ORIGINAL ARTICLE

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

Muhammad Ilham Abdul Hafidz, MRCP1,2, Khairil Khuzaini Zulkifli, MMed1,2, Thin Thin Win, MMed3, Anani Aila Mat Zin, MPath4,5, Nazri Mustaffa, PhD1,5

1Department of Medicine, Hospital Universiti Sains Malaysia, Kota Bharu, Malaysia, 2Faculty of Medicine, Universiti Teknologi Mara, Sungai Buloh, Malaysia, 3School of Medicine, International Medical University, Kuala Lumpur, Malaysia, 4Department of Pathology, Hospital Universiti Sains Malaysia, Kota Bharu, Malaysia, 5School of Medical Sciences, Universiti Sains Malaysia, Kota Bharu, Malaysia

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. 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. MC has a female preponderance, with a median age of 63 years at diagnosis. The number of MC cases is on the rise worldwide, mostly attributed to a greater awareness among physicians of this disease.

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. 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. 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. 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.

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. 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
Table I: Demographic and clinical data of microscopic colitis patients over 5-year period

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

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). 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. 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.

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. 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...
Western countries. 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. 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. 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. 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.
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. 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,
larger study. Scientists have found that it is more effective in treating people with slow bowel movements and is the treatment of choice for some people with chronic constipation.

We found that the majority of people who used it for less than a year had significant improvement in their symptoms. However, after a year, the improvement was not as significant. We also found that the majority of people who used it for more than a year had significant improvement in their symptoms. However, after two years, the improvement was not as significant.
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. 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. One case series highlighted patients with Crohn’s disease whose colonic biopsies showed focal morphology of either LC or CC. 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. 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.

Active smoker status has been associated with an increased risk for MC. 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 diarrhea. 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.

REFERENCES

Original Article

Med | Malaysia Vol 76 No 3 May 2021

324
A 5-year clinicopathological study on microscopic colitis at a Malaysian tertiary hospital