International Journal of Healthcare Sciences ISSN 2348-5728 (Online)
Vol. 4, Issue 2, pp: (1354-1361), Month: October 2016 - March 2017, Available at: www.researchpublish.com

Microscopic Colitis, Etiology, Diagnosis and Treatment Approaches: An Overview

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Abstract: **This study was aimed to focus in discussing the most important aspects of Microscopic Colitis (MC), Therefore reviewing the evidence on the causes, diagnosis and treatment of MC was performed. We conducted search of the literature of published studies discussing Microscopic Colitis (MC) by searching following database; PubMed/Midline, and Embase, using the following MeSH terms: "Microscopic colitis, collagenous colitis, lymphocytic colitis combined with causes, diagnosis, and treatment". Additional reports were found searching the reference list of identified studies. This search was restricted to English language with human subject's literature only. MC is a relatively typical reason for chronic diarrhea, especially in older patients. In some populations, the incidence of MC has stabilized after a period of substantial boost, while in others the occurrence continues to rise. Colon biopsies are required for medical diagnosis and needs to be thought about in any patient undergoing colonoscopy to evaluate chronic watery diarrhea. The two subtypes of MC, collagenous and lymphocytic colitis, are similar histologically and clinically and appear to react similarly to numerous medical therapies. Although there are fairly couple of regulated trials of therapies for MC, the treatment technique presented here normally results in satisfactory control of symptoms, although maintenance therapy is often needed.**

Keywords: **Microscopic Colitis (MC), Etiology, Diagnosis and Treatment approaches.**

1. INTRODUCTION

Microscopic colitis (MC) is a typical cause of chronic, watery non-bloody diarrhea. Approximately 10% -20% of chronic diarrhea is believed to be secondary to MC [(1)]. MC most frequently presents in older adults, with the average age at diagnosis usually between 50 and 70 years [(2,3,4)]. A Canadian research study discovered that patients aged > 65 years were 5.6 times most likely to be detected with MC than younger persons [(5)]. A broad age variety has been reported, consisting of children, and in one study, 25% of patients were aged < 45 years [(3, 6,7)]. MC is a reasonably common fi nding in patients undergoing colonoscopy for assessment of chronic watery diarrhea, being present in 8 - 16% of such patients [(2,8,9)]. In the elderly, this proportion is even higher [(2)].

Collagenous colitis (CC) and lymphocytic colitis (LC) are two subtypes of MC that have similar discussions. Histologically, nevertheless, they have distinct qualities. It is still a debate whether CC and LC are just truly one disease under MC, or if they should be considered as two unique diseases that share some functions. An evaluation of 226 research studies on CC and LC found little to no differences in epidemiology, medical presentation, risk factors, and reaction to treatment [(9,10)].

The etiology of microscopic colitis (MC) is unknown. There is a strong association with autoimmune disorders, cigarette smoking, and medications, such as non-steroidal anti-inflammatory drugs, proton pump inhibitors, and selective serotonin reuptake inhibitors [(9,10)].

MC usually affects patients in their 50-60 s and happens more often in ladies than males. The medical diagnosis is made by both clinical history and endoscopic biopsies. While chronic watery diarrhea is the most typical symptom, some patients with MC might also experience abdominal pain, fecal incontinence, and/or weight loss. Colonoscopy normally reveals typical colonic mucosa but colonic biopsy shows traditional histological features: > 20 intraepithelial lymphocytes per 100 epithelial cells in LC and 10-20 μm of a thickened subepithelial collagen band in CC (**Figure 1**) [(9)].

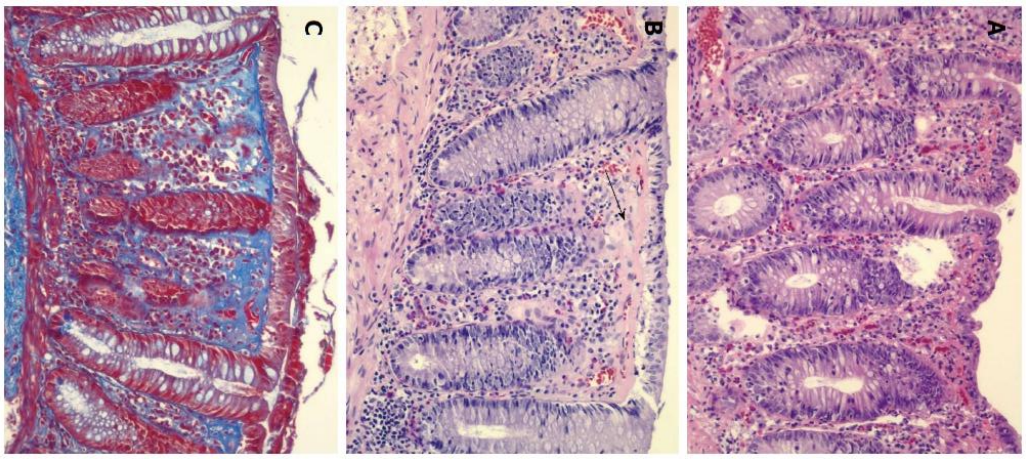

Figure 1: Colonic biopsy. A: Lymphocytic colitis, B: Collagenous colitis, C: Collagenous colitis [9]

This study was aimed to focus in discussing the most important aspects of Microscopic Colitis (MC), Therefore reviewing the evidence on the causes, diagnosis and treatment of MC was performed.

2. METHODOLOGY

We conducted search of the literature of published studies discussing Microscopic Colitis (MC) by searching following database; PubMed/Midline, and Embase, using the following MeSH terms: "Microscopic colitis, collagenous colitis, lymphocytic colitis combined with causes, diagnosis, and treatment". Additional reports were found searching the reference list of identified studies. This search was restricted to English language with human subject's literature only.

3. RESULTS

✓ ***ETIOLOGY of MC:***

Although the exact etiology of MC is unidentified, there are multiple research studies in the literature that suggest that MC may be immunologically mediated, because of its strong association with other autoimmune diseases. Population studies expose that around 30% of the patients with MC were found to have other concomitant autoimmune conditions [11] such as celiac disease (12.9%) and autoimmune thyroid disease (10.3%), Sjögren syndrome (3.4%), diabetes mellitus (1.7%), and other autoimmune conditions of the skin and joints (6.0%) [12]. Among all autoimmune disorders, celiac disease appears to have the strongest association. Patients with MC have a 50 to 70-fold increased risk of having celiac disease also compared with the basic population [13,14].

There is a strong association with autoimmune conditions, such as celiac disease, polyarthritis, and thyroid conditions (**Table 1**) [15]. Up to twenty to 60% of patients with LC and 17%-40% of patients with CC have autoimmune disease [15]. In fact, histological functions of MC in the colon exist in 30% of patients with celiac disease. While no specific genetic mutations have been determined as direct cause of MC, some studies have discovered typical genetic abnormalities. There is an increased occurrence of human leukocyte antigen (HLA) DR3 DQ2 allele in patients with MC, and metalloproteinase 9 gene variations have been associated with CC [16].

Table 1: Factors associated with microscopic colitis [15]

Autoimmune disorder	
✓	Type 1 diabetes
✓	Thyroid disorders
✓	Rheumatoid Arthritis
✓	Celiac disease
Other factors & Medications (Table 2)	
✓	Smoking

Smoking cigarettes is a risk factor for MC (**Table1**) [15]. In a prospective, case-control research study conducted from 2007 to 2010 in Spain including 255 patients, smoking was significantly related to LC and CC (OR = 3.8 in LC, OR = 2.4 in CC) [17]. Swedish research study conducted by Vigren et al (18) also showed that cigarette smoking is connected with

CC. Thirty-seven percent of patients with CC were cigarette smokers as compared to only 17% of patients in the control group (OR = 2.95). Subgroup analysis revealed that the association of smoking cigarettes with CC was most noteworthy in the age 16-44; 75% of patients in this age were cigarette smokers as compared with 15% in the control group (odd ratio: 16.54).

There is also a strong association of MC with making use of certain medications (**Table 2**) [11]. Whether these medications activated the inflammatory procedure is still an ongoing debate as all data offered have actually been retrospective. Using proton pump inhibitors (PPIs) (lansoprazole), low dose aspirin, β-blockers, angiotensin II receptor antagonists, nonsteroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRI), statins, and bisphosphonates have actually all been related to MC [11,17,19]. Remarkably, there was a greater proportion of patients with CC who took NSAIDs and PPI on a chronic basis than exactly what was discovered within the LC group. There was likewise a predominance of sertraline (SSRI) usage by LC patients. Because of these strong associations, it is advised that a crucial part of the assessment must concentrate on identifying each medication taken by the patient and ceasing medications that could possibly be getting worse the disease [11,17,19].

Table 2: Medications which have been associated with microscopic colitis [11]

Cardiovascular drugs
• Beta blockers
• Vinburnine (vasodilator)
• Lisinopril
• Simvastatin
• Angiotensin II receptor antagonist
Anti-platelet drugs
list-behavior=unordered prefix-word= mark-type=disc
• Ticlopidine
• Aspirin
Gastrointestinal drugs
• Proton pump inhibitors
• Ranitidine
• Acarbose
Centrally-acting drugs
• Paroxetine
• Sertraline
• Carbamazepine
• Madopar
Miscellaneous
• NSAIDs
• Tardyferon (iron supplementation)
• Bisphosphonates
• Flutamide

✓ ***CLINICAL FEATURES of MC:***

The most common symptom in patients with tiny colitis (MC) is chronic or intermittent watery diarrhea, varying in severity from mild to serious with dehydration and electrolyte irregularities. Other signs are typically present, consisting of stomach pain, weight reduction, and arthralgias, each present in approximately half of patients. Weight-loss is normally moderate, but when extreme it must raise the possibility of alternate diagnoses such as celiac disease (discussed listed below). Lifestyle is diminished to a similar degree as other chronic bowel conditions such as inflammatory bowel disease, influenced by gastrointestinal symptoms consisting of the degree of diarrhea, abdominal pain, urgency, and fecal incontinence [20,21,22] along with systemic signs such as fatigue, arthralgias, and myalgias [22]. The signs of MC are non-specific, and numerous patients fulfill the diagnostic requirements for irritable bowel syndrome [23,24,25]. For that reason, these requirements are not specifi c for irritable bowel syndrome, and colon biopsies are therefore required to definitively differentiate MC from the much more common irritable bowel syndrome. The presence or lack of certain scientific

features, such as older age, female sex, use of certain medications or current initiation of any medication, weight loss, nocturnal stools, and shorter period of diarrhea, may recognize patients at higher or lower risk of having MC [26,27], and in lower-risk patients, possibly empirical treatment with antidiarrheal medications might be pursued before devoting a patient to the expense of a colonoscopy or mucosal biopsy [27]. MC has 2 main subtypes, collagenous colitis and lymphocytic colitis, which are very comparable medically and epidemiologically, with the main difference being histological as gone over listed below. With the clinical and histological overlap between these conditions, reports of patients transitioning between subtypes or having findings of both on biopsies from a single colonoscopy and comparable response to treatment, it is uncertain whether lymphocytic and collagenous colitis are two different entities or part of a single disorder [27].

✓ ***DIAGNOSIS of MC:***

Microscopic evaluation of colonic mucosal biopsies is currently the only methods of confirming the medical diagnosis of MC. Just non-specific small laboratory problems are discovered. Stool tests expose no pathological bacteria. Barium enema and colonoscopy are typically regular, although subtle non-specific modifications such as oedema, erythema or unusual vascular pattern are seen in as much as 30% of the cases [28,29]. The medical diagnosis of MC depends on adequate histological assessment through lower endoscopy. Random consecutive biopsies throughout the colon should be performed, as the gross appearance of the colon is usually plain, though sometimes it can reveal mild edema (**Figure 1**) [30]. Although there is some belief that versatile sigmoidoscopy must be a first-line test and might supply a diagnosis in bulk of the cases, 23% of the patients will have MC that is limited to the ideal side and the medical diagnosis can ultimately be missed out on with sigmoidoscopy alone [30]. MC might present with a patchy circulation which can cause misdiagnosis in 40% of the patients who have biopsies done just in the rectosigmoid area [31]. For that reason, it is beneficial to perform a full colonoscopy to eliminate other differential diagnoses, such as inflammatory bowel disease and malignancy. This thoroughness is specifically essential for patients who have not had a current colonoscopy [31].

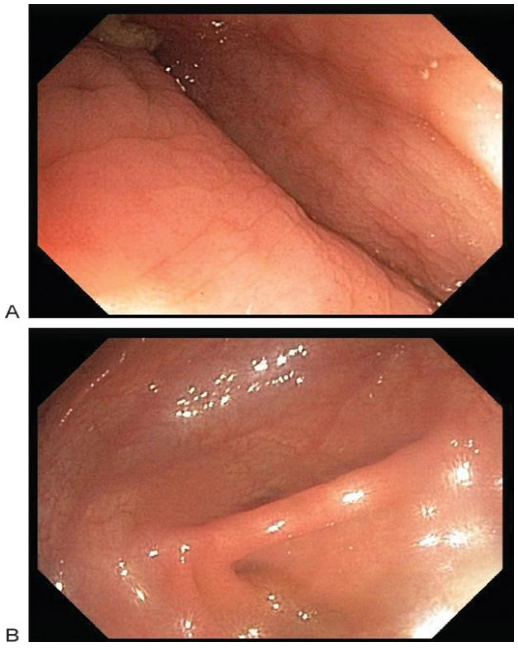

Figure 2: Endoscopic photos of a pediatric patient with suspected microscopic colitis. (A) Ascending colon image demonstrates some mild mucosal edema, (B) normal appearing cecum. [30]

HISTOPATHOLOGY for MC DIAGNOSIS:

The diagnosis of the various subtypes of MC relies on specific microscopic modifications seen in colonic mucosal biopsies [32]. In CC the most characteristic function is a thickening of the subepithelial collagen layer (SCL) underneath the basal membrane (**Figure 3**). The collagen layer is most popular in proximal colon and may be absent in biopsies from sigmoid colon and anus stressing the value of obtaining biopsies from the proximal colon when diagnosing CC [33]. Usually, the histopathological changes in CC are restricted to the large bowel, but a thickened collagen layer has infrequently been reported in the stomach, duodenum or terminal ileum. Cryptitis or Paneth cell metaplasia might be seen and does not dismiss a diagnosis of MC [34].

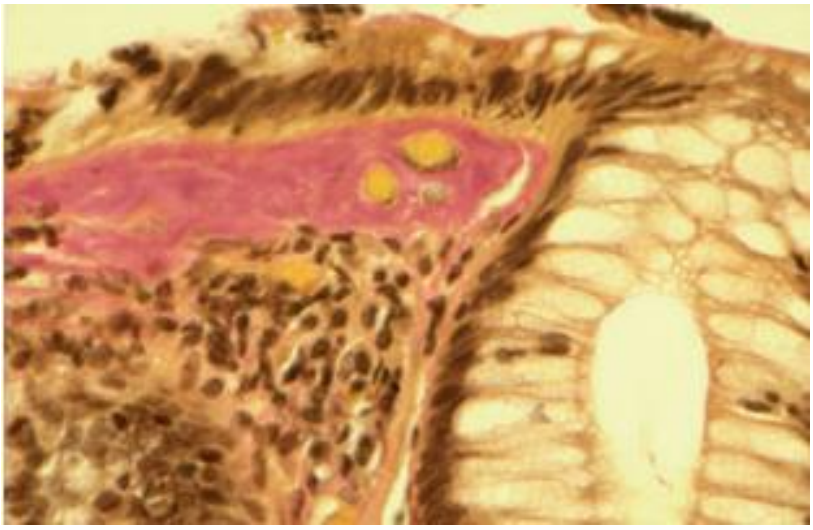

Figure 2: Biopsy from colon showing typical findings of collagenous colitis.

The histology found in MC (both CC and LC) shows lymphocytic infiltration of the lamina propria and the epithelium. CC differs from LC because there is marked thickening of the subepithelial layer (**Figure 1**). Intraepithelial lymphocytosis (IEL) can be found in both CC and LC, however is more pronounced in LC: ≥ 20 intraepithelial lymphocytes per 100 surface area epithelial cells are needed to make the diagnosis (**Table 3**) [35].

Table 3: Histological features of collagenous colitis and lymphocytic colitis

	Collagenous colitis	**Lymphocytic colitis**
Lamina propria	Lymphocytic infiltration of the lamina propria with little or no damage in mucosal architecture	
Subepithelial layer	Thickening of subepithelial layer > 10 µm	Subepithelial collagen layer not present or < 10 µm
Intraepithelial	Intraepithelial lymphocytosis could be present, but necessary for the diagnosis	Intraepithelial lymphocytosis (≥ 20 IEL per 100 surface epithelial cells)

✓ ***TREATMENT APPROCHES for MC:***

It is mandatory to omit inflammation secondary to another gastrointestinal disease, drug treatment or infection [36]. When secondary MC is the case, the MC needs to be regarded as a part of the initial disease, and the original disease or condition need to be dealt with. When MC was developed after such administration [19], withdrawal of toxic representatives and drugs is mandatory. As a number of these patients are present or past smokers, and older, intestinal ischemia needs to be considered [37]. Smoking abstaining should be encouraged, as past smoking cigarettes is related to short-term, and not persistent, MC [37]. After exemption of secondary MC, the medical diagnosis of real, primary MC can be set [38]. The primary goal in the treatment of MC is to accomplish scientific remission and improve the patient's lifestyle [39]. The secondary aim is maintenance of medical remission [40].

Corticosteroids therapy:

A multicentered, randomized controlled trial of 92 patients comparing budesonide, mesalamine, and placebo for MC showed that budesonide was more effective than mesalamine (80% vs 44%, P = 0.0035) and placebo (80% vs 59.5%, P = 0.072) in inducing scientific remission at 8 wk [41]. Histological remission rate was the highest in patients treated with budesonide (87%) as compared to mesalamine (45%) and placebo (50%) (41). The rates of negative events were similar amongst budesonide, placebo, and mesalamine groups (47%, 68%, 54%) [41]. The most regular adverse events were nasopharyngitis, headaches, and dyspepsia.

Although budesonide has actually been shown to rapidly cause scientific response, regression happens often after discontinuation of budesonide. Fall back rate is estimated to be as high as 26% -82%. Mean time to regression after stopping active treatment was 39 d [42]. Patients with baseline diarrhea frequency > 5 daily (HR = 1.67), duration of diarrhea > 12 mo (HR = 1.82), and lack of budesonide maintenance treatment (HR = 2.73) were found to be at greatest risk for regression [43]. Other factors associated with regression were advanced age (P = 0.047), a higher variety of

defecation each day at randomization after induction period (P = 0.009), and a greater variety of bowel movements daily at standard (P = 0.041) [44].

Diverting ileostomy:

There are case reports of patients effectively undergoing colectomy or diverting ileostomy for refractory and extreme MC. When bowel extension is brought back, the observational pattern from these case reports is that both signs and histology improve after surgery however can recur.

In one case report, a 33-year-old patient with 5 years of chronic diarrhea from CC not responsive to Asacol and prednisone underwent overall protocolectomy followed by ileal pouch anal anastomosis. At 2-year follow-up, she was having multiple defecation each day but diarrhea resolved and she was able to go back to full-time task [45].

In another, a 59-year-old patient with CC who formerly stopped working loperamide, prednisolone, budesonide, 5-aminosalicylic acid, cholestyramine, and norfloxacin went through loop ileostomy [46]. 2 to 4 mo. after loop ileostomy, colonic biopsies revealed resolution of subepithelial damage, but her medical course was complicated by Clostridium difficile infection and issues with the stoma. One year later, the patient enhanced medically and loop ileostomy was closed. The patient began budesonide 6mg daily after bowel restoration however relapsed with signs of CC.

In a series of patients, nine patients with MC refractory to medical treatment (sulfasalazine, mepacrine, corticosteroids, mesalamine, cholestyramine, loperamide, metronidazole) went through ileostomy in between 1981-1992 [47]. All patients experienced clinical and histological remission. The ileostomy was taken down in 5 patients after a diversion period of 4-15 mo. Diarrhea repeated in 4 out of 5 of these patients and 3 of them underwent extra surgery.

4. CONCLUSION

MC is a relatively typical reason for chronic diarrhea, especially in older patients. In some populations, the incidence of MC has stabilized after a period of substantial boost, while in others the occurrence continues to rise. Colon biopsies are required for medical diagnosis and needs to be thought about in any patient undergoing colonoscopy to evaluate chronic watery diarrhea. The two subtypes of MC, collagenous and lymphocytic colitis, are similar histologically and clinically and appear to react similarly to numerous medical therapies. Although there are fairly couple of regulated trials of therapies for MC, the treatment technique presented here normally results in satisfactory control of symptoms, although maintenance therapy is often needed.

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