# Microscopic Cholitis, An Increasingly Frequent Diagnosis

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**Abstract**

Microscopic colitis currently includes three subgroups. The classical ones are lymphocytic colitis and collagenous colitis which are distinguished histologically by the presence or absence of subepithelial thickening. The third subgroup is Incomplete Microscopic Colitis which includes patients who do not meet the classical criteria for Microscopic colitis but who have similar histological changes. Although prevalence and incidence are low, recent studies show that it has become slightly more common. Causative factors mentioned include immunological and infectious issue, and it has been related to some medications and to cigarette smoking. Clinically it is characterized by watery diarrhea which sometimes oscillate with periods of constipation. The three subgroups have similar clinical manifestations, so their diagnoses are usually histological. Colonoscopy with biopsy is the diagnostic pillar, and should be complemented by complete blood count, a parasitological examination, immunological studies (antinuclear antibodies, IgG) and thyroid function. Treatment is based on the suspension of related medications, changes in eating habits, and the use of medications such as steroids, bismuth subsalicylate, 5-ASA and cholestyramine. Improvement is achieved in the vast majority of patients, and recurrences are rare.

**Keywords**

Colitis, microscopic, lymphocytic, collagenase, colonoscopy, biopsies.

## INTRODUCTION

The first publication of a case of microscopic colitis is attributed to Lindstrom who reported the case of a patient with chronic watery diarrhea in 1976. Colon biopsies evidenced a significant deposition of subepithelial collagen. (1) In 1980, Read was the first to use the term microscopic colitis (MC) to refer to patients with chronic diarrhea whose enema and colonoscopy studies were mostly normal but whose biopsies showed histological alterations. (2) In 1993, the two now-classic MC subtypes, lymphocytic colitis (LC) and collagenous colitis (CC), were proposed. They are clinically similar but histologically distinguished by the presence or absence of a band of collagen indicating subepithelial thickening. (3-5) In recent decades there have been studies of patients who do not meet the classic criteria of MC, but who present similar histological changes. Now, the term "incomplete microscopic colitis (MIC)" has become universally accepted. (6)

In 2001, in the United States, the incidence of LC was 64 cases per 100,000 people and that of CC was 36 cases per 100,000 people. Prevalence was 2% to 16% in patients with chronic diarrhea. (7) There are only a few studies of microscopic colitis in Latin America, and they were done at the beginning of the last decade. Prevalence of up to 9% was found in patients with chronic diarrhea. (8-10) In the last decade, topical reviews have presented a slight increase in this pathology. (5, 11-13) We have no recent figures for this disease in Colombia.

 

## DISCUSSION

MC is a generic term which includes two main diseases either of which can be chronic or recurrent. Both have similar histopathological characteristics that include superficial epithelial lesions (mild in LC, and moderate to severe in CC), mild or absent architectural distortion in crypts, and occasional focal alterations such as cryptitis and cell metaplasia similar to those observed in inflammatory bowel disease (IBD). (6, 14)

LC is characterized by higher than normal quantities of intraepithelial lymphocytes (IEL) (More than 20 lymphocytes/100 epithelial cells) in the superficial epithelium and in the epithelium of the crypts, normal mucosal architecture with damage in the superficial epithelium, mixed mononuclear inflammatory infiltrate (plasmocytes, lymphocytes), small numbers of eosinophils in the lamina propria, and absence of a subepithelial collagen deposit. (11, 15, 16) CC is defined by a band of thickened subepithelial collagen measuring more than 10 μm thick. Measuring this band is costly and not practical, so the key to diagnosis is the abnormal distribution of the band as well as its the thickness. The band extends within the lamina propria and wraps and trap capillaries and fibroblasts. (11, 15, 17)

MC was initially considered a rare disease, and until 1992 only 446 cases of CC had been reported (18). In recent years, a greater number of studies assessing incidence and prevalence have been done, and they have found important geographical variations. According to a metaanalysis, the 2015 incidence of CC was 4.14/100,000 person-years (95% CI 2.89-5.4) and that of LC was 4.85/100,000 person-years (95% CI 3.45-6.25). (19) According to various studies, MC is more common in women, with a male: female ratio that varies from 1: 4 to 1: 9. (14, 15) CC occurs more frequently in people over 50 years old, although it can occur at any age, while LC occurs in younger patients. (20, 21)

## ETIOLOGY

Most commonly, theories about MC attribute it to activation of the immune system of the colonic mucosa in response to exposure to luminal antigenic factors such as toxins, infections, bile acids and drugs. (22) The existence of a human leukocyte antigen has recently been demonstrated. It is directly related to inflammatory mechanisms of the colonic mucosa. (23, 24)

The possibility of an infectious etiology of MC is based on several clinical observations including development of MC after a Clostridium difficile infection and the presence of a greater number of antibodies against Yersinia enterocolitis and other infectious agents in the serum of patients' with CC than in control subjects. Nevertheless, no single pathogen related to MC has yet been identified. (25-27)

The theory that bile acids may affect the development of MC is based on experimental animal models of the disease in which diarrhea frequently occurs due to malabsorption of bile acid after an ileal resection plus the observation of malabsorption in a significant proportion of patients with MC. (22, 28-32). Nevertheless, there is no evidence of an etiological role of bile acids in MC, and no remission of histological lesions has been observed in patients treated with bile acid sequestering agents. (33)

Since the 1990s, continuous use of some medications (Table 1) has been considered to be a cause or precipitant of MC. (34, 35) The MC management guidelines of the American Institute of Gastroenterology include nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, proton pump inhibitors (PPIs), selective serotonin reuptake inhibitors (SSRIs), clozapine and acarbose in this category. However, the purported degree of the cause and effect relationship varies widely in the various reports. (32, 36, 37)

**Table 1.** Medications associated with microscopic colitis

| | |
|---|---|
| **Cardiovascular** | β Blockers |
| | Vinburnine (vasodilator) |
| | Lisinopril |
| | Simvastatin |
| | Angiotensin II receptor antagonists |
| **Antiplatelet agents** | Ticlopidine |
| | Aspirin |
| **Centrally acting analgesics** | Paroxetine |
| | Sertraline |
| | Carbamazepine |
| **Gastrointestinal** | Proton Pump Inhibitors |
| | Ranitidine |
| **Others** | NSAIDs |
| | Ferro-Tardyferon (iron supplement) |
| | Bisphosphonates |
| | Flutamide |

Smoking is the best documented environmental risk factor for MC. Several studies have shown that smoking is associated with CC and LC. The occurrence of the disease has been observed 10 years earlier in a smoking group than in a non-smoking group, but smoking did not influence the subsequent course of the disease. Alcohol intake has also been implicated as a contributing factor to the genesis of MC. (38)

## DIAGNOSIS

MC is clinically characterized by chronic watery diarrhea without blood. It can be moderate or severe with urgent defecation, but cases of asymptomatic patients with MC

histopathology have been found. Almost half of patients with MC also meet criteria for irritable bowel syndrome (IBS) such as abdominal pain, bloating, and periods of constipation. (39) Since the clinical manifestations of LC and CC are very similar, it is not possible to clinically differentiate between them. (13)

Generally, the onset of symptoms is gradual, but in 25% to 40% of cases it is sudden. Most patients have a single episode. Remission occurs spontaneously in up to 10% of cases. About 30% of patients suffer chronic recurrences while up to 7% of patients are refractory to treatment. (40, 41)

Diagnosis should include a complete blood count, erythrocyte sedimentation rate, blood chemistry, stool cultures, parasitological examinations, thyroid test and tests for antinuclear antibodies and IgG. Recently, calprotectin measurement has also been recommended. The most important diagnostic study is a colonoscopy. Although up to 80% of cases look normal, biopsy samples must be taken from all segments of the colon. Histology will ultimately determine a diagnosis of microscopic colitis. (13, 42)

## TREATMENT

Initial treatment should start with evaluation of medications related to MC for suspension or modification of dosage. Also, suspension of caffeine and lactose may have some benefits. Spontaneous remission occurs in about 30% of patients, so they can be treated symptomatically with loperamide. The medications that have been used in the treatment of MC are steroids (budesonide and prednisone), bismuth subsalicylate, 5-ASA and cholestyramine (a bile acid binding agent). Of these, only budesonide has randomized trials that demonstrate that they effectively induce and maintain clinical remission for both LC and CC. Budesonide is a locally active corticosteroid which is well tolerated and has little systemic absorption. The recommended dose is 9 mg/day during the first month, with a decrease to 6 mg/day in the second month and to and 3 mg/day in the third month. Some studies suggest the use of immunosuppressants, such as azathioprine and antitumor necrosis factor agents, especially for refractory cases. (42-44)

The prognosis of MC is very good with adequate therapy and spontaneous remission is fairly common. Once clinical remission is achieved, the course is benign and most patients remain asymptomatic in the long term. Recurrences occur in less than 30% of patients but normally respond to treatment. Very few cases have reportedly required surgical treatment (ileostomy or total proctocolectomy). MC has not been associated with any significant mortality and there seems to be no potential of malignancy. (13, 45)

## CONCLUSIONS

Diagnoses of both lymphocytic colitis and collagenase colitis have become increasingly common. These diagnoses should always be suspected in patients with chronic diarrhea for whom performance of a colonoscopy with serial biopsy will facilitate histological diagnosis. Together with a clinical examination and blood tests, histology is necessary for diagnosis. There is no consensus regarding etiology or diagnostic criteria, but treatment generally achieves symptomatic remission. Nevertheless, relapses occur in almost a third of these patients. This pathology is reported more and more frequently and merits study to establish its true prevalence here in Colombia.

### Conflicts of Interest

The authors have no conflicts of interest related to this article.


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The authors.


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