ORIGINAL ARTICLE

A 5-year clinicopathological study on microscopic colitis at a Malaysian tertiary hospital

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ABSTRACT

Introduction: Microscopic colitis (MC) is a well-recognised cause of chronic diarrhoea in Western countries. It is classically associated with normal endoscopic findings and a higher prevalence among patients with autoimmune disease. Local information regarding this disease remains scarce. We identified patients diagnosed with MC over a five-year period, and then proceeded to analyse the clinical characteristics of these cases.

Materials and Methods: A retrospective study was conducted by identifying all histologically confirmed colitis cases diagnosed at Hospital Universiti Sains Malaysia from January 2015 until December 2019. Clinicodemographic data was retrieved from case notes of patients.

Results: Of the 299 cases with histological colitis, 23 (7.7%) were initially identified as MC. Two cases had incomplete data, while two others were excluded as the diagnoses were revised to inflammatory bowel disease. An incidence of 14 MC cases/1000 case-year was obtained using the 21 MC cases seen within the five-year period. MC subtypes for the 19 analysed cases i.e., lymphocytic colitis and collagenous colitis accounted for 13 (68.4%) and 6 (31.6%) cases, respectively. Eleven patients (57.9%) were females (M:F ratio 1:1.5) with a median age of 51 years. Only nine (47.3%) presented with diarrhoea; one subject (5.4%) had an autoimmune condition (Hashimoto thyroiditis). Normal endoscopic findings were found in 89.5% of patients.

Conclusion: Approximately half of the subjects in our study who had histologically confirmed MC did not present with diarrhoea. Adequate biopsy samples despite normal colonoscopy findings are important in order to not miss the diagnosis of MC.

KEYWORDS:
Collagenous colitis, Colonoscopy, Inflammatory bowel disease, Lymphocytic colitis, Microscopic colitis

INTRODUCTION

Microscopic colitis (MC), which consists of collagenous and lymphocytic colitis is a common cause of chronic non-bloody diarrhoea. Apart from diarrhoea, this entity is characterised by a macroscopically normal colonic mucosa observed during gastrointestinal endoscopy; however, diagnosis relies on characteristic histopathological findings.[1] Since MC was first described in the 1970's, it is recognised as one of the commonest causes of chronic diarrhoea in the West with a reported incidence of between 3-14 cases per 100,000 person-years in Europe.[2] MC has a female preponderance, with a median age of 65 years at diagnosis.[3] The number of MC cases is on the rise worldwide, mostly attributed to a greater awareness among physicians of this disease.[4]

The diagnosis of MC depends on findings of characteristic histopathologic features in colonic mucosal biopsies. As stated earlier, MC has two main histological subtypes i.e., lymphocytic colitis (LC) and collagenous colitis (CC). However, incomplete forms of MC (incomplete MC – MCi) have also been recognised.[5] Tong et al. in his systematic review and meta-analysis of 25 studies from North America and Europe found that the pooled incidence rate of CC and LC to be 4.14 and 4.85 per 100,000, respectively.[3] Nevertheless, as patients with MC often have normal endoscopic mucosal findings, the diagnosis may be missed unless clinically-indicated random biopsy samples are obtained during endoscopy.

The pathogenesis of MC remains unclear. It is thought to be due to a specific pathological reaction of the colonic mucosa towards luminal noxious agents in predisposed individuals and this eventually leads to an inappropriate immune response. Concomitantly, it has been shown that those with MC had higher rates of autoimmune conditions such as autoimmune thyroid disease, coeliac disease, and rheumatoid arthritis.[6-8] Common medications such as non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs) and statins have also been implicated as a cause for MC.[9-11]

The majority of published reports on MC are data from the West, very few being from the Southeast Asian region including Malaysia. Only two published articles on MC from Malaysia were identified: The first was a histological analysis of nine patients who were diagnosed with MC published in 1994.[12] The second, from 2013 was of a 63-year-old woman who had histologically confirmed MC among a cohort of 74 patients with diarrhoea-predominant irritable bowel

This article was accepted: 22 March 2021
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Table I: Demographic and clinical data of microscopic colitis patients over 5-year period

No.	Age	Sex	Presenting symptom	Colonoscopy finding	Biopsy site	Histopathology finding	Concomitant diseases	Treatment	Follow up
1	42	F	Diarrhoea	Polyps	Left only	LC	HTN, gastritis, uterine fibroid	Prednisolone	Asymptomatic
2	51	F	Diarrhoea	Normal	Right & left	CC (segmental)	HTN, DM, IHD, gastritis	Mesalazine, azathioprine	Asymptomatic
3	41	F	Diarrhoea	Normal	Right & left	LC	HTN	Nil	Asymptomatic
4	66	M	Diarrhoea	Normal	Right & left	LC	HTN, HPL, IHD, gastritis, multinodular goitre	Nil	Asymptomatic
5	56	F	Diarrhoea	Normal	Right & left	LC	GERD, bipolar disorder	Nil	Asymptomatic
6	57	M	Diarrhoea	Polyps	Right & left	LC	HTN	Nil	Asymptomatic
7	68	F	Diarrhoea	Normal	Right & left	CC	HTN, HPL, IHD, DM, CKD, GERD	Nil	Lost to follow up
8	54	F	Diarrhoea	Normal	Right & left	LC with infectious colitis	Asthma	Ciprofloxacin, metronidazole	Lost to follow up Lost to follow up
9	52	F	Diarrhoea	Normal	Right & left	LC (segmental)	HTN, HPL, asthma, gastritis	Nil	Lost to follow up
10	17	F	Constipation	Normal	Left only	LC	Gastritis	Nil	Asymptomatic
11	42	M	Constipation	Normal	Left only	CC	HTN, HPL, GERD, allergic dermatitis	Nil	Partial relief
12	45	M	Constipation	Normal	Right & left	CC (left only)	Functional constipation	Nil	Partial relief
13	64	M	Constipation	Polyps	Right & left	LC	HTN, gastritis, benign prostatic hyperplasia	Prednisolone	Lost to follow up
14	30	M	Constipation	Normal	Left only	LC	Nil	Nil	Lost to follow up
15	27	F	Blood in stool	Patchy inflammation	Right & left	LC	Hashimoto thyroiditis, GERD	Nil	Asymptomatic
16	33	F	Blood in stool	Normal	Right & left	LC	Nil	Prednisolone	Lost to follow up
17	52	F	Anaemia	Normal	Right & left	CC	GERD	Nil	Asymptomatic
18	59	M	Anaemia	Normal	Right & left	CC (segmental)	HTN, DM, CKD, gout	Nil	Asymptomatic
19	29	M	Abdominal pain	Patchy inflammation	Right & left	LC	GERD	Nil	Asymptomatic

LC: Lymphocytic colitis CC: Collagenous colitis HTN: Hypertension DM: Diabetes mellitus HPL: Hyperlipidaemia
IHD: Ischaemic heart disease GERD: Gastroesophageal reflux disease CKD: Chronic kidney disease

syndrome (IBS-D).[13] As the diagnosis of MC is based on histopathology, many cases could be missed as patients may present with minimal clinical and endoscopic findings. This study aimed to describe and analyse the clinicopathological findings of patients with MC over a 5-year period.

MATERIALS AND METHODS

We conducted a retrospective study on all cases of histologically confirmed MC diagnosed at Hospital Universiti Sains Malaysia (HUSM) over a period of five years from 1st January 2015 to 31st December 2019. A total of 299 colitis cases were collected.

Cases were identified from the Lab Information System (LIS) of the pathology department using the keywords "colitis", "microscopic colitis", "collagenous colitis" or "lymphocytic colitis". We included all colonic biopsies reported as MC or any of its subtypes.

Histopathological findings of all included cases were collected from the LIS database, clinical and demographic information were obtained from the case notes of subjects. The variables collected included age, sex, symptoms, colonoscopy findings, histological findings, comorbidities, concomitant medications, treatment administered and clinical course. Descriptive analysis of all collected data was performed.

Ethical approval was obtained from the Human Research Ethics Committee (USM/JEPeM/20020091) in accordance with the Helsinki Declaration of 1975, as revised in 2008.

RESULTS

Epidemiology

Of the 299 cases of colitis collected; 23 were reported as MC. From these 23 cases, four were excluded from the study, two cases due to incomplete online information and another two cases due to a revised diagnosis of IBD. In all 19 MC cases were therefore included for study analysis.

Lymphocytic colitis was diagnosed in 13 (68.4%) and collagenous colitis was diagnosed in six (31.6%) An annual incidence of 14 MC cases/1000 case-year was obtained using the 21 MC cases seen within the five-year period.

TABLE 1 summarises the characteristics of the 19 subjects with MC. Eleven (57.9%) were females, (male to female ratio of 1:1.5). The median age at diagnosis was 51 years and age ranged from 17 to 68 years (FIGURE 1). Fourteen (73.7%) patients were Malays. The presenting symptom in nine cases (47.3%) was diarrhoea. Other presenting symptoms were constipation (5, 26.3%), blood in stool (2, 10.5%), anaemia (2, 10.5%) and abdominal pain (1, 5.4%).

Endoscopic and histologic findings

Majority of the subjects (17, 89.5%) had normal colonic mucosa on endoscopic examination with three of them having small hyperplastic polyps which were confirmed in biopsy samples. Two cases displayed mucosal hypervascularity which involved several segments of the colon. Fifteen (78.9%) had random mucosal biopsies taken from both the right and left sides of the colon. The remaining cases only had colonic biopsy samples obtained from the left side of the colon.

Histologically, 12 (63.1%) were diagnosed as LC, the remaining seven (36.8%) as CC (Figures 2A and 2B). One of the cases displayed only left-sided CC with normal histology reported from the right side of the colon. Three cases showed histology consistent with MC in several segments of the colon, biopsies from the remaining colonic segments were reported as non-specific chronic colitis (NSC).

Concomitant diseases and medications

Two patients had no previous medical illness and no history of taking regular medications. One (5.4%) patient had underlying autoimmune disease, namely Hashimoto thyroiditis. The majority of patients (12, 63.1%) had concomitant gastritis or gastroesophageal reflux disease (GERD), ten (52.6%) with hypertension and three (15.8%) with type 2 diabetes mellitus. Medications was strongly associated with MC – PPIs, statins and NSAIDs were used by ten (52.6%), five (26.3%) and one (5.4%) patient(s), respectively. The number of subjects on each of these medications and their MC subtypes are shown in Figure 3.

Treatment and clinical follow up

Only four (21.1%) patients received treatment for MC upon diagnosis, either with steroid (prednisolone), mesalazine or azathioprine. One was found to have concomitant infectious colitis on histology, and therefore received a course of antibiotics (ciprofloxacin and metronidazole). Fourteen (73.7%) patients were treated conservatively. Almost 60% (11/19) of these patients reported resolution of symptom during clinic follow up, which were conducted at 3- or 4-monthly durations. Six were lost to follow up, while two others had partial relief of symptoms. Of three patients receiving prednisolone in tapering doses, only one returned to follow up and reported improvement, while two others defaulted. The only patient who received mesalazine and azathioprine responded to the treatment. All patients with an initial complaint of diarrhoea reported resolution of symptom on follow-up, even those who were treated conservatively.

DISCUSSION

Clinicopathological information regarding MC from Southeast Asia, specifically from Malaysia has not been updated since 2014. This lack of published reports could be influenced by the historical presumption that MC is rare among Asian patients, as supported by low reported incidences in East Asian countries.[14] One meta-analysis found that patients of East Asian descent living in the United States of America were affected by MC at a much lesser extent than those of other ancestries (odds ratio of 0.2), which reflects a possible presence of genetic factors.[14]

However, a small retrospective study in Japan on patients with chronic diarrhoea who had biopsies during colonoscopy showed that nearly 45% (12/27) of them had MC.[15] Likewise, in South Korea, a prospective study found that 22% of 100 patients investigated for chronic diarrhoea were diagnosed with MC, a figure which is almost similar to data from

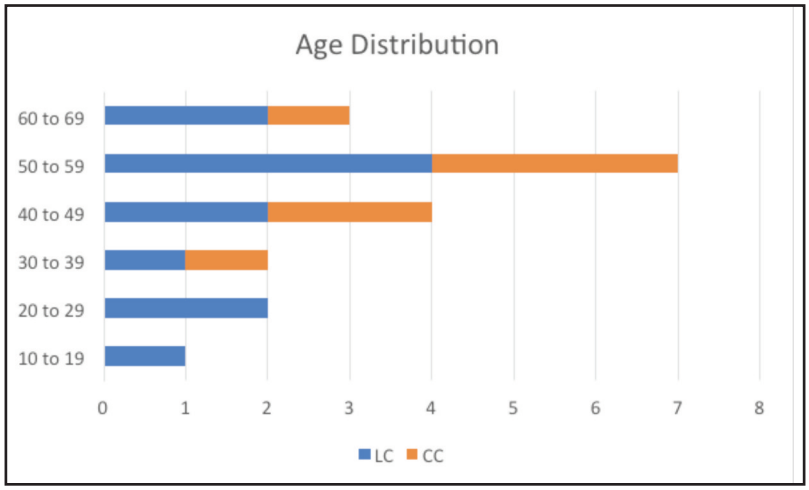


Fig. 1: Age distribution of patients according to MC subtypes (LC: lymphocytic colitis, CC: collagenous colitis)

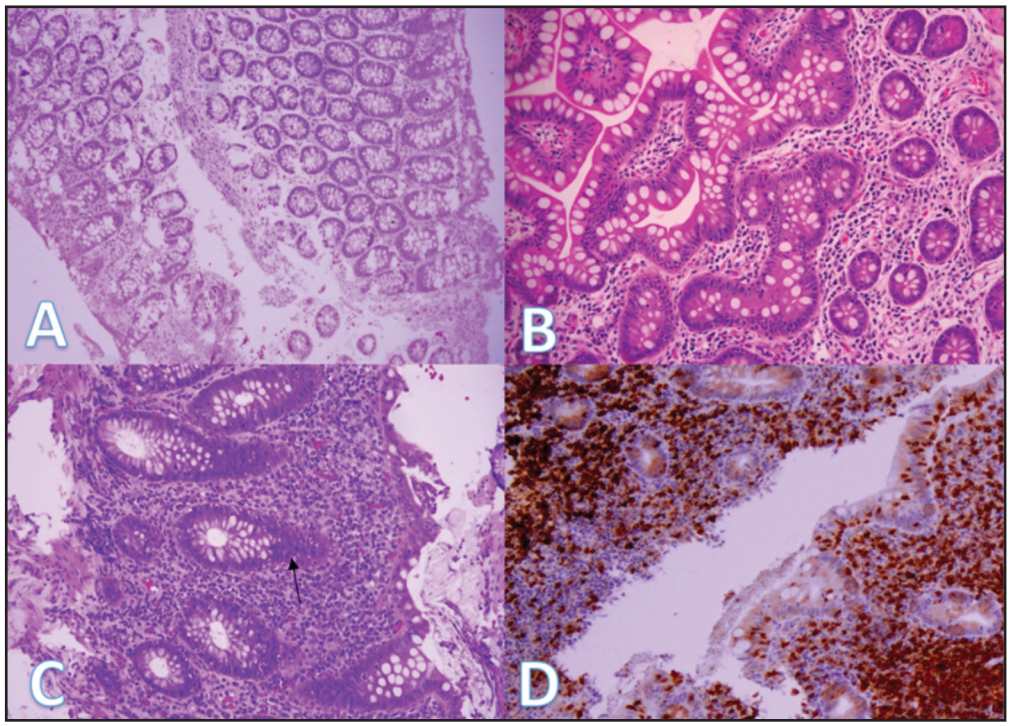


Fig. 2a: Microscopic pictures of lymphocytic colitis. (A) HPE image shows mucosal tissue is composed of well-spaced glands (100x magnification, H+E stain). (B) Some of the crypts appear branched (100x magnification, H+E stain). (C) Lamina propria is densely infiltrated by lymphoplasma cells with evidence of cryptitis seen (arrow) (200x magnification, H+E stain). (D) The increased epithelial lymphocytosis is confirmed with immunohistochemistry stain CD3 (200x magnification).

Western countries.[16] A larger prospective study of 613 patients with chronic diarrhoea in Southern China revealed that 9.6% and 4.5% of patients had LC and CC, respectively.[17] The results of these studies suggest that MC might not be as rare in Asian populations as it was initially thought.

Our study shows that the majority of patients with MC were aged more than 50 years, with a median age of 51 years. The incidence of MC is higher in the elderly, with a median age at diagnosis of over 60 years old.[3] Nevertheless, up to a quarter of patients with MC were aged 45 years or younger when first diagnosed, and cases were also seen among children.[1] The younger median age at diagnosis in our study may also reflect the age distribution of the local population; the proportion of elderly patients may not be as high as those seen in studies from the West. There were more female patients than males with MC, and this matches the current knowledge that MC has a higher female preponderance. Physical examination and thyroid function tests were unremarkable in all our patients. Subjects who presented with diarrhoea had stool samples which were sent for cultures and examined for parasites, ova, and cyst, all were reported as negative.

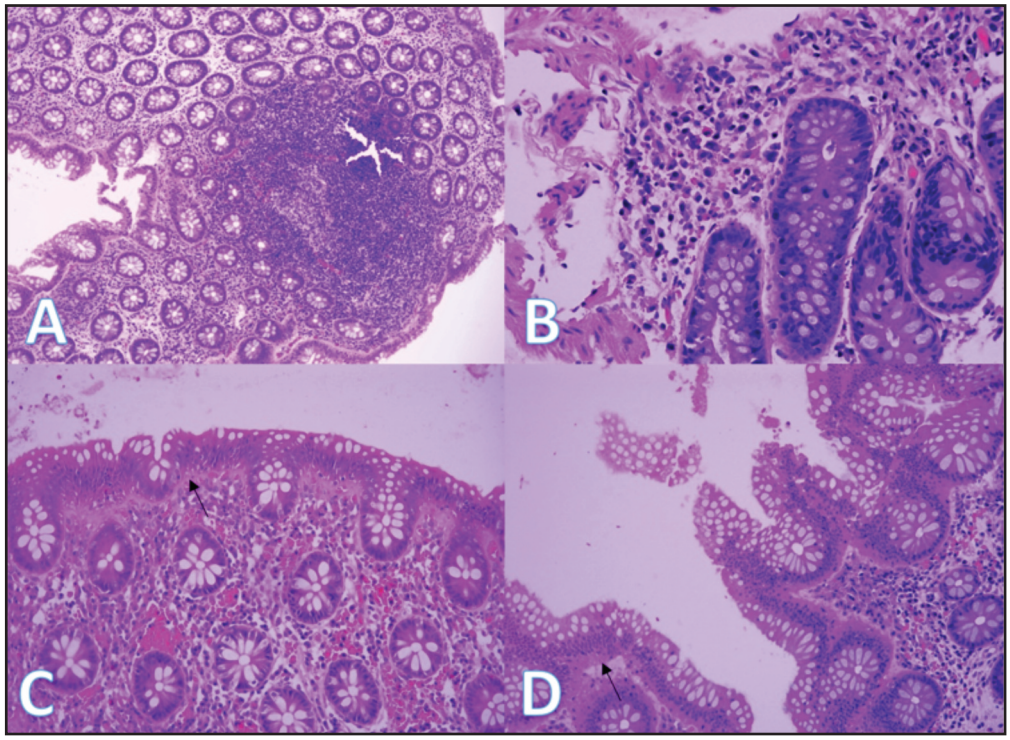
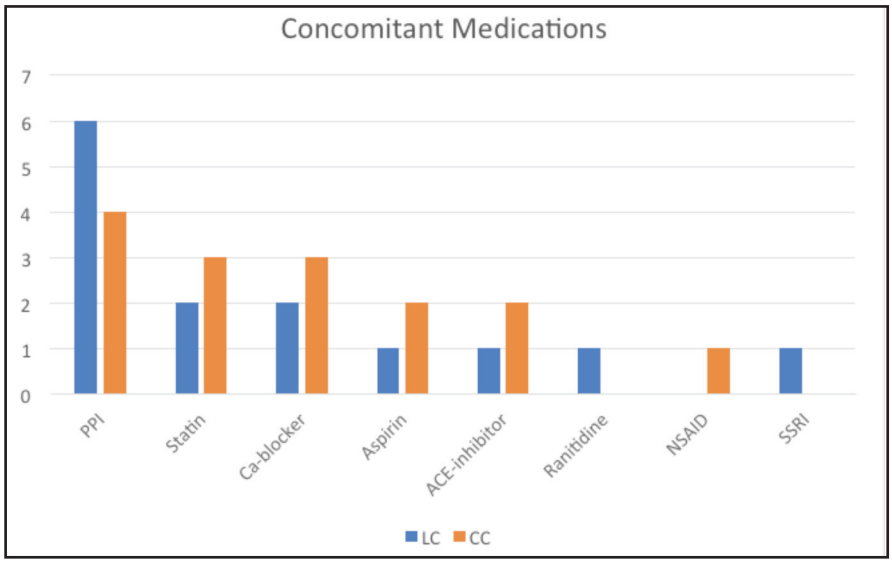


Fig. 2b: Microscopic pictures of collagenous colitis. (A) At 100x magnification, the mucosa is composed of well-spaced glands. Lymphocytic aggregates with germinal centre can be appreciated (H+E stain). (B) Lamina propria show moderate increase in lymphoplasma cells with cryptitis seen (200x magnification, H+E stain). (C&D) Presence of mild thickened subepithelial collagen layer (arrows) that entrap small capillaries and inflammatory cells (200x magnification, H+E stain).



PPI: proton pump inhibitor, Ca-blocker: calcium channel blocker, ACE-inhibitor: angiotensin converting enzyme inhibitor, NSAID: non-steroidal anti-inflammatory drugs, SSRI: selective serotonin receptor inhibitor

Fig. 3: Concomitant medications of patients according to MC subtypes (LC: lymphocytic colitis, CC: collagenous colitis)

It is an accepted notion that MC always presents as a chronic, watery, and non-bloody diarrhoea accompanied by weight loss, abdominal pain, nausea, or faecal incontinence. The exact mechanism of diarrhoea in MC is less understood and is likely to be multifactorial in nature; mucosal inflammation leading to secretory diarrhoea, bile salt malabsorption and mucosal injury from luminal contents may all play a role.[10]

In our case series though, only nine patients complained of diarrhoea while the others did not have diarrhoea-related complaints with five of them having constipation.

Nevertheless, CC and LC cases that present with constipation have been documented. Most of the time the constipation is of a short duration. Chronic constipation does occur,

however.[18] Barta et al., reported 43% of their patients (23/53) with histologically proven MC had constipation as a presenting complaint.[19] In our study, one of the five patients who complained of constipation was known to have functional bowel disease. In one meta-analysis, overall prevalence of MC among patients with all types of functional bowel disorders was 7%, and prevalence with diarrhoea-dominant irritable bowel syndrome (IBS) was not significantly higher compared to constipation-dominant IBS or mixed-type IBS.[20] However, one of the latest guidelines states that MC should not be diagnosed in patients that fulfil the criteria for functional bowel disease; this is still open to debate as the studies that form the basis for this statement had heterogenous results.[1] Two of our patients had bloody stools as the presenting complaint, with both being diagnosed as having LC. At least two studies reported a similar presentation; the superficial mucosal inflammation of LC was thought to be a possible explanation for the bleeding.[21,22] As for the presence of MC among those with concomitant autoimmune disease, we only had one female patient who was diagnosed as having Hashimoto thyroiditis in 2013 and was investigated for per rectal bleeding. The patient was found to have LC; at the time of MC diagnosis she was euthyroid on thyroxine replacement.

MC is classically associated with normal appearance of colonic mucosa during endoscopy. However, Park et al. reported half of their cohort of LC cases (7/14) had mucosal lesions, namely hypervascularity, exudative bleeding and mucosal oedema.[23] There was also a case report of CC that presented with skip lesions mimicking Crohn's disease and was complicated by intestinal obstruction.[24] A large Swedish study of 795 patients reported endoscopic abnormalities in 37% of patients with CC and 25% of patients with LC.[21]

Two of our patients exhibited significant mucosal hypervascularity involving only several segments of the colon. One patient showed diffuse changes, while the other had clear demarcations between diseased and normal mucosa. Interestingly, this was our patient that had underlying autoimmune disease. It is uncertain whether these two findings correlate.

To a certain degree however, this underlines the importance of having an awareness of the disease and the significance of obtaining multiple random biopsies despite normal colonoscopy mucosal findings. There have been many instances when no biopsy sample was taken during colonoscopy if the visual findings were deemed normal by the endoscopist, regardless of the indication for the procedure.

We recognise that this is a significant limitation of our study as MC may be missed if mucosal biopsies were not obtained during visually-normal colonoscopies. Virine et al. proposed the use of a Western protocol to assist in the diagnosis of MC where two biopsies should be taken from the ascending colon, and another two from the descending colon.[25] European guidelines, however, recommend ileocolonoscopy with biopsies from at least the right and left side of the colon.[5] Nevertheless, Andrews et al. showed that endoscopists with an academic practice, gastroenterologists and those with lower annual endoscopy volumes were more likely to make a diagnosis of MC.[26] Thus, in HUSM based on clinical suspicion the majority of cases would have had random colonic biopsies obtained despite having normal colonoscopy findings as the histological report would be of valuable assistance in determining the underlying pathology.

Approximately half of the subjects in our study were on proton-pump inhibitors; a quarter were on statins. These medications have been known to be strongly associated with MC. One common theory proposes that certain drugs act as luminal antigens, increasing immune system activity in the colonic mucosa and thus resulting in MC.[27] Several hypotheses for PPI-induced MC have been suggested, including colonic intraepithelial lymphocytosis following PPI exposure,[28] impaired colonic barrier function contributed by acid suppression related dysbiosis,[29] and possible idiosyncratic type drug reaction.[30] Identification and subsequent withdrawal of the offending drug contributes to spontaneous remission of MC, as demonstrated in this study. However, discontinuation of statins can be associated with an increased risk of cardiovascular event in high risk individuals;[31,32] before this is decided a cardiology consultation should be obtained and alternatives offered to the patient regarding lipid lowering therapies. Some of our patients reported symptom resolution with discontinuation or dose reduction of the PPI pantoprazole; it has been shown that PPI use is associated with an increased risk of MC (OR 2.68, 95% CI 1.73–4.17).[3]

As for treatment, locally acting budesonide, released in the terminal ileum and right colon, is preferred over systemic corticosteroids as first line treatment for MC due to its efficacy and favourable side effect profile.[10] Due to unavailability of budesonide, three of our patients were treated with a tapering prednisolone dose. One patient had reported success, but two others defaulted follow up. Despite reports that immunosuppressive agents have no clear effects in MC,[4] one of our patients showed therapeutic response to azathioprine and aminosalicylate. It has been shown that those who had spontaneous disease remission had better long term outcomes than those who needed medications for treatment of MC; 93% of MC patients who had spontaneous reduction in disease will have sustained remission after one year, while only 60.5% of those with drug-induced remission will still be in remission a year later.[33]

In the context of MC, since both CC and LC have distinct histological characteristics, Geboes et al. found many cases not fitting into these two subtypes were generally classified as non-specific colitis.[34] In the early 2000's, the terms "incomplete MC" and "MC not otherwise specified" (MC-NOS) were introduced to describe a subgroup of patients not completely fulfilling the classical criteria for MC diagnosis. Later on, several authors proposed expanding the MC spectrum further into five subtypes, adding "minimal change colitis" and "MC with giant cells".[35] By and large however, the majority of studies from Asia only consider LC and CC in the context of MC diagnosis.

According to Mantzaris et al., factors leading to categorisation failure and thus NSC include a) endoscopist-related factors e.g., inadequate biopsies, timing of biopsies vs

course of inflammation, and having incomplete clinical data; and b) pathologist-related factors e.g., handling and sample processing issues as well as personal interest and experience in examining colonic mucosa.[36] These may explain differing histologic diagnoses of biopsies which were obtained from various colonic segments.

During our screening, there were two patients who had histologically confirmed MC, but were subsequently excluded as they were treated as IBD after further investigation and follow up. There is still no conclusive answer whether IBD and MC are two separate entities, or a same disease at occurring at a different spectrum of progression. Freeman et al. for example, reported a case of CC refractory to treatment but later progressed to ulcerative colitis requiring surgical resection.[37] One case series highlighted patients with Crohn's disease whose colonic biopsies showed focal morphology of either LC or CC.[38] Jegadeesan et al. reported a series of six ulcerative colitis patients under complete remission whose surveillance colonoscopy biopsies were consistent with either LC or CC.[39] More recent evidence from a study on the clinicopathological significance of MC in IBD reported that MC may occur either before or after the onset of IBD. It also suggested that MC may be an initial presentation of IBD, especially in older IBD patients.[40]

Active smoker status has been associated with an increased risk for MC.[5] Although there is insufficient evidence to strongly recommend smoking cessation as a means to alter MC disease activity, advice to quit smoking may still be given for its health benefits. Due to the nature of this study however, this was not analysed as there was limited information on subject smoking status.

CONCLUSION

We demonstrated that a significant percentage of cases diagnosed as MC at HUSM did not present with diarrhoea. Therefore, a high clinical suspicion is needed, which requires an awareness of the disease by the clinicians involved. The variety of symptoms MC can present with means that it is very likely that a significant proportion of patients with MC remain undiagnosed. Adequate biopsy samples despite normal colonoscopy findings are important in order to not to miss a diagnosis of MC.

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