ORIGINAL ARTICLE

FREQUENCY AND RISK FACTORS OF MICROSCOPIC COLITIS AS A CAUSE OF CHRONIC WATERY DIARRHOEA

Sabhita Shabir Shaikh✉, Raheela Khalid, Uzma Bukhari, Hafeezullah Shaikh, Syeda Aamna Ijtaba Rizvi, Alveena Shabbir

Dow University of Health Sciences, Karachi-Pakistan

Background: Microscopic colitis (MC) is one of the most underdiagnosed conditions leading to chronic watery diarrhoea in patients worldwide. This is the first study of this kind in Pakistan and we aimed to calculate the frequency as well as study the risk factors behind the disease. **Methods:** This was a prospective cross-sectional study in a tertiary care hospital in Pakistan. A total of 58 participants with chronic watery diarrhoea who had normal colonoscopy were recruited for the study and biopsies were obtained for diagnosing MC. **Results:** 2 participants out of 58 (3.4%) had biopsy proven microscopic colitis; one patient had a lymphocytic colitis variant and the other had a collagenous colitis variant. The average score based on the MC scoring system was 7.53 in the entire study group. The patient with lymphocytic colitis had a score of 06 while the patient with collagenous colitis had a score of 8. **Conclusion:** The frequency of microscopic colitis was found to be 3.4% of all cases of chronic watery diarrhoea. A link between MC and autoimmune diseases was also observed. However, we had a limited sample size and encouraged future studies to employ a larger sample size to get a multifaceted look at the disease process.

Keywords: Colonoscopy; Lymphocytic colitis; Eosinophilic colitis

Citation: Shaikh SS, Khalid R, Bukhari U, Shaikh H, Rizvi SAI, Shabbir A. Frequency and risk factors of microscopic colitis as a cause of chronic watery diarrhoea. J Ayub Med Coll Abbottabad 2023;35(3):394–9.

DOI: 10.55519/JAMC-03-11935

INTRODUCTION

Chronic diarrhoea is among the leading causes of patient presentation in gastrointestinal clinics. When patients present with this complaint; infectious colitis, celiac disease, irritable bowel syndrome, inflammatory bowel disease, and lactose intolerance are among the most frequently encountered diagnosis.[1] Additionally, there are a few more uncommon aetiologies which include lymphomas, neuroendocrine tumours, and microscopic colitis. Among these, one disease leading to chronic diarrhoea, which is on an insidious rise and yet often remains undiagnosed, is microscopic colitis.[2]

Literature has shown its prevalence to be somewhere between 0.5–42% and incidence range from 3–5 per 10000 to 7.1 per 100,000 people with a predisposition to female gender.[3] In general, the incidence of microscopic colitis has increased over time and it is no longer the rare disease process that it once was.[4] A meta-analysis has revealed a pooled worldwide incidence of microscopic colitis of 4.9 (95% CI 4.2–5.7) cases per 100,000 patient-years for collagenous colitis and 5.0 (95% CI 4.0–6.1) cases per 100,000 patient-years for lymphocytic colitis.[5]

While data has been inconclusive in highlighting the collective burden of microscopic colitis within Asia, several studies demonstrate the distribution of MC among the prevalent Asian ethnic groups residing in other countries. Microscopic colitis was found to be significantly less common among patients from India and East Asia.[6] However, due to scanty data as well as the failure of microscopic colitis to present as a gross finding in colonoscopy, the disease remains one of the most missed and underdiagnosed conditions in the country.[7]

On the basis of histopathologic changes microscopic colitis has been categorised into (i) lymphocytic colitis in which there are increased intraepithelial lymphocytes per 100 epithelial cells and (ii) collagenous colitis in which increased collagen deposit at the subepithelial area.[8] Non-steroidal anti-inflammatory drug use, proton pump inhibitor use, selective serotonin reuptake inhibitor use, and tobacco use have all been linked to an increased risk of developing microscopic colitis in trials.[9] Besides this it has been seen in literature that there is some association of microscopic colitis with celiac disease around 12.9%, and other autoimmune diseases like rheumatoid disease, thyroid disease(10.3%) and Type 1 Diabetes mellitus(1.7%).[10]

Geographical and cyclical variations in disease incidence may be caused by a number of

factors, including differences in the prevalence of risk factors and discrepancies in the recognition of this condition among pathologists and gastroenterologists. On the contrary, the diarrhoea-predominant type of irritable bowel syndrome is a frequent patient diagnosis in gastroenterology outpatient offices. Depending on the patient's symptoms, a gastroscopy, colonoscopy, or both may be recommended. If the endoscopic results are normal, the patient is generally given the diagnosis of IBS. Microscopic colitis is often placed at the bottom of the list of differentials when encountering patients. So much so, that despite IBS being a diagnosis of exclusion, in the setting of seemingly normal endoscopic and laboratory evaluation, patients are often categorized under irritable bowel syndrome (diarrhoea-predominant subtype) before they are advised biopsies.[11] This is very common as gastroenterologists do not routinely obtain biopsy samples of colonic mucosa that seem healthy in order to identify microscopic colitis. Therefore, the diagnosis of microscopic colitis is frequently missed.

This in turn leads to inadequate treatment response and repeat colonoscopies which add to the mounting medical costs over time. Eventually, it further worsens the poor quality of life and psychological anguish suffered by chronically-ill patients. In the setting of microscopic colitis, a few studies support obtaining biopsy samples from the transverse colon as it increases the yield of diagnosis of microscopic colitis, while others suggest biopsy samples should be obtained from every segment of the colon to increase sensitivity to around 95%.[12,13]

So far, no studies highlighting the role of microscopic colitis in the setting of chronic diarrhoea have been conducted in Pakistan. Considering the incidence and studies carried out in neighbouring countries, there is a pressing need to evaluate the disease burden of microscopic colitis within Pakistan as well.

MATERIAL AND METHODS

This was a prospective cross-sectional study, conducted at the endoscopy department of NILGID over a span of one year between 11th April 2020 to 11th April 2021 after approval was issued from the IRB. The samples were collected through a non-probability consecutive sampling technique.

The inclusion criteria considered both males and females, ages above 12 years, suffering from chronic watery diarrhoea who presented to the endoscopy unit for colonoscopy as part of the evaluation were included in the study. Meanwhile, the exclusion criteria included patients who did not issue consent for the study or refused colonoscopy or biopsy. Children, and pregnant and lactating mothers, patients who had gross significant findings like growth, features suggestive of classical inflammatory bowel diseases, tuberculosis or strictures were also excluded. Another group that was excluded were patients whose colonoscopy examinations could not be completed.

Our IRB approval reference number is IRB-1652/DUHS/Approval/2020/. For the sake of confidentiality and privacy, patient names are not included in the questionnaire. Data has only been used for approved research purposes.

After informed consent, the written questionnaire based proforma were filled out prior to the colonoscopic procedure, regarding detailed history, associated diseases or risk factors and drug history. The patients were then preceded for colonoscopy procedures and biopsy samples were obtained and sent for histopathology. A scoring system for identifying patients with MC is then applied to predict the likelihood of the development of MC in these individuals on the basis of a few distinct parameters.[14] The biopsy samples were then viewed and reported by a single pathologist and the diagnosis of microscopic colitis has been made on standard histopathological criteria.[15]

The biopsy reports were later collected by the PI/co-investigator from the medical records (through an electronic database) to maintain the integrity of the research.

RESULTS

A total of 58 candidates with normal colonoscopies were recruited for analysis after clinical presentation with chronic watery diarrhoea. Table 1 describes the baseline demographics, clinical characteristics, associated diseases/ comorbid conditions and drug intake. The mean age for the patients was 40.93 and consisted predominantly of females. The majority of the patients were non-smokers (94.8%). Most of the patients had diarrhoea lasting more than 6 months (67.3%) with less than 5 episodes/day (51.7%) and associated with abdominal pain (68.9%). The greatest percentage of respondents (56.89%) seemed to have no concurrent comorbid conditions. There was also an increasing trend (94.8%) of chronic diarrhoea noted in participants who reported PPI use. Biopsy reports revealed that the majority of the patients (94.6%) had mild to moderate chronic nonspecific colitis and only 3.4% (2 out of 58 candidates) had microscopic colitis. Of the two patients who had microscopic colitis; one had the lymphocytic colitis variant while the other had biopsy proven collagenous colitis subtype. The average score to predict MC among the total study participants (irrespective of histopathology findings) was 7.53. Table-2 highlights detailed clinical characteristics and associated

diseases/features of biopsy proven MC patients. One male participant (age 24) was diagnosed with lymphocytic colitis and one female participant (age 54) was diagnosed with collagenous colitis. The male participant with LC had diarrhoea for more than 6 months with more than 5 bowel movements a day and associated with abdominal pain. The female participant with CC had diarrhoea for less than 6 months with less than 6 bowel movements a day. Both the participants had a BMI of less than 30kg/m2 and reported PPI use. The male candidate did not have a family history of any autoimmune disease meanwhile the female candidate reported a family history of Rheumatoid arthritis. Figure-1a is showing the colonic mucosal fragments with moderate chronic inflammation in the lamina propria. Sub epithelial collage bands are noted which are further confirmed on special stain trichrome (1b). Figure-2a is showing epithelial lymphocytes. This figure is from microscopic exhibiting fragments of colon with raised intraepithelial lymphocytes, which further confirm on Immuno-histochemical stain CD3 (2b).

Table-1: Demographic and clinical characteristics of chronic watery diarrhoea patients with normal colonoscopy

Baseline characteristics	Number of patients (%)/ Mean*
Mean Age	40.93 years*
Gender	
Female	31 (53.3)
Male	27 (46.6)
BMI	
Less than 30 kg/m^2	29 (50)
More than 30 kg/m^2	29 (50)
Duration of diarrhoea	
Less than 6 months	19 (32.7)
More than 6 months	39 (67.3)
Number of bowel movements	
Less than 5 times	30 (51.7)
More than 5 times	28 (48.2)
Consistency of stools	
Watery	11 (18.9)
Paste like	26 (44.8)
Both	21 (36.2)
Associated symptoms	
Weight loss	31 (53.4)
Abdominal pain	40 (68.9)
Fecal incontinence	4 (6.8)
Altered bowel habits	24 (41.3)
Tenesmus	2 (3.4)
Comorbid conditions	
Diabetes Mellitus	8 (13.7)
Hypertension	8 (13.7)
Both DM & HTN	2 (3.4)
None	33 (56.89)
Others*	7 (12.06)
Smoking status	3 (5.1)
Current smoker	55 (94.8)
Non-smoker	
Drug use	
PPI use	55 (94.8)
NSAID use	7 (12.06)
SSRI/SNRI use	5 (8.6)
Colonoscopy findings	
Normal	40 (68.9)
Internal haemorrhoids	11 (18.6)
Nodular terminal ileum	3 (5.1)
Mild colitis	3 (5.1)
Rectal polyp	1 (1.7)
Histopathological findings	
Moderate chronic nonspecific colitis	29 (50)
Mild chronic nonspecific colitis	26 (44.8)
Microscopic colitis	2 (3.4)
Others£	1 (1.7)
Laboratory findings	
Haemoglobin	11.99 g/dl*
Platelets	238.17*
TSH	0.72 IU*
TTGs IgA & IgG	Negative/not available
Stool DR	Normal
Average Score predicting risk of Microscopic colitis (≥10)	53. *

*CLD, Leukaemia, Lymphoma, IHD, CHK and a combination of these. £ Solitary rectal ulcer, infective colitis.

Table-2: Clinical characteristics of patients with microscopic colitis

Components	Lymphocytic colitis	Collagenous colitis
Age	24 years	54 years
Gender	Male	Female
BMI	Less than 30 kg/m^2	Less than 30 kg/m^2
Duration of diarrhoea	More than 6 months	Less than 6 months
Bowel movements per day	More than 5 times	Less than 5 times
Consistency of stools	watery	Paste like
Associated symptoms	Abdominal pain	Abdominal pain
Co-morbid conditions	None	Hypertension
Personal history **Celiac disease** **Autoimmune hepatitis** **Thyroid disease** **Lactose intolerance** **Smoking**	 None None None Yes No	 None None None No No
Drugs used **PPI** **NSAID** **SSRI/SNRI**	 Yes (6 months) No No	 Yes (12 months) No No
Family history of autoimmune disease	No	Yes (Rheumatoid arthritis)
Endoscopic findings	Normal mucosa	Normal mucosa
Histopathological findings	Raised IEL	Thick subepithilial collagen band
Laboratory parameters HB TSH TTGs IgA & IgG Stool DR	 15.3 N/A Not done N/A	 N/A 1.2 IU Not done Normal
Scoring system predicting risk of MC	06	08

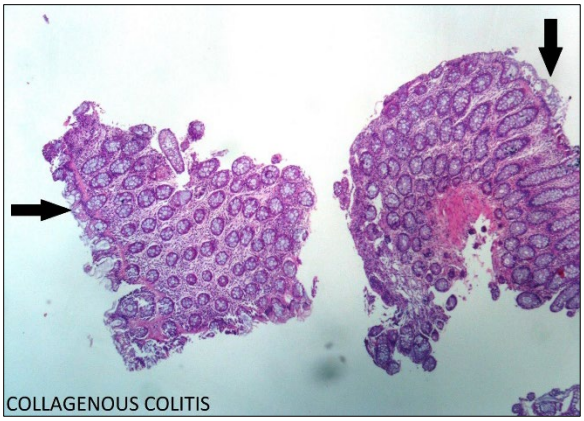

Figure-1 a: H&E.4X. Highlighting subepithelial collagen band.

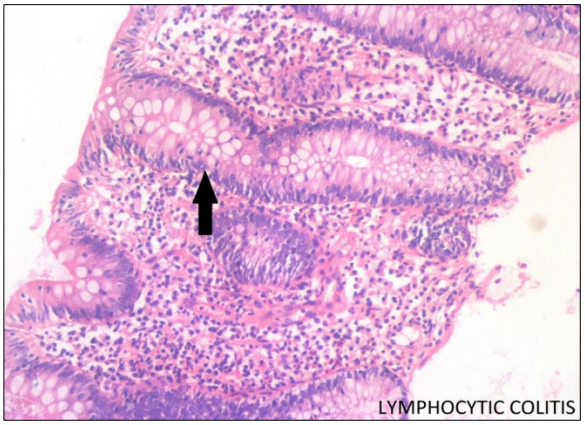

Figure-2a: H&E. 10X. Lymphocytic colitis.

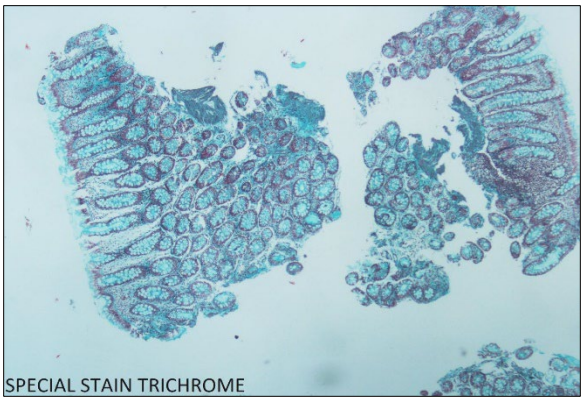

Figure-1b: 4X. Trichrome stain. Collagenous colitis. This figure highlights subepithelial collagen bands.

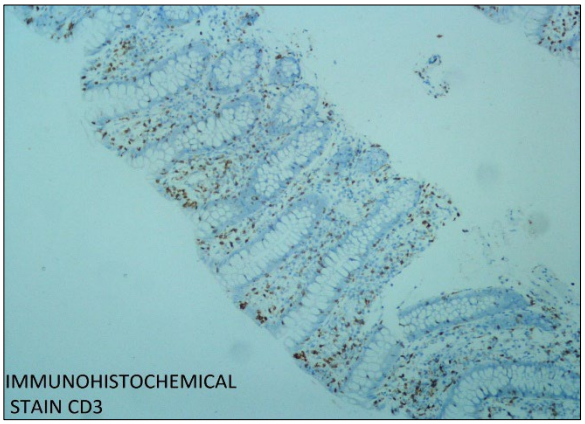

Figure-2b 4X Immunohistochemical stain CD3 highlighting T- Lymphocytes.

DISCUSSION

In terms of studies conducted within Pakistan to evaluate the burden of MC in patients with chronic diarrhoea, this study is the first of its kind. While the disease burden of microscopic colitis (MC) is an insidious and steep graph worldwide; data focusing on Asian and Pakistani prevalence is sparse.[16,17] No cross-country data is available that focuses on disease burden within the country.

In all ethnic groups alike, microscopic colitis is found to be more common in women than men (78% versus 22%) and the prevalence of microscopic colitis shows a continuous age-dependent rise. However, in our study, the distribution of microscopic colitis according to gender was 1:1. Similarly, one of our 2 patients with microscopic colitis was a 24-year-old young man. We advise future studies to make use of a bigger sample size in the Pakistani or Asian population to verify whether there's a gender and age predilection for the disease in the region.

In reality, microscopic colitis calls for a very new approach to treatment. These patients most frequently respond to budesonide, while other available treatments which are beneficial in microscopic colitis are anti-diarrhoeal agents such as loperamide and bismuth salicylates.[6] Anti-diarrhoeal agents work by reducing inflammation in the intestine and hence the diarrhoea gets better.[18] Therefore, before diagnosing someone with IBS, a biopsy should be performed, even on patients with normal gross appearance of the colon and especially those with persistent chronic symptoms.

There is an exceedingly alarming rate of misdiagnosis of microscopic colitis as IBS (diarrhoea predominant) in Pakistan's neighbouring countries too. Often upto 50% of the patients who are unresponsive to treatment while being treated as IBS-D, when biopsied, reveal they have nonspecific microscopic colitis as the real reason for chronic diarrhoea.[19] There is no denying that studies have been consistent with the fact that there is a considerable symptom overlap between the patients of IBS-D and patients with microscopic colitis; deeming biopsies indispensable in the diagnosis and treatment of the disease.[20]

A variety of characteristics, such as a favourable correlation with a wide range of autoimmune disorders, such as celiac disease, type 1 diabetes mellitus, rheumatoid arthritis, polyarthritis, and thyroiditis, are associated with an increased incidence of microscopic colitis.[21,13] Of the two patients in our sample who have MC, one has lactose intolerance and the other has a positive family history for autoimmune diseases such as Rheumatoid arthritis. This again highlights a strong association with autoimmune disorders.

Smoking status must also be carefully investigated as it is an additional risk factor for microscopic colitis. Smokers appear to be at up to five times greater risk, with the onset of MC being noted at least ten years sooner than in that in non-smokers but in our study, both the patients who tested positive for MC were nonsmokers.[22]

Using the diagnostic and clinical tool of the scoring system on patients is of value however, it is important to highlight that in this study, despite low scores, the patients had biopsy-proven MC. The mean score was found to be low in the non-MC group as well, however, we cannot accurately compare the two due to discrepancy in a sample size of MC vs non-MC group.

Ultimately, in light of all new data, MC is no longer the rare disease it was previously regarded as. While this was a smaller sample size, it was still found that 3.4% of the sufferers of chronic watery diarrhoea had microscopic colitis as the underlying disease process. Other researchers have identified that when endoscopy displays a normal macroscopic image in the setting of persistent non-bloody diarrhoea, 8–16% of the time, MC is the culprit.[23] Perhaps; in larger sample sizes the high frequency of microscopic colitis will be better illuminated. We believe the scoring system can prove its considerable usefulness and value in future studies with greater sample sizes. For this reason, we urge future studies to employ the scoring system as its application might reveal new information regarding microscopic colitis and parallels between the patients suffering from the disease.

We believe that this predictive scoring might also be a useful modality in guiding patient selection for carrying out biopsies in the presence of macroscopically normal mucosa, hence encouraging clinicians to be more confident when carrying out routine biopsies and eliminating unnecessary ones in the setting of chronic diarrhoea. Such practice might help in the disease diagnosis as well as treatment, hence alleviating the disease burden in the sufferers of microscopic colitis.

Our efforts in including MC among other classical IBD as a differential diagnosis when dealing with chronic diarrhoea are a testament to treating the debilitating life experience that this disease encompasses. However, this study is not without its limitations. Among this study's key limitations is the small sample size used to study the prevalence of MC in chronic diarrhoea. Another obstacle is the scoring system used to evaluate the patient's likelihood of developing MC. Due to the inequalities in the sample distribution (58:2); the scoring system was low in both groups and cannot be compared between the groups. This means that the scoring system might not be accurately applied in this particular study and its importance as a diagnostic tool cannot be implicated in this study. Moreover, due to the low sample size, specific risk factors cannot be accurately assessed in our study.

CONCLUSION

Our study found the frequency of microscopic colitis to be 3.4% of all cases of chronic watery diarrhoea. However, we had a limited sample size and encouraged future studies to employ a larger sample size so that a more comprehensive view can be obtained of microscopic colitis as a disease.

Conflict of interest: None.
Grant support and financial disclosure: None.
Acknowledgements: The authors are thankful for the cooperation of the participants and their caregivers.

AUTHORS' CONTRIBUTION

SSS: Conceptualization of the study design, proofreading. RS: Data collection. UB: Data interpretation, proofreading. HS: Data analysis, proofreading. AM, AS: Write-up, literature search.

REFERENCES

1. Sun J, Lin J, Parashette K, Zhang J, Fan R. Association of lymphocytic colitis and lactase deficiency in pediatric population. Pathol Res Pract 2015;211(2):138–44.
2. Bo-Linn GW, Vendrell DD, Lee E, Fordtran JS. An evaluation of the significance of microscopic colitis in patients with chronic diarrhoea. J Clin Invest 1985;75(5):1559–69.
3. Storr MA. Microscopic colitis: epidemiology, pathophysiology, diagnosis and current management—an update 2013. ISRN Gastroenterol 2013;2013:352718.
4. Maye H, Safroneeva E, Godat S, Sempoux C, Yan P, Bouzourène H, *et al*. Increasing incidence of microscopic colitis in a population-based cohort study in Switzerland. Clin Gastroenterol Hepatol 2021;19(10):2205–6.
5. Miehlke S, Guagnozzi D, Zabana Y, Tontini GE, Kanstrup Fiehn AM, Wildt S, *et al*. European guidelines on microscopic colitis: United European Gastroenterology and European Microscopic Colitis Group statements and recommendations. United European Gastroenterol J 2021;9(1):13–7.
6. Turner K, Genta RM, Sonnenberg A. Ethnic distribution of microscopic colitis in the United States. Inflamm Bowel Dis 2015;21(11):2634–9.
7. Mohamed N, Marais M, Bezuidenhout J. Microscopic colitis as a missed cause of chronic diarrhoea. World J Gastroenterol 2011;17(15):1996–2002.
8. Hempel KA, Sharma AV. Collagenous and lymphocytic colitis. InStatPearls [Internet] 2021 Sep 18. StatPearls Publishing. [cited 2023 Mar 24]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK541100/
9. Yen EF, Amusin DB, Yoo J, Ture A, Gentile NM, Goldberg MJ, *et al*. Nonsteroidal anti-inflammatory drug exposure and the risk of microscopic colitis. BMC Gastroenterol 2022;22(1):367.
10. Nimri FM, Muhanna A, Almomani Z, Khazaaleh S, Alomari M, Almomani L, *et al*. The association between microscopic colitis and celiac disease: a systematic review and meta-analysis. Ann Gastroenterol 2022;35(3):281–9.
11. Bachani P, Kumar L, Kumar N, Fatima M, Naz S, Memon MK, *et al*. Prevalence of irritable bowel syndrome and frequency of symptoms in the general population of Pakistan. Cureus 2021;13(1):e12541.
12. Virine B, Chande N, Driman DK. Biopsies from ascending and descending colon are sufficient for diagnosis of microscopic colitis. Clin Gastroenterol Hepatol 2020;18(9):2003–9.
13. Nielsen OH, Fernandez-Banares F, Sato T, Pardi DS. Microscopic colitis: Etiopathology, diagnosis, and rational management. Elife 2022;11:e79397.
14. Kane JS, Rotimi O, Everett SM, Samji S, Michelotti F, Ford AC. Development and validation of a scoring system to identify patients with microscopic colitis. Clin Gastroenterol Hepatol 2015;13(6):1125–31.
15. Aust DE. Histopathology of microscopic colitis. Pathology 2012;33(Suppl 2):221–4.
16. Gentile N, Yen EF. Prevalence, pathogenesis, diagnosis, and management of microscopic colitis. Gut Liver 2018;12(3):227–35.
17. Weimers P, Ankersen DV, Lophaven S, Bonderup OK, Münch A, Løkkegaard EC, *et al*. Incidence and prevalence of microscopic colitis between 2001 and 2016: a Danish nationwide cohort study. J Crohns Colitis 2020;14(12):1717–23.
18. Rojo E, Casanova MJ, Gisbert JP. Treatment of microscopic colitis: the role of budesonide and new alternatives for refractory patients. Rev Esp Enferm Dig 2020;112(1):53–8.
19. Rahman MA, Raihan AS, Ahamed DS, Masud H, Safiullah AB, Khair KB, *et al*. Symptomatic overlap in patients with diarrhoea predominant irritable bowel syndrome and microscopic colitis in a sub group of Bangladeshi population. Bangladesh Med Res Counc Bull 2012;38(1):33–8.
20. Khalili H, Burke KE, Roelstraete B, Sachs MC, Olén O, Ludvigsson JF. Microscopic colitis and risk of inflammatory bowel disease in a nationwide cohort study. Gastroenterology 2020;158(6):1574–83.
21. Takahashi K, Anno T, Matsuda A, Kimura Y, Kawasaki F, Kaku K, *et al*. Case Report: Onset of Type 1 Diabetes Mellitus in a Patient With Ulcerative Colitis and Sjogren's Syndrome Under Euthyroid Hashimoto's Thyroiditis. Front Endocrinol (Lausanne) 2022;13:836102.
22. Jaruvongvanich V, Poonsombudlert K, Ungprasert P. Smoking and risk of microscopic colitis: a systematic review and meta-analysis. Inflamm Bowel Dis 2019;25(4):672–8.
23. Abdel Monem SM, Sharaf AL, Alabiad MA, Ibrahim IM. Microscopic Colitis in Patients with Unexplained Chronic Watery non-Bloody Diarrhoea: A Cross Sectional Study. Afro-Egypt J Infect Endem Dis 2022;12(2):124–33.

Submitted: March 29, 2023	*Revised: April 19, 2023*	*Accepted: May 13, 2023*

Address for Correspondence:

Sabhita Shabir Shaikh, Flat No. 006, Block-1, Al Khizra Heights. Gulistan e Johar, Block-3, Karachi-Pakistan.
Cell: +92 336 228 1624
Email: sabhita.shabbir@gmail.com