Microscopic Colitis Syndrome—A Review Article

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Diarrhea is a common symptom worldwide and especially so in developing countries. Whereas better diagnostic modalities in the developed world have helped to elucidate the causes of diarrhea, the situation in developing countries is not the same. Rather, most diarrhea cases are assumed to be of infective origin, and many people self-medicate. However, such a prevailing situation is unlikely to be correct, and it denies appropriate treatment to patients with other noninfective causes of diarrhea. This review is on microscopic colitis syndrome, a recently described cause of chronic diarrhea in which there is a dearth of publication from the developing countries.

Key words: microscopic ■ colitis ■ diarrhea ■ developing countries

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INTRODUCTION

Worldwide, diarrhea usually brings to mind the suspicion of a form of gastroenteritis, typically viral in the developed world, and bacterial or protozoan in developing countries. Consequently, in developing countries, the usual response to diarrhea is the continued use of antibiotics, most times self-prescribed. Facilities for endoscopy in these countries are limited and unaffordable, and there are myriad home remedies and unorthodox medical practices available and more accessible to the people. Therefore, many cases of chronic diarrhea go unreported, and the few that are reported are often inadequately investigated. On the other hand, in the western society, recurrent diarrhea is a cause of major concern, and easy access to medical facilities means that the underlying pathology can be investigated thoroughly. Therefore, many conditions have been delineated as being responsible for recurrent or chronic diarrhea and can thus be managed appropriately. These include the idiopathic chronic inflammatory bowel diseases (IBD), irritable bowel syndrome and, more recently, microscopic colitis.

Definition

Microscopic colitis is now regarded as a clinicopathological syndrome characterized by chronic watery diarrhea, normal endoscopic appearances of the colonic mucosa and microscopic colonic abnormalities.[1] The specific microscopic changes are diffuse lymphocytic and plasmacytic inflammation of the lamina propria and intraepithelial lymphocytosis with or without thickening of the subepithelial collagen band.[2] There are no significant crypt architectural changes in microscopic colitis, an important distinction from IBD.

Epidemiology

Most of the data on the incidence or prevalence of microscopic colitis is from developed countries where it accounts for 4–13% of cases of chronic watery diarrhea.[2] There are rather very few reports on microscopic colitis from developing countries. A single study in Peru, a developing country with a

high prevalence of infective gastroenteritis, revealed microscopic colitis in 40% of patients with chronic diarrhea, more commonly of the lymphocytic type.[3] A case of collagenous colitis has been reported in a Nigerian.[4] It is pertinent to know what the incidence is in developing countries where a good proportion of the population are treated frequently—usually by self-medication—for what is typically thought to be infective gastroenteritis.

Risk Factors

The typical patient with microscopic colitis is an elderly female, but slight variations have been noted in the risk factors associated with the two main subtypes of the disease. Patients with collagenous colitis are usually younger at an average of 57 years (65 years in the lymphocytic type), and the female predominance is slightly higher in the collagenous type.[1,5] Cigarette smoking is associated with the disease and is more common in the collagenous type.[2,5] A significantly higher number of patients with associated diseases of possible autoimmune origin have been noted in microscopic colitis as compared to patients with functional diarrhea. These include rheumatoid arthritis, thyroid disorders and diabetes. The importance of genetic predisposition in the etiology and pathogenesis of microscopic colitis is as yet unclear. There are a number of reported cases of familial occurrence, typically a sister-sister relationship.[6,7]

Etiology

Several hypotheses on the etiology of microscopic colitis have been postulated. The inconclusive nature of the evidence supporting these theories and the variety of clinical settings in which the disease occurs suggest that the syndrome may be the histological endpoint of several different diseases.

The association of microscopic colitis with various autoimmune conditions and markers may support an autoimmune process. Some studies have shown abnormal HLA DR expression on colonic epithelial cells of patients with microscopic colitis, suggesting major histocompatibility complex-restricted immune activation.[2] An increased expression of HLA DQ2 and HLA DQ1,3 has also been associated with microscopic colitis, a pattern similar to celiac sprue.[8] The observation of lymphocytic colitis in patients with celiac sprue and the induction of colitic changes with a gluten enema in patients with sprue have also suggested an abnormal reaction to an unknown luminal antigen.[2] Patients with celiac disease who have been treated with a gluten-free diet but still present with histological evidence of lymphocytic colitis have proved that the offending antigen is unlikely to be gluten.[7] The resolution of both symptoms and histological changes of microscopic colitis after a diverting ileostomy[2] strengthen this theory. Pertinent to this, perhaps, is a record of a temporary loop ileostomy that brought about a normalization of colorectal morphology and a return of diarrhea, inflammation and collagen plate thickening following reversal of the loop in a patient who had features of both collagenous and lymphocytic colitis.[9]

Bile acid malabsorption (BAM) has also been implicated in the pathogenesis of microscopic colitis. Bile acids infused in an animal colon have been shown to induce epithelial damage and colitis.[2] Furthermore, patients with known BAM develop diarrhea, and BAM has been detected in varying percentages of patients with microscopic colitis.[10] Some studies however refute this theory,[7,11] arguing that despite the positive clinical response, bile acid binders have shown no evidence of improvement in mucosal inflammation and propose that the improvement seen may be due to the binding of substances other than bile acids. Perhaps in tune with this is the result of a study[12] that showed marked

Figure 1. Increased mononuclear infiltrate in the lamina propria, a thickened subepithelial collagen layer (arrow). Hematoxylin and Eosin

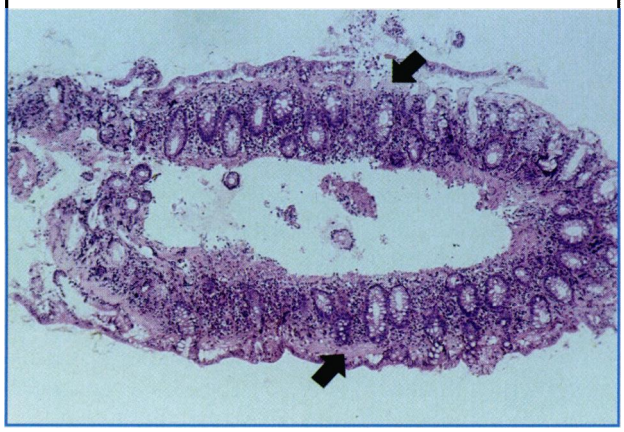
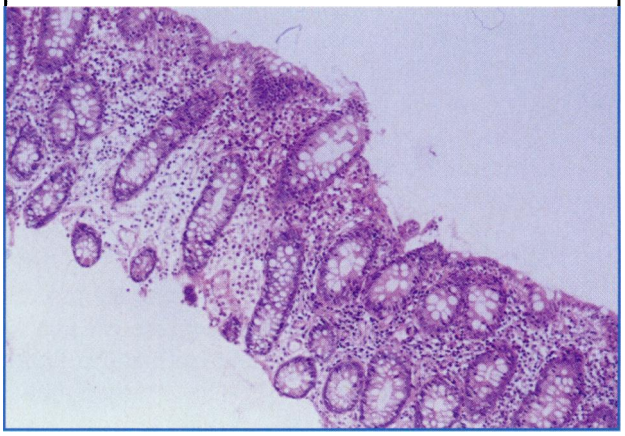


Figure 2. Increased mononuclear infiltrate in the lamina propria, a high number of intraepithelial lymphocytes. Hematoxylin and Eosin



improvement in 78% of collagenous colitis patients treated with bile acid binders, even though only 44% of them had clinical evidence of BAM using the ^{75}Se-homocholic acid taurine (^{75}SeHCAT) test.

Another interesting theory is that infectious gastroenteritis may, under certain conditions, precipitate microscopic colitis, probably by an autoimmune reaction.[3] The finding of acute inflammation on biopsy as well as histories suggesting acute infection in many patients with microscopic colitis support this, although no organism has been identified. In this regard, the disease is similar to Brainerd diarrhea, which is an acute watery diarrhea associated with mucosal lymphocytosis without crypt distortion, epithelial destruction or collagen deposition that can last for years and is also thought to be postinfectious.[2] Some patients with microscopic colitis also respond to antimicrobial treatment. Studies comparing the prevalence of the disease in developing countries as compared to developed countries may shed more light on the possibility of a postinfectious etiology.

Some drugs, including histamine-2 receptor blockers,[13] carbamazepine, simvastatin, flutamide and ticlopidine,[5] have been implicated as possible causes, though evidence supporting this is little. In particular, a causal relationship between non-steroidal anti-inflammatory drugs (NSAIDs) and microscopic colitis has been proposed by different studies, with the link thought to be more significant with collagenous colitis.[1,2] Some patients have shown improvement by discontinuing NSAIDs.[14,15] There have been, however, a considerable number of studies debunking this association.[5,8] It has been suggested that NSAIDs use in patients with microscopic colitis may actually be for the relief of arthralgia associated with this condition, implying that the disease was already present before the drug was commenced.[2]

Finally, there is the possibility that the features of microscopic colitis represent the fore end of the spectrum of IBD. There are reports of patients who progressed from microscopic colitis to IBD[16,17] and also of patients with IBD developing the characteristic histological features of microscopic colitis.[2,18] There is good evidence that a number of histological features seen in IBD could be seen in microscopic colitis. In one study,[19] 44% of 79 collagenous colitis cases showed Paneth cell metaplasia and a mild crypt architectural irregularity. These are features typical of IBD. These features are also occasionally seen in lymphocytic colitis, though to a lesser degree.

Histopathology

The most striking histological feature of microscopic colitis is an intraepithelial lymphocytosis on a background of lamina propria chronic inflammation of lymphocytic and plasma cells. The intraepithelial lymphocytosis is more pronounced in the surface lining epithelium than the crypts. Based on the presence or otherwise of a thickened subepithelial collagen band in the histological picture, two distinct subtypes of microscopic colitis, collagenous colitis and lymphocytic colitis, are recognized (Figures 1 and 2). These two differ in that the subepithelial collagen band (normally 5–7 μm) is abnormally thickened in the collagenous type ranging from 10–80 μm. Intraepithelial lymphocytosis is more marked in the lymphocytic type, with more than 10 lymphocytes for every 100 epithelial cells (normal is <5/100). However, it would be appropriate to say that there is a spectrum between these two subtypes in which there is a pure lymphocytic subtype with intraepithelial lymphocytosis and lamina propria inflammation and a pure collagenous having the collagenous band and lamina propria inflammation without significant intraepithelial lymphocytosis. Between these extremes is the mixed microscopic colitis with both thickening of the collagenous plate and intraepithelial lymphocytosis. No conclusive long-term follow-up study has shown a definite transformation from one type to another, but current view holds that this probably does not occur.[3]

Some other histological findings have been noted in microscopic colitis. One is of patients whose biopsies show an inflammatory infiltrate in the lamina propria without a collagen band or intraepithelial lymphocytes.[2] Another is the newly described microscopic colitis with giant cells,[20] but the existence of this entity has been challenged.[21] It has been observed and well-documented that eosinophils and neutrophils can also infiltrate the lamina propria in cases of microscopic colitis.[22-24] The presence of neutrophils does not negate the diagnosis of microscopic colitis as initially thought as long as the other histological and clinical features support the diagnosis.

In collagenous colitis, there are qualitative changes in the collagen band in addition to the thickness of >7 μm. These include entrapment of red blood cells and inflammatory cells and a ragged inferior edge. Most times, the epithelium above this band is degenerate and sloughed off. The collagen band is often discontinuous and more pronounced in the right colon. In contrast, the intraepithelial lymphocytosis is often continuous throughout the colon and rectum.

Pathophysiology of Diarrhea in Microscopic Colitis

Diarrhea in microscopic colitis is essentially of a secretory nature and, in the collagenous type, there is an additional malabsorptive cofactor due to the collagenous bands.[25] One study suggests that eosinophils, which may be markedly increased in collagenous colitis, are responsible for an excessive production of transforming growth factor (TGF)-beta 1, which causes collagen accumulation beneath the epithelium.[26]

It is evident that luminal nitric oxide is greatly increased in both collagenous and lymphocytic colitis. The strongly elevated expression of inducible nitric oxide synthase (iNOS) on colonic surface epithelium is responsible for this.[27,28] There is, therefore, a net secretion of fluid into the lumen. There is a shift of net flux of chloride from absorption to active secretion. The slightly impaired epithelium also promotes a passive back leak of ions and water into the intestinal lumen.[19]

Clinical Features

Microscopic colitis is characterized by chronic or intermittent watery diarrhea of varying severity. Abdominal pain and mild weight loss have been reported in many patients.[29,30] Incontinence, urgency and flatulence may also be seen. Dehydration is a rare occurrence. The presence of significant fever, vomiting or hematochezia should raise the possibility of an alternative diagnosis, as features of colitis by history, clinical examination or stool analyses are absent. Steatorrhea is quite uncommon except in patients with underlying villous atrophy, leading to malabsorption of fat. There is no macroscopic abnormality seen at colonoscopy.

Features of associated autoimmune diseases , of which arthralgia is most common, could also occur. Patients may have been on long-term NSAIDs use, and the inflammatory changes brought about by these drugs in the colonic mucosa may influence diagnosis at endoscopy of overt inflammatory bowel disease.[2]

The natural history of microscopic colitis is variable, and severity of the diarrhea usually correlates with the degree of mucosal inflammation on histology. Spontaneous resolution has been reported in some cases and is a more common occurrence in the lymphocytic type.[31]

Management

Diagnosis of microscopic colitis can only be made by colonoscopy and biopsy histology. It should be performed in all patients with unexplained chronic watery diarrhea. Discontinuing the use of NSAIDs, caffeine, alcohol, dairy products and any other agents that may worsen diarrhea is a first step in management of patients. Nonspecific antidiarrheal drugs, such as loperamide, are usually the first-line drugs and are often effective. Bismuth subsalicylate is beneficial if the former agents are unsuccessful.[32,33]

When BAM is thought to be the underlying condition, cholestyramine is beneficial.[1,2] The aminosalicylates, such as mesalazine and sulfasalazine, also have proven efficacy.[3,4] Corticosteroids, like budesonide, are recommended for patients who are refractory to the aminosalicylates after alternative diagnoses have been excluded. Budesonide is highly effective and well-tolerated, but there is a high risk of relapse after discontinuing treatment.[32] Steroid refractory or dependent patients may benefit from immune modifiers, such as azathioprine.[2] Antibiotics may be beneficial in some patients, although diarrhea tends to recur after discontinuing the drug.[35] Other treatments reported to be of potential benefit include octreotide[36] and other immune modifiers, such as methotrexate or cyclosporin.[37]

Surgical intervention is rarely necessary but, as mentioned earlier, in some recalcitrant cases, ileostomies with or without a colectomy or an ileal pouch anal anastomosis have resolved symptoms and histologic features.[38]

CONCLUSION

Microscopic colitis syndrome is a fairly common cause of chronic watery diarrhea in developed countries where it has been looked for. In developing countries, such as Nigeria, almost every diarrhea case is assigned to infective causes, but is this always the case? With increasing availability of endoscopic facilities, we want to advocate that clinicians should include microscopic colitis in their differential diagnosis of patients with chronic watery diarrhea, especially in middle-aged/elderly females. The keys to diagnosis are remembering to perform endoscopy and biopsy in the normal-appearing colonic mucosa in patients presenting with chronic watery diarrhea and having a skilled pathologist to report the slides. If this is done, all diarrhea may not be infective after all.

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