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# Symptomatic overlap in patients with diarrhea predominant irritable bowel syndrome and microscopic colitis in a sub group of Bangladeshi population

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**Abstract**

Microscopic Colitis (MC) and diarrhea predominant irritable bowel syndrome (IBS-D) has almost similar clinical feature but MC is diagnosed by histologic criteria and IBS is diagnosed by symptom-based criteria. There is ongoing debate about the importance of biopsies from endoscopically normal colonic mucosa in the investigation of patients with IBS-D. Aim of this study was to assess the prevalence of MC in patient with IBS-D and to determine the distribution of MC in the colon. This observational study was conducted in department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from January 2008 to December 2009. Patients were evaluated thoroughly & who meet Rome–II criteria with normal routine laboratory tests, were included in the study. Colonoscopy was done and biopsies were taken from the caecum, transverse colon, descending colon, and rectum. Out of total 60 patients, 22 had Lymphocytic Colitis (LC), 28 had nonspecific microscopic colitis (NSMC) and 10 had irritable bowel syndrome noninflamed (IBSNI). The distribution of LC was restricted to proximal colon in 15 patients, in the left colon in 2 patients and diffuses throughout the colon in 5 patients. There is considerable symptom overlap between the patients of IBS-D and patients with microscopic colitis. Without colonoscopic biopsy from multiple sites, possibility of MC cannot be excluded in patients with IBS-D and it can be said that clinical symptom based criteria for irritable bowel syndrome are not sufficient enough to rule out the diagnosis of microscopic colitis.

## Introduction

Microscopic colitis (MC) is a new form of idiopathic inflammatory bowel disease. Clinical manifestations are substantially milder than other form of idiopathic inflammatory bowel disease[1]. The term MC was first introduced by Read et al. in 1980 to describe a subset of patients with chronic diarrhea of unknown origin with normal endoscopic or radiologic findings[2]. The diagnosis of MC is dependent on well-defined histologic criteria. In the presence of appropriate clinical setting, the diagnosis of MC is made by the presence of intraepithelial lymphocytosis and a mixed inflammatory cell infiltrate in the lamina propria. Microscopic colitis includes two primary subtypes: Collagenous Colitis (CC) and Lymphocytic Colitis (LC). They are similar clinically and histologically but are distinguished by the presence or absence of a thickened sub epithelial collagen band[3]. Microscopic colitis accounts for 2%–16% of patients with chronic diarrhea[4]. Some believes the prevalence of both LC and CC has been markedly underestimated. One recent study suggests that MC now represent up to 20% of cases of IBS[5]. MC typically present in the sixth or seventh decade of life, but it has been reported in all age groups, including children[6].

Irritable bowel syndrome (IBS) is defined as a functional bowel disorder in which abdominal pain or discomfort is associated with defecation or a change in bowel habit. Most common diagnosis made in patients with chronic diarrhea is IBS[7]. Patient with IBS are classified into diarrhea predominant (IBS-D), constipation predominant (IBS-C) and mixed type (IBS-M). Community based data indicate that IBS-D and IBS-M subtypes are more prevalent than IBS-C[8]. Colonoscopy and biopsies were thought to be unremarkable in patients with IBS. The diagnosis

is therefore symptom-based and experts have developed criteria for the diagnosis of IBS. The Manning, Rome, and Rome II criteria are widely used to identify IBS patients in research studies[9-12]. But only a fraction of patients with chronic diarrhea actually meet the criteria for diagnosis of IBS. It is possible that many of the patients labeled as IBS-D has actually microscopic abnormality in the colorectum[13]. The symptoms of MC have been frequently attributed to IBS-D, often for many years before diagnosis[14]. Thus, differentiating patients with functional bowel disorders from those with MC can be difficult particularly when colonoscopy is not conclusive.

This study aimed to assess the prevalence of MC in patients considered as IBS-D with endoscopically normal mucosa and to determine the distribution of MC in the colon whether diffuse or focal.

## Materials and Methods

This observational study was carried out in the department of gastroenterology, BSMMU, Dhaka during the period from December 2008 to October 2009. Patients presented with chronic non-bloody diarrhea and abdominal pain or discomfort, were initially selected for the study from the outpatient department. Patients who met Rome-II criteria and who had completed a full negative evaluation for other organic disease were finally included. The evaluation included detailed history, physical examination, complete blood count, thyroid function test, blood glucose, stool routine and microscopic examination, fecal fat estimation (qualitative) and chest X-ray P/A view. All the study population was evaluated for the safety and possible complication of colonoscopy. There after a preparation for full colonoscopy was given. Patients were prepared for colonoscopy with 350 ml of 20% manitol taken orally. Informed written consent was taken from every patient. Sixty four patients were diagnosed as IBS-D on the basis of Rome II criteria and underwent colonoscopy. Four had endoscopic abnormality, of these four, two had colonic tuberculosis, one had amoebic ulcer, and one had nonspecific ulcer in the ascending colon and were excluded from the study. In 60 patients colonoscopy was found to be normal and biopsy specimens were taken from caecum, transverse colon, descending colon, and rectum, two bites from each site. Biopsy specimen were fixed in 10% formalin in separate container and sent for histopathology. No sedation or procedure related complication was occurred.

Tissue sections were stained with hematoxylin and eosin, and Masson's trichrome stain. Measurement of thickness of the sub epithelial collagen layer and counts of IEL were performed on well-oriented biopsies (sections perpendicular to the mucosal surface). The number of intra epithelial lymphocytes (IEL) was estimated by counting the lymphocytes per 100 intercryptal epithelial cells. At least five noncontiguous intercryptal spaces, excluding areas over lymphoid follicles were examined, and the mean number of IEL was expressed per 100 epithelial cells. The thickness of the sub epithelial collagen band was measured with an optical micrometer. Chronic inflammatory cells (lymphocytes, plasma cells and histiocytes) in the lamina propria were categorized as mild, moderate and numerous arbitrarily. Histological assessment of biopsy specimens were categorized into different groups according to the method used in previous study[15]. IBSNI were considered when IEL were found to be <20/100 EC and lamina propria revealed no chronic inflammatory cell infiltration. NSMC was considered if IEL were found to be <20/100 EC and lamina propria shows focal neutrophil infiltration and apparent increase in lamina propria cellularity. LC was considered when IEL were found to be $\geq$20/100 EC and chronic inflammatory cell infiltration in the lamina propria. Collagenous colitis would be considered if, IEL$\geq$ 20/100 EC and chronic inflammatory cell infiltration in the lamina propria with sub epithelial collagen band thickening $\geq$10 µm. For descriptive and analytical purpose large bowel was divided into left colon including rectum and descending colon, and proximal colon including the splenic flexure transverse colon, ascending colon and the caecum. The inflammation was considered to be focal when limited to either proximal or into the left colon and diffuse if inflammation involved both proximal and left colon[16]. Histopathological examination of the biopsy specimens was studied by one of the senior, expert pathologist who was blind to the patient's underlying symptom and colonoscopic finding.

Data were expressed as mean±SD (range) unless otherwise stated. Informed written consent was taken from every patient. Permission was taken from the concerned ethical committee of BSMMU in order to undertake the study. All patients enrolled in this study were explained about the nature and purpose of the study.

## Results

A total of 64 subjects were studied with colonoscopy on the basis of their symptoms suggestive IBS-D according to Rome II criteria. Out of sixty four patients two patients were found to be have colonic tuberculosis, one had amoebic ulcer in the caecum and one had nonspecific ulcer

in the ascending colon. Colonoscopic biopsies were taken from sixty patients who had normal colonoscopic finding and were studied for evidence of mucosal inflammatory cell infiltration. Among them 52(86.67%) patients were male and 8(13.33%) were female. Demographic data are shown in table I.

**Table I:** Demographic Data

| | |
|---|---|
| Total no of patients | 60 |
| Age (years) Mean±SD | 31.07±8.16 |
| Male | 52 |
| Female | 8 |
| Symptom duration (months) | 67(12-216) |
| Monthly income (Average in taka) | 5500 |

Intraepithelial lymphocytes were studied. Result is shown in table II. Twenty two (36.7%) of study subjects had ≥20 IEL/100EC and 38(63%) had <20IEL/100EC. None shows total absence of intraepithelial lymphocytes.

**Table II:** Pattern of IEL of colonic mucosa (n=60)

| Number of IEL | No. of patients (%) |
|---|---|
| ≥ 20/100 epithelial cell (EC) | 22 (36.7%) |
| < 20 /100 epithelial cell (EC) | 38 (63.3%) |

Chronic inflammatory cells in the lamina propria were studied including lymphocytes, plasma cells and histiocytes altogether. Table III reveled that all patients who had IEL ≥20/100 EC also had increased chronic inflammatory cells infiltration in the lamina propria. Where as in patients those with IEL <20/100 EC, out of 38 patients 28 person showed increased chronic inflammatory cells infiltration and remaining 10 had no chronic inflammatory cell infiltration in the lamina propria.

**Table III:** Pattern of chronic inflammatory cell (lymphocytes, plasma cells and histiocytes) in the lamina propria (n=60)

| | IEL≥20/100 EC group (n=22) | IEL<20/100 EC group (n=38) |
|---|---|---|
| Increased | 22 | 28 |
| Not increased | 0 | 10 |

Mean thickness of the subepithelial collagen band were studied in two groups. Table IV shows that mean thickness of the sub epithelial collagen band is <10 µm in all patients of both groups.

**Table IV:** Mean Thickness of subepithelial collagen band in two groups (n=60).

| | IEL>20/100 EC group n=22 | IEL< 20 / 100 EC group n=38 |
|---|---|---|
| Thickness in µm (Mean ± SD) | 1.77 ± 0.92 | 1.47 ± 0.56 |

Histologic assessment of biopsy specimens were categorized into three groups, as is shown in table V. Lymphocytic colitis was considered when IEL were found to be ≥20/100 EC and chronic inflammatory cell infiltration in the lamina propria. Nonspecific microscpopic colitis was considered if IEL were found to be <20/100 EC but lamina propria shows focal neutrophil infiltration and apparent increase in lamina propria cellularity. Irritable bowel syndrome non inflammed were considered when IEL were found to be <20/100 EC and lamina propria revealed no chronic inflammatory cell infiltration. Out of 60 patients, 22(36.7%) were LC, 28 NSMC, 10 patients were considered as IBSNI and none was found to have CC.

**Table V:** Classification of inflammatory change in colonic mucosa on the basis of histologic assessment

| Diagnosis | No. of patient (%) (n=60) |
|---|---|
| Lymphocytic colitis | 22 (36.7%) |
| NSMC | 28 (46.5%) |
| IBSNI | 10 (16.8%) |

Mean number of IEL was studied in different groups as is shown in table VI. Mean number of IEL is highest in patients with LC (22.7±2.41) than IBSNI (9.95±2.15), NSMC (11.71±1.83).

**Table VI:** Mean number of IEL / 100 EC in different group.

| | LC (n=22) | NSMC (n=28) | IBSNI (n=10) |
|---|---|---|---|
| IEL/100EC (Mean ± SD) | 22.7±2.41 | 11.71±1.83 | 9.95±2.15 |

Site of involvement of microscopic colitis was studied. Colonic involvement was found to be confined only in the proximal colon in most of the cases (68.2%), two patients (9.1%) had only left sided involvement. Five patients (22.7%) had diffuse disease involving the whole colon as is shown in table VII.

**Table VII:** Distribution of LC in the colon (n=22).

| | Frequency | Percentage |
|---|---|---|
| Proximal colon | 15 | 68.2 |
| Left colon | 2 | 9.1 |
| Diffuse | 5 | 22.7 |
| Total | 22 | 100 |

The table VIII shows the frequency of disease in different segment of the colon. Disease was found to be in the caecum in 9 patients (40.91%), in the transverse colon in 6 (27.27%), in the rectum in 2(9.09%) patients, and none had isolated disease in the descending colon but 5 (22.73%) patients had disease both in the proximal colon and in the left colon simultaneously.

**Table VIII:** Segmental distribution of the disease (n=22).

| Site | Frequency | Percentage (%) |
|---|---|---|
| Caecum | 9 | 40.91 |
| Transverse colon | 6 | 27.27 |
| Descending colon | 0 | 0 |
| Rectum | 2 | 9.09 |
| Diffuse | 5 | 22.73 |

## Discussion

Microscopic colitis and IBS-D are two important cause of chronic diarrhea. Since the first description of MC syndromes (CC and LC), the importance of obtaining mucosal biopsy specimens when the colon is endoscopically normal in patients with diarrhea has been widely recognized. Increased recognition of MC in recent years is likely due to increased awareness of its existence. Therefore, the reported prevalence seems to change within years.

In this study patients with chronic non bloody diarrhea who were initially considered as IBS-D under Rome II definition, histopathological study of colonic mucosa demonstrate considerable overlap with the features of MC in a significant number of patients. In this study out of 60 patients, who were initially diagnosed as IBS-D, 22 (36.7%) patients (86.36% male and 13.64% female) fulfilled the histologic criteria of MC.

A prospective study of 77 patients meeting Rome criteria, by Chadwick VS found that 10% fulfilled histologic criteria for microscopic colitis[15]. David Limsui et al. in their study identified one hundred thirty-one cases of microscopic colitis. Sixty-nine (53%) and 73(56%) of these patients met Rome and Rome II criteria for IBS, respectively. Fifty-four (41%) had three or more Manning criteria[4]. Study by Hamid Tavakkoli et al. included a total of 138 patients of IBS with mean age of 34.7 years (female 55.1% and male 44.9%) after meeting Rome-II criteria. All underwent colonoscopy and biopsy. The histologic findings revealed MC in 13 (9.42%) patients[17]. A Turkish study of 129 patient with non-bloody diarrhea revealed LC in 12 (9%) patients (Mean age: 45 year, range: 27-63) and CC was diagnosed in only 3 (2.5%) patients (mean age: 60 years, range: 54-65)[14]. In Sweden, MC was reported in 4% of patients with non-bloody chronic diarrhea in 1993, but this rate was reported as 10% in 1998[18-20]. Patients fulfilling the criteria of LC is found to be high (36.7%) in this study comparing to other studies done in different countries. This may be due to referral bias as the study was done in a tertiary centre or prevalence of MC may be truly high in our country.

Patients meeting criteria for MC in present study were younger (average: 31.13±7.54 years) because most of the patients selected for the study were under 55 years of age. The proportion of male patient was more in all the age group and this may be a selection bias. In this study we found all patients with MC to have LC, none had CC. Of these 19(86.36%) were male, 3(13.64%) were female.

The reason of absence of CC in our study might be duo to that, most of the patients (86.67%) in our study were younger male and only small number of patients (13.33%) were female and CC may be uncommon in our country. This finding is consistent with the other studies. It was stated in different studies that, LC is more common than CC and CC is more common in female and elderly people[18,20-22]. The gender difference for lymphocytic colitis is less striking than for collagenous colitis in some studies. A female predominance has been described, particularly for CC, with female-to-male ratio as high as 20:1[21]. LC is more common than CC in USA. In one study the prevalence of LC and CC was 12.6% & 7.1% respectively[23]. Female/male ratio was reported as 5/1 from Iceland and 2.1 from Sweden[18,20-22,24,25]. Fernandez-Banares F et al. in a study showed the incidence of LC is three times higher than that of CC[22]. Tuncer C et al. in a study of 30 patients with IBS found 23.3% to have LC and none had CC[26].

In the present study of the remaining 38 (63.7%) patients, 28 were considered as nonspecific microscopic colitis (NSMC) and 10 patients were considered as irritable bowel syndrome non inflamed (IBSNI), which was supported by the study of Chadwick et al[15].

The observed increases in lymphocyte populations in all subgroups of patients, including those with no apparent inflammation on conventional histology (IBSNI), suggest that immune activation is an important feature of patients with IBS. Such changes in lymphocytic populations would be unlikely to occur over the time course of bowel preparation, and it is reasonable to speculate that they are related to the pathophysiology of the disease[15].

This study showed that in 68.2% disease (MC) were limited to proximal colon, in 9.1% limited to left colon and in 22.8 % the disease was diffuse. Disease was found most frequently in the caecum (40.91%), none of the patient had isolated disease in the descending colon but two patients (9.09%) revealed presence of the disease in the rectum. Disease was confined to transverse colon in 6 (27.27%) patients. Five patients (22.73%) showed disease within proximal and left colon at the same time (i.e. these patients had disease either in caecum plus transverse colon plus descending colon and rectum or caecum plus descending colon

or caecum plus rectum), and were considered diffuse disease. So our study results imply that a diagnosis of MC cannot be excluded without a total colonoscopy with biopsy being performed and biopsy should taken not only from distal colon but caecum & transverse colon should also be included.

The presence of histopathological changes diffusely throughout the colon has been described in different studies, but the microscopic abnormalities may be limited to the right and transverse colon[27]. Study by Thijs W.J et al. found MC in 13 out of 103 patients. The distribution was diffuse throughout the colon in ten (77%) and restricted to the right colon, i.e. only in the transverse colon and ascending colon in three (23%) patients. In these three the diagnosis would have been missed if only sigmoidoscopy had been performed[28]. Tanaka et al found a 27% false negative rate in a group of patients with CC if only biopsies were taken within the reach of a 60cm sigmoidoscope[16]. Another study reports that in 40% of patients, the diagnosis of MC would be missed if sigmoidoscopy would have been performed instead of colonoscopy, implying that sigmoidoscopy is insufficient for diagnosing this disease[29]. MacIntosh et al obtained rectal biopsy in 89 patients with IBS and found no significant pathologic findings. They concluded that patients with normal colonoscopy and diagnosis of IBS are unlikely to have histologic abnormalities in the rectum and rectal biopsies are unnecessary in the investigation of IBS[30].

The patients with LC in this study had a mean intraepithelial lymphocyte count of 22.72 (±2.41) cells per 100 intercryptal epithelial cells.

In the studies of Baert et al and Lazenby et al. mean IEL per 100 intercryptal epithelial cells was 29.4 and 34.7 respectively[21,31]. Study by David Limsui et al.showed that patients with MC had a mean intraepithelial lymphocyte count of 50.2 per 100 epithelial cells (range, 20-120)[4]. Another study by Fernando Ferna´ndez-Ban˜ares included thirty-seven patients with CC and 44 with LC. All patients with MC had an increase in the number of IEL, with a mean value of 23.6±1.1% (range 12-40%) in patients with CC, and 36.6±1.7% (range 24-57%) in those with LC[32]. There is increasing interest in the possible role of inflammatory processes in the pathogenesis of IBS. Studies have found low-grade infiltration of lymphocytes in the myenteric plexus in jejunal biopsies and increased mast cells in ileal and caecal biopsies of IBS patients[4]. In one of the study of post infectious irritable bowel syndrome (PI-IBS) showed that patients did not have an increase in intraepithelial lymphocytes (8.2 lymphocytes per 100 epithelial cells versus 8.6 per 100 epithelial cells in controls) and no patients met histologic criteria for MC[33]. The other study noted a minor initial increase of intraepithelial lymphocytes in patients with PI-IBS following Campylobacter enteritis (2.5 IEL per 100 epithelial cells versus 0.5 IEL per 100 epithelial cells in controls), but this increase declined significantly over 12 weeks to 0.9 IEL per 100 epithelial cells[34]. Another study also found no significant increase in intraepithelial lymphocytes in PI-IBS patients (9.6 per 100 epithelial cells versus 6.7 per 100 epithelial cells in controls)[35]. This degree of lymphocytosis does not meet the accepted histologic criteria for the diagnosis of microscopic colitis.

*Conclusion:* In conclusion, this study demonstrates significant symptom overlap between MC and IBS-D. It is also evident that involvement of the left colon seems to be less intense than that of the proximal. The distributions of histopathological abnormalities are located mainly in the caecum and transverse colon but the disease is also diffuse in considerable patients. Prospective studies with large sample size are needed to validate these findings and to give treatment and follow up.

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