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# Beyond the Endoscope: Unmasking the Hidden Cause of Chronic Watery Diarrhoea in a Middle-Aged Lady-from IBS-D to Microscopic Colitis

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## ABSTRACT

Microscopic colitis is a chronic inflammatory disease of the colon that is characterized by chronic, watery, non-bloody diarrhea. It typically occurs in middle-aged patients and has a female preponderance. The colon appears typically normal or almost normal on colonoscopy in patients with microscopic colitis. The diagnosis is established by biopsy of the colonic mucosa demonstrating characteristic histologic changes. Microscopic colitis has two main histologic subtypes, lymphocytic colitis, more specifically defined in 1989, and collagenous colitis. It is treatable, but in the developing world, its diagnosis may often prove difficult. Data and reports of this condition in Bangladesh are scarce because most medical centers lack a functional gastrointestinal endoscopy unit that would aid in the diagnosis. We here in present a case of a 55-year-old lady who was getting treatment for refractory Irritable Bowel Syndrome-Diarrhea (IBS-D). Eventually she was diagnosed with lymphocytic microscopic Colitis. She started treatment with steroid, cholestyramine, later with azathioprine and improved dramatically.

**Keywords:** Colonoscopy; Diarrhea; Microscopic colitis; Irritable bowel syndrome; Steroid

## INTRODUCTION

In the developing world where there is scarcity of facilities for endoscopy in many medical centers, patients presenting with chronic or recurrent diarrhea for which no infective, metabolic or mechanical cause is found are usually thought to have the diarrheal type of irritable bowel syndrome and therefore managed empirically as such. Lymphocytic colitis and collagenous colitis make up a group of uncommon large bowel inflammatory conditions called microscopic colitis which were first described in 1980 [1]. It is yet to be fully ascertained if these two clinical conditions are separate entities, albeit with similar clinical presentation, or if they are clinical manifestations of a spectrum of clinical conditions [2]. The implication of certain drugs such as ranitidine, ticlopidine, flutamide, carbamazepine, sertraline, paroxetine, simvastatin in the etiopathogenesis makes the clinical picture more com plex [3]. Information on prevalence, clinical features, clinical course and response to therapy is not well documented in Bangladesh. Microscopic colitides are potentially treatable if a high index of suspicion is maintained and facilities are available for endoscopy and histological diagnosis. We present a case of lymphocytic colitis in a Bangladeshi woman

who was successfully treated with steroid, cholestyramine and azathioprine.

## CASE PRESENTATION

A 55-year-old Bangladeshi woman with a 15-years history of recurrent passage of loose watery stools was referred to our facility following several unsuccessful anti diarrheal therapies for diarrhea predominant irritable bowel syndrome including rifaximin, loperamide, amitriptyline, duloxetine, probiotics, mebeverine and a suspicion of colonic tumor. She had eight to ten episodes daily of watery, non-mucoid and non-bloody stools not associated with vomiting, abdominal pain or cramps. There was no weight loss or history of passage of undigested food particles and there were no features of fluid retention. There was also no history of joint pains and swelling or use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). Physical examination did not reveal any abnormalities. There was a positive family history of chronic diarrhea in the younger brother.

The laboratory investigation revealed no ova or cyst of parasitic origin in the stools, and the stool culture yielded no pathogens. Complete blood count, liver function tests, thyroid function tests, erythrocyte sedimentation rate, lipid profile, and serum electrolytes, urea and creatinine levels were within the normal range. The Human Immuno Virus (HIV) screening was non-reactive. Anti Tissue Transglutaminase (TTG) was negative. After bowel preparation, she underwent fiberoptic colonoscopy with random biopsies taken at the ascending and descending colons after no mass lesion or inflammation were found (Figure 1). The histopathology report of the colonic biopsy showed benign surface columnar epithelium mixed with goblet cells and many simple glands lined by a layer of goblet cells within the lamina propria. There was moderate infiltrate of a mixed population of chronic inflammatory cells within a mildly edematous lamina propria, consisting of lymphocytes and plasma cells with a focus of lymphoid follicle formation. There were also a few eosinophils and neutrophil polymorphs, with focal intraepithelial infiltration by lymphocytes. These features were in keeping lymphocytic colitis (Figure 2).

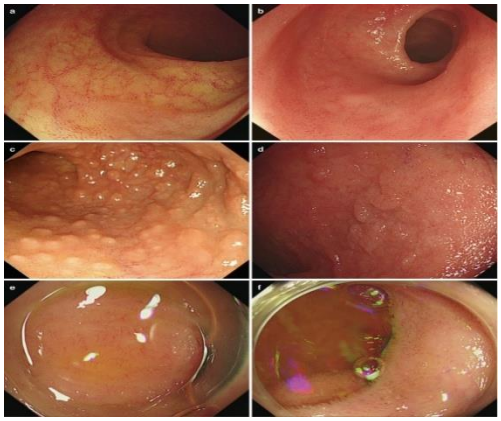

**Figure 1:** Showing normal appearance of colonic mucosa

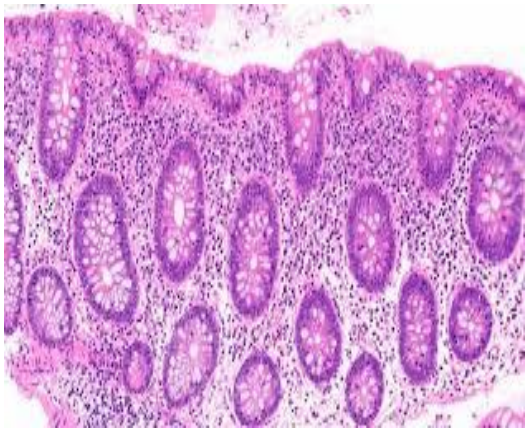

**Figure 2:** Histopathology of colonic mucosa showing moderate infiltrate of a mixed population of chronic inflammatory cells within a mildly edematous lamina propria, consisting of lymphocytes and plasma cells.

The patient was subsequently placed on prednisolone, cholestyramine. This resulted in the complete resolution of diarrhea after about two months of therapy. But while tapering prednisolone, she again had a relapse of diarrhea. So along with the lowest possible dose of steroid, azathioprine was added. With this combination she showed dramatic improvement in her symptoms over the next 6 months. There is a plan to withdraw steroid over the next 6 months. She is still being followed up in clinic.

## RESULTS AND DISCUSSION

Lymphocytic Colitis (LC) and Collagenous Colitis (CC) belong to the group of microscopic colitides, a term which was first introduced by Read et al. in 1980 [1]. LC was first described by Lazenby et al. in 1989 to replace the term microscopic colitis and to

distinguish it from infectious colitis and inflammatory bowel disease (ulcerative colitis and Crohn's disease) [4]. LC and CC are relatively rare conditions diagnosed when a patient with chronic, watery and non-bloody diarrhea has an endoscopically or radiographically normal colon, but colonic biopsies show unique inflammatory changes. Because the mucosa is not ulcerated or otherwise disrupted, diarrhea generally does not contain blood or pus [5].

The estimated incidence of collagenous colitis and lymphocytic colitis are 2.0 to 10.8 and 2.3 to 16 per 100,000 per year, respectively [6]. The median age at diagnosis of microscopic colitis is approximately 65 years [7]. Microscopic colitis has a higher incidence in women [8].

No definite aetiology has been determined for LC and CC. Nonetheless, many case reports describe patients with pre-existing, presumed autoimmune conditions, such as celiac sprue and rheumatoid arthritis, who subsequently are diagnosed with LC and CC. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been implicated as being causative or triggering flares of microscopic colitis [9]. Several other drugs have also been implicated as potential causes of microscopic colitis, including Proton Pump Inhibitors (PPIs), specifically lansoprazole, statins, selective serotonin reuptake inhibitors and other drugs, (eg, pembrolizumab) [10]. Smoking may play a role in the development of microscopic colitis and the clinical outcome [11]. On average, smokers also develop microscopic colitis more than 10 years earlier than non-smokers [12].

The pathogenesis of microscopic colitis is unclear; however, it is likely to be multifactorial, involving mucosal immune responses to luminal factors in a genetically predisposed individual [13]. Studies have also demonstrated an association between microscopic colitis and Human Leukocyte Antigen (HLA) DQ2 or DQ1, 3, as well as a higher frequency of HLA-DR3DQ2 haplotype and tumor necrosis factor 2 allele carriage in microscopic colitis, as compared with controls [14]. Abnormal collagen metabolism may be responsible for the thick collagen band in collagenous colitis. Increased transcriptional activity of nuclear factor kappa B causes upregulation of inducible NO synthase activity and, subsequently, increased production of NO in the colonic epithelium, which might be a direct cause of secretory diarrhea in patients with collagenous colitis [15]. An alternative hypothesis is that a defect in epithelial barrier function and luminal factors may lead to an increased transmucosal permeability of antigens and bacteria, leading to immune dysregulation and intestinal inflammation seen in microscopic colitis [16].

Microscopic colitis is characterized by chronic, non-bloody, watery diarrhea [7,13,17]. The onset of diarrhea is often insidious, but sudden onset was reported in approximately 40 percent of patients [7]. Patients with microscopic colitis usually have between four and nine watery stools per day, but in rare cases, bowel movements can exceed 15 or up to 2 liters per day [7,18]. Patients may have associated fecal urgency (70 percent), incontinence (40 percent), and nocturnal episodes (50 percent). Abdominal pain occurs in up to 50 percent of patients with active microscopic colitis (≥3 stools or ≥1 watery stool per day) [19,20]. Patients may have associated weight loss due to fluid loss or decreased oral intake. Extraintestinal symptoms, such as arthralgia, arthritis, or uveitis can occur. The quality of life is reduced [21].

Laboratory findings in microscopic colitis are generally nonspecific. Mild anemia, elevated erythrocyte sedimentation rate, and autoantibodies are found in approximately one-half of patients [7,22,23]. These autoantibodies include rheumatoid factor, antinuclear and antimitochondrial antibodies, antineutrophilic cytoplasmic antibodies, anti-Saccharomyces cerevisiae antibodies, and antithyroid peroxidase antibodies. Stool studies should include stool Clostridioides difficile toxin, routine stool cultures (Salmonella, Shigella, Campylobacter, Yersinia), and specific testing for Escherichia coli O157:H7. Microscopy for ova and parasites (three samples) and a Giardia stool antigen test should also be performed, particularly if the patient has risk factors such as recent travel to endemic areas. The use of calprotectin to exclude or monitor microscopic colitis is not recommended [24,25].

The endoscopic appearance of the colon is typically normal. Macroscopic features can include slight edema, erythema, friability, exudative lesions, and scars [26]. The inflammatory cell response is similar in lymphocytic and collagenous colitis, consisting mainly of mononuclear infiltrates, with few neutrophils and eosinophils in the lamina propria. However, there are certain key histological features that are used to diagnose collagenous and lymphocytic colitis. Collagenous colitis is characterized by a colonic subepithelial collagen band ≥10 micrometers in diameter [27]. The band is most evident between the crypts. Lymphocytic colitis is characterized by ≥20 Intraepithelial Lymphocytes (IEL) per 100 surface epithelial cells

[17]. Crypt architecture is usually not distorted, but focal cryptitis may be present.

The primary goal of management in patients with microscopic colitis is to achieve clinical remission (<3 stools per day and no watery stool during a one-week period) and to improve the patient's quality of life. It is unclear if histological remission is necessary. Active disease is defined ≥3 stools daily or ≥1 watery stool daily [28].

Patients should be advised to avoid nonsteroidal anti-inflammatory drugs and, if possible, discontinue medications associated with microscopic colitis. For symptomatic management of diarrhea, the antidiarrheal agent, loperamide, particularly at night can be used to decrease the frequency of nocturnal episodes [29]. In patients with active disease (≥3 stools daily or ≥1 watery stool daily) or diarrhea that persists despite the use of antidiarrheals, budesonide (9 mg daily for six to eight weeks) can be added. Budesonide is a locally active corticosteroid with extensive first-pass metabolism in the liver and low systemic exposure [30]. Budesonide can be continued for at least eight weeks and then gradually taper budesonide in patients in clinical remission (<3 stools daily and no watery stools). Budesonide can be tapered to 6 mg for two weeks, followed by 3 mg for another two weeks, and then can be discontinued. In patients who are not in clinical remission at eight weeks, or if symptoms recur on tapering, the budesonide dose of 9 mg can be continued for 12 weeks or longer before tapering the dose. The use of prednisolone for the treatment of microscopic colitis is reserved in whom budesonide therapy is not feasible. While indirect evidence suggests that prednisone should induce clinical remission, its efficacy has not been demonstrated. In addition, systemic glucocorticoids have a higher risk of adverse events. As compared with budesonide, prednisone is associated with a lower response rate (53 versus 83 percent), more side effects, and a higher risk of relapse when therapy is withdrawn [31,32].

In patients with mild, persistent diarrhea despite budesonide, concomitant therapy with loperamide and cholestyramine (4 g four times per day) can be used. Cholestyramine is a bile acid binding resin that is used to treat diarrhea that is due to concurrent bile acid malabsorption in patients with microscopic colitis [33]. In patients who fail to respond to a two-week trial of cholestyramine, bismuth subsalicylate (three 262 mg tablets three times daily) can be used [33]. However, there are limited data to support bismuth subsalicylate, and its use is controversial [34]. In patients with refractory microscopic colitis, anti-Tumor Necrosis Factor (TNF) therapy (eg, infliximab, adalimumab) or immunomodulators (eg, 6-mercaptopurine, azathioprine) can be used. Limited evidence from small case series and retrospective studies suggest that anti-TNF agents and immunomodulators can induce remission in patients with refractory microscopic colitis [35,36]. Biologic agents and immunomodulators including vedolizumab [37] could be considered in selected patients with severe symptoms refractory to budesonide 6 mg. We do not use methotrexate for the treatment of microscopic colitis. Aminosalicylates including mesalamine appear to be ineffective in the treatment of collagenous colitis and lymphocytic colitis [38].

Surgery (ileostomy, sigmoidostomy, colectomy) should be reserved for management of microscopic colitis that is refractory to medical therapy [39,40]. Ileostomy may be the procedure of choice in older patients with refractory disease [40].

Symptomatic relapse occurs in up to 80 percent of patients after cessation of initial budesonide treatment [41]. However, routine maintenance treatment with budesonide in all patients with microscopic colitis is controversial as long-term treatment may increase the risk of steroid-related side effects. In patients with relapse following remission continuous maintenance therapy at the lowest dose that maintains clinical remission (no more than 6 mg per day then tapered to the lowest effective dose and continued for 6 to 12 months) can be used [42,43]. Alternatively, patients can either be retreated with intermittent courses (six to eight weeks) of budesonide. Unlike patients with inflammatory bowel disease, the risk of osteoporosis is not increased in patients with microscopic colitis in the absence of glucocorticoid use. However, patients with active disease requiring long-standing glucocorticoid treatment may require supplementation of calcium and vitamin D [44].

Microscopic colitis has a chronic, intermittent course in most patients [45]. Diarrhea may resolve within weeks with or without treatment, but relapses are common (approximately 30 to 60 percent) [41,46]. Patients were treated with a variety of interventions, including withdrawal of implicated medications and the use of salicylates, cholestyramine, prednisone, and budesonide. These interventions were associated with long-term cessation of diarrhea in approximately 70 percent of patients, while 25 to 30 percent relapsed. The long-term course of patients with lymphocytic colitis may be more favorable than with collagenous colitis [2,47]. A retrospective study compared the natural

history of 96 patients with collagenous colitis and 80 patients with lymphocytic colitis [2]. Resolutions or significant improvement occurred significantly more often in those with lymphocytic colitis, as compared with collagenous colitis (84 versus 74 percent). Microscopic colitis has not been associated with an increased risk of colorectal cancer, and transformation between collagenous and lymphocytic colitis is rare [17, 47].

## CONCLUSION

Lymphocytic colitis and collagenous colitis exist in the African population. In less-developed economies where there is a lack of endoscopic facilities, efforts should be made to ensure colonoscopy and biopsies for all patients with watery diarrhea when the common infective causes have been excluded. This will help clinicians recognize a potentially treatable condition and allow institution of adequate treatment measures.

## DECLARATIONS

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None declared


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### Authors' contributions

The author solely contributed to the conception, design, drafting, and final approval of this manuscript.

### Ethical approval and consent to participate

Not applicable, as this article does not contain any studies with human participants or animals performed by the author.

### Consent for publication

Not applicable.

### Availability of data and materials

Not applicable.

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