9 patients for stool frequency

Table 2 Histopathological findings by colonic segment in collagenous colitis, patients with data for ≥ 1 segment included in analysis. Only significant *p* values are provided

	C/A	T	D	S	R	*p* values
Number of segments*	151	143	160	118	134	
Lamina propria inflammation						
None (%)	0.7	0.7	1.3	2.5	8.2	< 0.05[1]
Mild (%)	29.1	25.2	37.5	55.1	63.4	
Moderate (%)	58.9	65.0	57.5	40.7	28.4	< 0.05[2] < 0.0001[3]
Severe (%)	11.3	9.1	3.8	1.7	0.0	
Collagen band thickness (μm)						
Number of segments*	151	142	159	118	134	
Mean and 95% CI	19.8 (18.4–21.2)	19.6 (17.8–21.4)	19.8 (18.3–21.3)	17.9 (16.1–19.7)	14.6 (12.7–16.4)	
Median and range	18.0 (3–51)	16.5 (3–75)	18.0 (3–56)	15.0 (3–50)	12.8 (3–56)	
Patients with collagenous band > 10 μm (%) and 95% CI	94.0 (89.0–97.2)	91.5 (85.7–95.6)	90.6 (84.9–94.6)	85.6 (77.9–91.4)	64.9 (56.2–73.0)	< 0.05[4] < 0.0001[5]
IELs/100 ECs†						
Number of segments	90	79	80	52	63	
Mean and 95% CI	28.6 (25.7–31.6)	33.5 (30.0–37.0)	31.8 (28.3–35.3)	32.5 (28.4–36.5)	30.7 (27.8–33.6)	< 0.05[6]
Median and range	28.5 (3–72)	32.0 (6–73)	32.0 (5–83)	30.0 (5–78)	30.0 (8–59)	
Patients with > 20 IELs/100 ECs (%) and 95% CI	68.9 (58.3–78.2)	75.9 (65.0–84.9)	73.8 (62.7–83.0)	78.8 (65.3–88.9)	81.0 (69.1–89.8)	

C/A cecum/ascending; *T* transverse; *D* descending; *S* sigmoid; *R* rectum; *CI* confidence interval; *IELs* intraepithelial lymphocytes; *ECs* epithelial cells

* For a few patients, both of lamina propria inflammation and the collagenous band were not assessed which explains why the total number of segments for each of these is lower compared with the total number of segments (*N* = 707)

† Only assessed in patients from the BUC-63 study

[1] No inflammation vs. mild, moderate, or severe inflammation in the rectum vs. sigmoid, descending, transverse, cecum/ascending

[2] No/mild inflammation vs. moderate/severe inflammation in descending vs. transverse and cecum/ascending, and in sigmoid vs. descending and the rectum

[3] No/mild inflammation vs. moderate/severe inflammation in sigmoid vs. transverse and ascending/cecum, and in the rectum vs. descending, transverse, and ascending/cecum

[4] Collagenous band > 10 μm in sigmoid vs. descending and cecum/ascending

[5] Collagenous band > 10 μm in the rectum vs. sigmoid, descending, transverse, and ascending/cecum

[6] Number of IELs/100 EC in cecum/ascending vs. sigmoid, descending, and transverse

The highest diagnostic rate for LC was reached in the descending colon and an additional number of segments were diagnostic for LCi. One patient included as LC by the local pathologist actually had a thickened collagenous band > 10 μm in three segments and thus fulfilled the criteria for CC. Furthermore, 20.5–33.3% of segments fulfilled the criteria not only for LC or LCi but also those for CCi.

Subgroup analysis of patients fulfilling the diagnostic criteria of MC or MCi in patients with biopsies from all five colonic segments

Biopsies from all five segments were available from 80 patients with a final diagnosis of CC and from 22 patients with a final diagnosis of LC. This subgroup did not deviate substantially from the overall group except for a higher number of patients with a final diagnosis of LC also showing features of CCi (Table 4 and Table 5).

Subgroup analysis of patients fulfilling the diagnostic criteria of LC or CC in biopsies from the rectum and/or sigmoid colon

For 41 patients with LC and 133 patients with CC, biopsies were available from at least one evaluable segment of the rectum or the sigmoid and at least one evaluable segment oral to the sigmoid colon. In 92.7% (95% CI 84.7–100%) of the patients with LC and 81.2% (95% CI 74.6–87.8%) of the patients with CC, the diagnosis was confirmed in biopsies from only the rectum and/or sigmoid colon. Thus, the correct diagnosis of LC or CC, respectively, would have been missed in 7.3% and 18.8% of the patients by a sigmoidoscopy only.

Table 3 Histopathological findings by colonic segment in lymphocytic colitis, patients with data ≥ 1 segment included in analysis. Only significant *p* values are provided

	C/A	T	D	S	R	*p* values
Number of segments	37	39	44	46	33	
Lamina propria inflammation						
None (%)	0.0	0.0	0.0	0.0	6.1	
Mild (%)	21.6	20.5	25.0	23.9	30.3	
Moderate (%)	78.4	76.9	72.7	73.9	63.6	< 0.05[1]
Severe (%)	0.0	2.6	2.3	2.2	0.0	
IELs/100 ECs						
Mean and 95% CI	35.4 (31.3–39.6)	36.3 (32.3–40.4)	36.0 (31.9–40.2)	33.2 (29.9–36.5)	30.8 (26.4–35.1)	< 0.05[2]
Median and range	38.0 (10–60)	37.0 (8–60)	32.0 (20–70)	30.0 (12–60)	26.0 (10–60)	
Patients with > 20 IELs/100 ECs (%) and 95 CI	86.5 (71.2–95.5)	87.2 (72.6–95.7)	93.2 (81.3–98.6)	89.1 (76.4–96.4)	78.8 (61.1–91.0)	
Collagen band thickness (μm)						
Mean and 95% CI	3.6 (3.1–4.1)	3.9 (3.1–4.6)	3.9 (3.3–4.4)	3.8 (3.4–4.2)	3.8 (3.3–4.4)	
Median and range	3.0 (1–10)	4.0 (1–16)	3.0 (1–12)	3.5 (1–9)	4.0 (1–7)	

C/A cecum/ascending; *T* transverse; *D* descending; *S* sigmoid; *R* rectum; *CI* confidence interval; *IELs* intraepithelial lymphocytes; *ECs* epithelial cells

[1] No/mild inflammation vs. moderate/severe inflammation in the rectum vs. sigmoid, descending, transverse, and cecum/ascending

[2] Number of IELs/100 EC in sigmoid vs. descending and transverse, and in the rectum vs. descending and transverse

Discussion

The histological changes of MC and especially CC are traditionally described as having a patchy distribution throughout the colon. In this study, we challenge this notion by a systematic evaluation of the inflammation in the lamina propria, the thickness of the collagenous band, and the number of IELs in each colonic segment of patients included in prior clinical trials. We have shown that overall, the changes are more pronounced in the proximal colon, but the minimum required histopathological criteria for the diagnosis were also fulfilled in 90% of the left-sided biopsies demonstrating that MC is a pancolitis.

The demographic characteristics of the study cohort were typical with respect to age, gender, and smoking habits [14, 15] and clinical criteria for MC were met. Other common causes of diarrhea had been excluded in all patients.

The lamina propria inflammation was more pronounced in LC compared with CC, although not significantly in all segments. In LC, inflammation with varying intensity was observed in biopsies from all segments except for the rectum, while in CC, no inflammation was reported in a few cases in other segments too. The thickness of the collagenous band also showed a gradient from a maximum thickness in the right to the left. The lowest diagnostic rate was observed in the subgroup of CC patients with biopsies from all five segments with 88.8% of the left-sided biopsies being diagnostic. Similarly, higher mean counts of IELs were observed in the right side of the colon in patients with LC. However, the lowest rate of diagnostic biopsies at 86.4%, from patients with LC, was observed in right-sided biopsies in the subgroup of patients with biopsies from all five segments. In 97.5% of left-sided biopsies from patients with CC, the criteria for CCi were fulfilled, and 100% of left-sided biopsies from patients with LC fulfilled the criteria for LCi. Patients with characteristic clinical symptoms and a histological diagnosis of MCi are believed to benefit from the same treatment as patients with MC, and results from an ongoing study are awaited to clarify if even MCi patients benefit from budesonide, the standard treatment for MC.

Our findings are in line with three large recent studies comparing histopathological changes in matched biopsies from the right and left sides showing that 95–99% of patients present with diagnostic criteria of MC in both sides of the colon [16, 17, 21]. The previous studies were based on the histology report with reassessment of the material in only one of these studies. None used exact measurement of the collagenous band, exact count of the number of IELs, or semiquantitative estimation of the inflammatory infiltrate in the lamina propria. Thus, these studies were not able to differentiate, whether the changes were more pronounced in one side but could conclude that biopsies from both sides were diagnostic for MC. CD3 staining was only performed in the BUG-1 trial and not even consequently used, which could possibly explain the minimally lower concordance in our study. Previously, supplementary CD3 staining has been shown to increase the counts of IELs resulting in a higher number of cases fulfilling the diagnostic criteria for LC [22]. Beside these studies of

Table 4 Percentage of patients with a final diagnosis of CC fulfilling the diagnostic criteria of CC, CCi, LC, or LCi according to colonic segment. Patients with data ≥ 1 segment with assessment of both lamina propria inflammation and number of IELs or thickness of the collagenous band included in analysis. The lower part of the table shows data from patients where biopsies from all segments were available. IELs were only assessed in patients from the BUC-63 study

	C/A	T	D	S	R
Number of segments	151	142	159	118	133
CC	94.0	91.5	89.9	85.6	63.9
CCi	98.0	97.9	97.5	94.9	82.0
Number of segments*	90	79	80	52	62
LC	68.9	75.9	73.8	78.8	77.4
LCi	88.9	97.5	95.0	88.5	88.7
Patients with biopsies from all five segments					
Number of segments	80	80	80	80	80
CC	92.5	90.0	88.8	85.0	62.5
CCi	97.5	97.5	97.5	95.0	82.5
Number of segments*	37	36	37	35	39
LC	67.6	75.0	75.7	80.0	82.1
LCi	89.2	100	97.3	88.6	89.7

C/A cecum/ascending; *T* transverse; *D* descending; *S* sigmoid; *R* rectum; *CC* collagenous colitis; *CCi* incomplete collagenous colitis; *LC* lymphocytic colitis; *LCi* incomplete lymphocytic colitis; *IELs* intraepithelial lymphocytes

* IELs only assessed in patients from the BUC-63 study ($N = 40$). Data on IELs were missing for some patients

Table 5 Percentage of patients with a final diagnosis of LC fulfilling the diagnostic criteria of LC, LCi, CC, or CCi according to colonic segment. Patients with data ≥ 1 segment with assessment of both lamina propria inflammation and number of intraepithelial lymphocytes or thickness of the collagenous band included in analysis. The lower part of the table shows data from patients where biopsies from all segments were available

	C/A	T	D	S	R
Number of segments	37	39	44	46	33
LC	86.5	87.2	93.2	89.1	75.8
LCi	97.3	97.4	100	100	90.9
CC	2.7	2.6	2.3	0	0
CCi	24.3	20.5	25.0	21.7	33.3
Patients with biopsies from all five segments					
Number of segments	22	22	22	22	22
LC	81.8	86.4	90.9	86.4	77.3
LCi	95.5	95.5	100	100	86.4
CC	4.5	4.5	4.5	0	0
CCi	40.9	31.8	40.9	22.7	36.4

C/A cecum/ascending; *T* transverse; *D* descending; *S* sigmoid; *R* rectum; *CC* collagenous colitis; *CCi* incomplete collagenous colitis; *LC* lymphocytic colitis; *LCi* incomplete lymphocytic colitis

matched biopsies from the right and left sides, Virine et al. have recently published a retrospective study including 101 patients with MC analyzing individual biopsy fragments from the colon mucosa. They reported 78–97% of individual biopsies from different segments as diagnostic. When combining two biopsies from the ascending and two biopsies from the descending colon, 100% of cases were detected [23]. As this was a retrospective pathology study, the biopsy protocol was not standardized, matched biopsies were not available, and the clinical symptoms were unknown. Further studies including fewer patients also report a high rate of concordance between the right and left-sided biopsies [24–27]. On the other hand, some studies report the number of diagnostic biopsies from the left side to be lower [28–31]. It is well-known that biopsies exclusively from the rectum are not sufficient which is supported by the findings of the present study [28, 31–33].

Interestingly, in the present study, the mean number of IELs in patients diagnosed with CC was 28.6–33.5/100 epithelial cells in the surface epithelium, which was almost as high as what was seen in LC with mean numbers of 30.8–36.3/100 epithelial cells. This partly contrasts with previous literature saying that the number of IELs in CC may be elevated, but not to the same extent as in LC [6, 12]. Although the mean number of IELs was higher in LC compared with CC in this study, most of the patients with a final diagnosis of CC fulfilled the histological criteria of LC also. This implicates an overlap between the two subtypes, which has also been reported previously [16]. Opposite to this, the mean thickness of the collagenous band in patients with LC was not higher than 3.9 μm, which is in the normal range. This seems reasonable and a result of the inclusion criteria since a thickened collagenous band should lead to classify the case as CC. However, a high proportion of LC did also meet the criteria of CCi.

From a clinical point of view, discriminating between CC and LC is of minor importance, as the symptoms and treatment are identical [1, 15]. Distinguishing between the subtypes is of higher relevance for the pathologist since the differential diagnoses are quite different. In relation to CC, it is important to consider ischemia, mucosa prolapse, amyloid colitis, and radiation damage, while for LC, the most common differential diagnoses are resolving infections, drug-induced changes, and IBD [5, 6]. However, our results also confirm that different forms of MC may be present at different sites at the same time in the colon in accordance with what has been described previously [6, 16].

A limitation of the present study may be that the biopsies originate from three different clinical trials with a different central pathologist assessing the biopsies in each of the trials which might have led to differences in the histological examination and interpretation. However, previous studies have shown a good reproducibility of MC among pathologists [34, 35]. Therefore, we assume this did not influence the results noticeably. In the optimal scenario, we would have had

biopsies from all five segments from all patients. Still, the mean number of 3.6 of represented segments is high, with biopsies being available from all segments from 40% of the patients, and the results from this subgroup did not differ from the overall.

Left-sided biopsies of the colon seem to be diagnostic for the specific subtype of MC in > 90% of the patients. Furthermore, a sigmoidoscopy without including biopsies from the descending colon will miss the specific subtype in 7.3% and 18.8% of the patients with LC and CC. In the clinical setting, full colonoscopy is required to exclude IBD and malignancy, but biopsies from all segments in a macroscopic normal bowel appear to be unnecessary. Because of the consistent observation in the literature and in the present study of more pronounced inflammatory changes in the proximal vs. distal colon, European guidelines on clinical management of MC recommend to obtain biopsies at least from the right and left colon, rectum excluded [2]. In situations with e.g., patients recently having a full colonoscopy or in high-risk patients, a colonoscopy to the left colonic flexure is sufficient to detect MC.

The number of biopsies needed to diagnose or exclude MC is still not clarified. Previous guidelines suggest a minimum of eight biopsies from different segments [13, 14], which others have recently proposed to reduce [23, 36]. In the present study, the biopsies were not assessed individually, but as an overall assessment for each segment and therefore our data do not contribute to clarify this issue.

Conclusion

The results of our study based on colonic biopsies from a European cohort of prospectively included and clinically well-described patients show that, although the severity of the histological changes in MC differs in the segments of the colon, the minimum criteria required for the diagnosis are present in random biopsies in all segments, excluding the rectum. The findings suggest that MC is more uniformly distributed than previously described and resembles a pancolitis with a gradient of inflammation from the proximal to the distal colon. We suggest reducing the number of segments to include only biopsies from the right and left side of the colon.

Authors' contributions SM, AMÜ: conception and design of the work.

DA, MV, SM, OB, FF, EM, JK, AMA, LM, AMÜ: acquisition of data.

AF, SM, TN, RMO, RMÜ, RG, AMÜ: analysis and interpretation of data.

AF: drafted the work.

All: revised the work critically for important intellectual content.

All: approved the final version.

All: agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part or the work are appropriately investigated and resolved.

Data availability Available on request

Compliance with ethical standards

Conflict of interest SM has served as a consultant for Dr. Falk Pharma and Tillotts, and received speaker fees from the Falk Foundation. AMA has served as a consultant for Dr. Falk Pharma and Tilllotts. AMÜ has served as a consultant for Dr. Falk Pharma, Ferring, and Tillotts. TN, RMO, RMÜ, and RG are employees at Dr. Falk Pharma.

Ethical approval The studies were approved by the ethical committees in the participating countries.

Consent to participate All patients have provided written informed consent.

Consent for publication All authors have approved the final version of the manuscript.

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