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The Temporal Evolution of Histological Abnormalities in Microscopic Colitis

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Abstract

Background and Aims: Microscopic colitis (MC) is a common cause of chronic watery diarrhoea but long-term follow-up data are sparse.
Methods: We performed a retrospective review of health records and all pathology reports in a regional cohort of patients with MC to describe the change in pre- and post-diagnostic colon biopsies.
Results: MC was diagnosed in 468 patients with collagenous colitis (CC), 361 with lymphocytic colitis (LC) and 226 with incomplete MC (MCi). The 2014 incidence of CC, LC and MCi was 14.5, 14.9 and 5 per 10^5. Biopsies from both right and left colon were obtained in 237 (51%) patients with CC, 200 (55%) with LC and 107 (47%) with MCi. The diagnostic sensitivities of both left- and right-sided biopsies for MC were high and did not differ. Pre-diagnostic biopsies were obtained in 150 patients and lamina propria inflammation was described in 59, 47 and 43% of patients with a diagnosis of CC, LC and MCi respectively within 1 year, while histology was normal in 16, 13 and 21%. Post-diagnostic biopsies were obtained in 283 patients. MC persisted for up to one year in 77% with CC, 64% with LC and 45% with MCi, of whom 6, 9 and 18% respectively changed to a different MC subgroup.
Conclusions: Colonic biopsies obtained prior to the MC diagnosis often revealed increased lamina propria inflammation. The pathological changes of CC and LC are more persistent than those of MCi. Biopsies from the descending or sigmoid colon are sufficient to elucidate whether a patient with chronic watery diarrhoea has MC.

Key Words: Microscopic colitis; endoscopy; pathology

1. Introduction

The prevalence of microscopic colitis (MC) exceeds 20 per 10^6 in many countries [1–5] and MC is found in ~10–15% of patients with chronic watery diarrhoea undergoing endoscopy with biopsy, with higher detection rates in the elderly.[6–9] MC is characterized by chronic watery diarrhoea in patients with a macroscopically normal or near-normal colonic mucosa and characteristic changes in the biopsies.[10,11] Three histological subtypes have been described: collagenous colitis (CC), lymphocytic colitis (LC) and incomplete microscopic colitis (MCi).[11,12] The clinical symptoms and findings do not differ between MC subgroups.[1,13]

While relapse following treatment in controlled trials is common,[14] the long-term course of MC, particularly of MCi, is less well described.[13,15–20] Clinical remission was reported in 63% of 212 patients with LC and CC after a median follow-up of 6 years.[15] Persistence of histological changes has been reported in small series

of CC and LC only[16–25] and no reports on persistence of symptoms and pathology in MCi have been published. Furthermore, it may be difficult to discriminate between non-specific inflammatory changes in colonic mucosa and MC, particularly in the incomplete forms.[26,27]

We have established a regional database comprising a complete, non-selected population of patients diagnosed with MC.[13] The main purpose of this study was to update incidence rates in the population, describe the persistence and interchangeability of histology in patients with subsequent endoscopies, and evaluate whether pre-diagnostic histological changes could be associated with later development of MC.

2. Methods

All consecutive MC patients diagnosed at Roskilde Pathology Department from January 2000 to December 2014 were identified by means of SNOMED codes (http://www.patobank.dk). No patients were excluded. The pathology department performs all histological examinations from hospitals and private practices in a large part of Region Zealand and the regional database has been complete, covering all of Region Zealand, since January 2014. We did a complete retrospective review of all gastrointestinal pathology reports in the Danish National Pathology Database for each patient and extracted date, indication, type of endoscopy, location in the colon and number of biopsies obtained.

We extracted indications for endoscopy and patient treatment after the endoscopy from referral notes and from the electronic health charts. If there were several treatments, the most potent was registered using this hierarchy: budesonide, cholestyramine, loperamide, psyllium, mesalazine, others including elimination diet, natural herbs and alternative medicine, none and not known. Biochemical screening for coeliac disease (IgA anti-glutaminase antibody and IgG deamidated gliadin antibody) and duodenal and ileal biopsy reports were identified and scrutinized for evidence of coeliac disease.

The date of the first diagnostic endoscopy was considered the date of diagnosis. If a patient had more than two biopsy sets from lower endoscopies performed prior to diagnosis, only the findings of the oldest and the most recent were included. All post-diagnostic endoscopies with colonic biopsies were registered and pooled into three time slots according to time since the diagnostic endoscopy. Within each time slot, only the result of the most recent endoscopy was included. This study includes updated data on the 539 patients described in a previously published report.[13] The study was approved by the Regional Research Unit (Region Sjaellands number 12-000 179) and the Danish Data Protection Agency (number 2008-58-0020).

Histological descriptions were based on haematoxylin and eosin (HE) staining. Special stains were applied in borderline cases: immunohistochemical staining for CD3 and van Gieson staining (VG) to detect LC and CC respectively. Biopsies from the colon oral to the splenic flexure were classified as right-sided and biopsies from the sigmoid and descending colon as left-sided. We disregarded rectal biopsies. The pathological reports included descriptions of findings in each biopsy vial and in our analysis we pooled these into right and left colon respectively. Biopsies were classified as colon if no exact biopsy site was stated. We used the original pathology reports as these were performed by expert pathologists with knowledge of MC and during the last 10–15 years by experts who were specialists in gastrointestinal pathology. Biopsies were not re-evaluated for this study.

The diagnostic criteria of MC and MCi used in the pathology reports were as previously described:[11,12,16,22,28–30] CC, lamina propria inflammation and a collagenous subepithelial band of ≥10 µm; LC, lamina propria inflammation with ≥20 intraepithelial lymphocytes per 100 epithelial cells; MCi, slight lamina propria inflammation and either a subepithelial collagenous band of 5–9 µm or an increased number of intraepithelial lymphocytes (>5 and <20). The specific term 'MCi' was used systematically from 2010. Earlier endoscopies with the histological description 'MC could be suspected, but criteria not fulfilled' were classified as MCi. If the histology findings fulfilled the criteria for more than one MC subgroup, the hierarchy of classification was CC, LC, MCi. Based on the written pathology reports, biopsies described with an increased lymphoplasma cellular infiltrate of the lamina propria were classified as lamina propria inflammation. Biopsies described with a minimal increase in the number of lymphocytes and plasma cells in the lamina propria were classified as representing non-specific changes.[26]

All results were anonymized and entered into Excel for analysis. Results are presented as median with ranges. Frequencies, diagnostic sensitivities and calculations are given as percentages with 95% confidence intervals (CIs).

3. Results

3.1. Patients and endoscopy

Microscopic colitis was diagnosed in 1055 patients: 468 with CC, 361 with LC and 226 with MCi. The median age was 67, 67 and 61 years in patients with CC, LC and MCi respectively and 74, 64 and 69% were women. The 1055 patients had a total of 1623 lower endoscopies performed, of which 1064 were colonoscopies. The 1055 diagnostic procedures were sigmoidoscopy in 150 (32%) with CC, 107 (30%) with LC and 82 (36%) in MCi, and colonoscopy in 318 (68%) with CC, 254 (70%) with LC and 144 (64%) with MCi. A history of watery diarrhoea was documented in 450/462 (97%; 95% CI 95–99%) with CC, 315/345 (91%; 87–95%) with LC and 183/214 (86%; 80–90%) with MCi. The median number of biopsies taken at the diagnostic endoscopy was 7 (range 1–26) in CC, 7 (1–28) in LC and 7 (1–21) in MCi. Coeliac disease was confirmed in 5/387 (1%; 95% CI 0–3%) with CC, 4/300 (1%; 0–3%) and 2/176 (1%; 0–3%) with MCi. From January 2014 the database contains all MC patients diagnosed in Region Zealand, with 819 385 inhabitants. The overall regional incidence of MC in 2014 was 34.4 per 10^5 inhabitants and that of CC, LC and MCi was 14.5, 14.9 and 5 per 10^5 inhabitants.

3.2. Pre-diagnostic findings

Altogether, 156 endoscopies with biopsy prior to the diagnostic endoscopy were performed in 150 patients (Table 1). Separate biopsies had been taken from both right and left colon in 24 (35%; 95% CI 24–48%), 11 (27%; 14–43%) and 16 (39%; 24–56%) with later CC, LC and MCi respectively. The indication for endoscopy was watery diarrhoea in 75% (46/61; 95% CI 63–85%) of patients having an endoscopy within 1 year before diagnosis and 46% (44/95; 36–47%) in patients having an endoscopy more than 1 year before diagnosis (Table 1). The median number of biopsies taken at the most recent endoscopy was 6 (range 1–22) in patients with CC, 4 (1–10) in LC and 5 (1–21) in MCi. The histological findings in pre-diagnostic endoscopies according to time before diagnosis are shown in Table 2. Lamina propria inflammation was the most frequent finding (Table 2), and was described in 87% (27/31; 95% CI 70–96%), 75% (9/12; 43–95%) and 71% (10/14; 42–92%) of patients with a later diagnosis of CC, LC and MCi respectively. Normal histology was described in a minority (Table 2).

Table 1. Indications for pre-diagnostic endoscopies according to time before diagnosis.[1]

Indication	Collagenous colitis		Lymphocytic colitis		Incomplete microscopic colitis	
	0–12 months (*n* = 32)	>12 months (*n* = 47)	0–12 months (*n* = 15)	>12 months (*n* = 23)	0–12 months (*n* = 14)	>12 months (*n* = 25)
Diarrhoea	78 (0–91)	53 (38–68)	67 (38–88)	39 (20–61)	79 (49–95)	36 (21–61)
Blood in stool	–	–	–	22 (7–44)	7 (0–34)	8 (1–26)
Weight loss	–	–	–	4 (0–22)	–	–
Constipation	–	–	–	4 (0–22)	–	–
Pain	3 (0–16)	9 (2–20)	–	–	7 0–34)	
No diarrhoea or not stated	19 (7–36)	38 (25–54)	33 (12–62)	30 (12–62)	7 (0–34)	52 (31–72)

Data are % (95% confidence interval).
[1]Six patients had an endoscopy in both periods.

Table 2. Histological findings in pre-diagnostic endoscopies according to time before diagnosis[1].

	Collagenous colitis		Lymphocytic colitis		Incomplete microscopic colitis	
	0–12 months (*n* = 32)	>12 months (*n* = 47)	0–12 months (*n* = 15)	>12 months (*n* = 23)	0–12 months (*n* = 14)	>12 months (*n* = 25)
Normal	16 (5–33)	28 (16–43)	13 (2–40)	17 (5–39)	21 (5–51)	15 (5–36)
Lamina propria inflammation	59 (41–76)	32 (19–47)	47 (21–73)	34 (16–57)	43 (18–71)	27 (12–49)
Non-specific changes	6 (1–21)	15 (6–28)	13 (2–40)	9 1–28)	29 (8–58)	35 (18–57)
Inflammatory bowel disease	3 (0–16)	2 (0–11)	–	–	7 (0–34)	–
Adenoma or polyp	6 (1–21)	14 (6–28)	13 (2–40)	26 (10–48)	–	12 (3–31)
Dysplasia	–	–	7 (0–26)	–	–	4 (5–36)
Cancer	–	6 (1–18)	–	9 (1–28)	–	4 (0–20)
Ischaemia	3 (0–16)	2 (0–11)	–	–	–	–
Infectious colitis	6 (1–21)	–	7 (0–26)	–	–	–
Fibrosis	–	–	–	–	–	4 (0–20)

Data are % (95% confidence interval).
[1]Six patients had an endoscopy in both periods.

3.4. Post-diagnostic findings

One or more subsequent endoscopies with biopsy following the diagnostic procedure were performed in 149 (32%) with CC, 72 (20%) with LC and 62 (27%) with MCi. The indication for early (0–12 months) post-diagnostic endoscopy was watery diarrhoea in 40/49 (82%; 95% CI 68–91%) with CC, 23/31 (74%; 55–88%) with LC and 33/43 (77%; 61–88%) with MCi. For endoscopies performed 13–24 months after the diagnostic endoscopy, 31/44 (70%; 95% CI 55–83%), 6/7 (86%; 42–100%) and 4/6 (67%; 22–96%) of patients with CC, LC and MCi respectively had watery diarrhoea. For late endoscopies (>24 months) the numbers were 31/37 (84%; 68–94%), 27/36 (75%; 58–88%) and 17/25 (68%; 47–85%) for CC, LC and MCi respectively. A number of patients had a second endoscopy due to indications other than diarrhoea, including cancer screening endoscopies and abdominal pain. The histological findings in the post-diagnostic biopsies according to time from diagnosis are shown in Table 3. A diagnosis of MC persisted in at least one post-diagnostic biopsy in 83% with CC, 63% with LC and 54% with MCi. The MC subtype changed in 35% (22/63) patients with MCi to CC or LC.

3.5. Treatment

Table 4 specifies the most potent treatment of diarrhoea given to the patients after the initial diagnosis according to MC subgroups Table 4. Treatment given after subsequent endoscopies is shown in Supplementary Table S1. Diarrhoea stopped shortly after endoscopy in 71 patients and these were therefore not treated. This was particularly evident for patients with MCi.

3.6. Diagnostic sensitivity

Separate biopsies from both right and left colon were obtained at the diagnostic colonoscopy in 237 patients with CC (51%), 124 (55%) with LC and 107 (47%) with MCi. Discrepancy between histopathology in the right and left colon was rare; 4 patients had histological changes of MC in the right colon only and 16 in the left colon only. Thus, the sensitivity of biopsies from the right and left colon did not differ for MC in general or MC subgroups (Table 5). The histological findings in the contralateral colonic half without signs of MC were non-specific changes (10), normal (4), lamina propria inflammation (4), polyp (1), dysplasia (1) and focal cryptitis (1). In 2 patients LC was found in the right colon and CC in the left, and in one patient MCi in the right colon and LC in the left.

4. Discussion

This study presents endoscopic and histological findings in colonic biopsies obtained from a large regional cohort of consecutive, non-selected patients diagnosed with MC. Due to the large sample size, a complete cohort and long-term follow-up the results are most likely representative of the MC population as a whole. Access to the national pathology database and the systematic description of each biopsy using SNOMED terms provided complete and systematic

Table 3. Histological findings at post-diagnostic endoscopies according to time elapsed since the diagnostic endoscopy. If a patient had more than one endoscopy in one period, only the result of the latest endoscopy was included.

	Collagenous colitis			Lymphocytic colitis			Incomplete microscopic colitis		
	0–12 months (n = 63)	13–24 months (n = 52)	>24 months (n = 56)	0–12 months (n = 33)	13–24 months (n = 9)	>24 months (n = 42)	0–12 months (n = 49)	13–24 months (n = 7)	>24 months (n = 32)
Normal	6 (2–15)	4 (1–13)	13 (5–24)	9 (2–14)	–	12 (4–26)	4 (1–14)	29 (4–71)	25 (11–43)
Same MC group	71 (59–82)	73 (59–84)	59 (45–72)	55* (36–72)	44 (14–79)	43* (28–59)	27 (15–41)	14 (0–58)	3 (0–16)
New CC	–	–	–	3 (0–16)	11 (0–48)	17 (7–31)	18 (9–32)	14 (0–58)	28 (14–47)
New LC	2 (0–9)	–	11 (4–22)	–	–	–	–	14 (0–58)	16 (5–33)
New MCi	3 (1–11)	2 (0–10)	4 (1–12)	6 (1–20)	–	2 (0–13)	–	–	–
Lamina propria inflammation	5 (1–13)	2 (0–10)	4 (1–12)	6 (1–20)	33 (7–70)	2 (0–13)	20 (27–56)	–	6 (1–21)
Non-specific changes	8 (3–18)	8 (2–19)	7 (2–17)	15 (5–32)	11 (0–34)	24 (12–39)	22 (12–37)	–	16 (5–33)
Inflammatory bowel disease	2 (0–9)	–	–	–	–	–	2 (0–11)	–	–
Adenoma or polyp	3 (1–11)	8 (2–19)	2 (0–10)	–	–	–	4 (1–14)	–	6 (1–21)
Dysplasia or cancer	–	–	–	6 (1–20)	–	–	2 (0–11)	14 (0–58)	–
Ischaemia	–	–	2 (0–10)	–	–	–			
Diverticulosis								14 (0–58)	

Data are % (95% confidence interval).
CC, collagenous colitis; LC, lymphocytic colitis; MCi, incomplete microscopic colitis.
*One patient had both LC and CC.

data for all patients. Almost all patients had diarrhoea at the time of MC diagnosis and the diagnosis was thus based on both clinical and pathological findings.

Previously published detailed clinical data on a subgroup of these patients demonstrated that clinical symptoms and findings are similar in the three MC subgroups.[13] Median age, gender distribution and the low co-incidence of coeliac disease have not changed significantly in the enlarged cohort. The present study thus confirms our previous findings and reports the highest regional incidence rates hitherto reported. However, the main purpose is to provide an analysis of histological changes in consecutive biopsies before and after the index endoscopy, including indications for endoscopy.

Several patients with a later diagnosis of MC had an endoscopy with biopsy prior to the diagnosis. The indication for the majority of these was chronic watery diarrhoea and lamina propria inflammation was a frequent finding, particularly in biopsies obtained within 1 year of diagnosis. This observation is in accordance with a previously published small series.[23] Thus, the finding of lamina propria inflammation in patients with chronic watery diarrhoea should prompt the physician to consider whether the patient could in fact have MC or be in the process of developing MC. Microscopic colitis is a debilitating disease[15,31] with an efficient therapy,[10] which is why the diagnostic delay should be minimized. A short therapeutic trial of budesonide rather than yet another endoscopy could be considered in more fragile patients with persistent watery diarrhoea and chronic inflammation in an otherwise normal endoscopy, as the risk of colon cancer during follow-up was very low and was found only in patients with prior polyps. Several case reports have described the development of Crohn's disease and ulcerative colitis in patients with MC,[10] but we detected classic inflammatory bowel disease in only 10 individuals in the present large cohort. It thus appears that there is no clear association between MC and ulcerative colitis or Crohn's disease.

Knowledge of the long-term prognosis of patients with MC is sparse. Relapse rates are high in clinical trials; however, these populations are highly selected.[10] Conflicting results have been reported in retrospective follow-up studies with both high rates of continuous or intermittent diarrhoea [15,32] and mild symptoms or resolution.[16,18–20,22,33] Histological follow-up data are rarely reported.[21, 23] Our data show that histology normalizes in only a small proportion of patients with continuous or recurrent diarrhoea subjected to subsequent endoscopy, which is in line with findings in previous small series.[21,23] Histological changes diagnostic for MC persisted in 70–73, 55–64 and 42–47% of patients with a primary diagnosis of CC, LC and MCi respectively (Table 3), indicating that histology appears to normalize more often in patients with MCi. A second endoscopy (colonoscopy) was done in several patients within the first months after the diagnostic endoscopy to confirm the diagnosis. This practice was abandoned after our previously reported findings.[13] However, full colonoscopy is performed to rule out other pathology in patients with alarm symptoms and in those that do not respond immediately to therapy. The indications for the later post-diagnostic endoscopies were mainly persistent or recurrent diarrhoea. The histological changes persisted beyond the first year in a significant number of patients in this selected subgroup, indicating that the persistent symptoms are in fact due to persistent MC. However, histological changes of MC also persisted in patients in whom the diarrhoea had resolved and not recurred, indicating that there is no direct relation between histological changes and MC pathophysiology.

While the frequency of normal histology in post-diagnostic biopsies did not differ significantly between groups, the findings of CC appear

Table 4. Treatment initiated after diagnostic endoscopy.

	CC (n = 468)	LC (n = 361)	Mci (n = 226)
Budesonide	50 (46–54)	52 (47–57)	24 (18–31)
Colestyramine	6 (4–8)	6 (4–8)	9 (6–13)
Loperamide	3 (2–5)	1 (0–3)	1 (0–3)
Psyllium	6 (4–8)	7 (4–10)	6 (3–9)
Mesalazine	1 (0–2)	0 (0–1)	1 % (3)
Other[1]	3 (2–5)	3 (1–5)	5 (2–9)
None	17 (13–20)	18 (14–22)	36 (29–42)
Unknown	13 (11–15)	12 (9–16)	16 (11–22)

The table shows the most potent treatment given to each patient using this hierarchy: budesonide, cholestyramine, loperamide, psyllium, mesalazine, others, none and unknown.

Data are % (95% confidence interval).

CC, collagenous colitis; LC, lymphocytic colitis; MCi, incomplete microscopic colitis.

[1]Others include diet, natural herbs and alternative medicine.

Table 5. Sensitivity of biopsies from the right and left colon at the diagnostic colonoscopy.

Sensitivity	Collagenous colitis (n = 237)	Lymphocytic colitis (n = 200)	Incomplete microscopic colitis (n = 107)
Right colon	98 (95–100)	99 (97–100)	91 (84–96)
Left colon	99 (97–100)	100 (98–100)	97 (91–99)

Data are % (95% confidence interval).

more persistent in both the early and late post-diagnostic endoscopies. This could reflect either more persistent disease compared with the other MC subgroups or that CC is a more readily recognizable histological diagnosis compared with LC.[26,27] It might also be caused by the collagenous band in CC being less reversible compared with the intraepithelial lymphocytes in LC, which may be mobile and thus capable of fluctuating in and out of the epithelia. Prospective follow-up cohort studies using validated measures of disease activity and quality of life scores[15,31] should be initiated to better inform us and patients on the clinical course of MC and MC subgroups.

The concept of MCi is more recent than that of the classical MC subgroups,[11–13,28–30] and the condition is not used everywhere as an independent diagnosis. The fact that MCi seems less persistent than LC and CC could imply that MCi is an early form of MC, as demonstrated by the change in histological diagnosis from MCi to LC or CC at the second endoscopy. At the same time, the high rate of non-specific changes in repeat biopsies from patients with MCi indicates that the histological changes of MCi may be difficult to distinguish from non-specific changes.[26,34] During the study period the use of immunohistochemical staining has increased, which could have led to more patients being diagnosed with LC or CC rather than MCi. In fact, the widespread use of immunohistochemical staining does challenge the diagnostic criteria of MC, which are based on HE-stained slides. It should be noted that the incidence of MCi in our cohort appears constant while the incidence of LC and CC has increased further,[1,13] indicating that the use of CD3 staining did not increase the number of biopsies classified as MCi.

Our results provide no information on the number of biopsies needed to exclude the presence of MC. We accepted the MC diagnosis if histological changes were present in one biopsy only while others require histological changes in at least two biopsies and two colonic segments.[4,5,15,25] The clinical relevance of our diagnostic approach is supported by the therapeutic effect of budesonide demonstrated in a subgroup of our cohort,[13] comparable to that reported in clinical trials.[10,35] We have confirmed that histological discrepancy between the right and left colon is rare, that diagnostic sensitivity is extremely high and identical throughout the entire colon, excluding the rectum, and that this is true for MC overall and for each MC subgroup. Small series[10] and data from controlled trials[36] indicate that biopsies from the caecum are needed to detect all cases of MC. We and others could not reproduce these findings.[13,21,37–41] It can be concluded that normal histology in biopsies obtained from the descending and sigmoid colon has high negative predictive value for MC. However, normal colonic histology in patients with chronic watery diarrhoea does not completely rule out the possibility of MC being diagnosed at a repeat endoscopy. Visualization of the right colon by colonoscopy as part of the diagnostic work-up in patients with chronic watery diarrhoea is justified in order to rule out other diseases.

The incidence of MC differs between countries, being much lower in Sweden and the Netherlands[5,42] compared with Denmark, Canada and the USA.[1–3] As discussed above, these differences cannot be explained by the more strict diagnostic criteria demanding that histological findings must be present in two colonic segments.[4] Differences between pathologists' concept of MC appear to be a more likely explanation. The diagnostic criteria of CC and LC are based on HE staining and remain those proposed in the initial descriptions of small case series.[10,11] Inter-observer variation studies have involved only pathologists from local institutions.[21,26,27] It is critical that the recent European consensus statements be discussed in order to agree on similar methods of tissue staining, classification of MC and MC subgroups when using immunohistochemical staining, and the number of biopsies and colonic segments needed for a diagnosis of MC. Consensus on these topics is mandatory for comparisons of cohorts and for facilitating collaboration on clinical trials and prospective follow-up studies across centres and nations.

The limitations of our study are the retrospective design and the lack of systematic clinical and endoscopic follow-up. While early re-endoscopies were often performed in order to examine the right colon, the indication for late repeat endoscopies was often persistent or recurrent diarrhoea. In any case, the patients submitted for multiple endoscopies will most often be those with persistent or recurrent symptoms and those with neoplastic polyps. Thus, the histological changes found at post-diagnostic endoscopies may well overestimate the persistence of histological changes and do not reflect the changes in the MC population as a whole. Likewise, data on patients with a pre-endoscopic histological diagnosis of chronic inflammation in the lamina propria will probably only apply to patients with continuous or recurrent diarrhoea and no diagnosis after the primary work-up. The pathologists at our centre have had a particular interest in MC for more than 10 years, which could have led to overestimation of both diagnosis and persistence. Furthermore, as discussed above, the concept of MCi was revitalized during the study period, and immunohistochemical stains have been used more extensively (P. Engel, personal communication). The incidence rates in the most recently included patients (2014) are somewhat higher than the older Danish national rates[2] and our previous estimates[1] and the highest reported to date.[4] Additional factors that could have contributed to this are the tremendous increase in the number of endoscopies performed and greater awareness among endoscopists.

In conclusion, we demonstrate that histological manifestations of MC may be preceded by inflammation in the lamina propria, and that histology normalizes only in a minority of patients with recurrence or persistent diarrhoea. It is confirmed that biopsies from any segment of the colon oral to the rectum suffice for diagnosing or ruling out MC as the cause of chronic watery diarrhoea.

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Conflict of Interest

Each author has confirmed that they have no conflicts of interest.

Author Contributions

Lars K. Munck guarantees the work and initially proposed the study design. Peter Engel and Anne-Marie Fiehn provided the regional pathology reports. Julie Rasmussen did the calculations for the paper and provided the first draft. Julie Rasmussen and Lars K. Munck extracted reports from the national registry. Signe Wildt and Lars K. Munck conceived the study. All authors contributed to the discussions, data analysis and interpretation and participated in critical revision of the manuscript.

Supplementary Data

Supplementary data to this article can be found at *ECCO-JCC* online.

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