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Microscopic colitis: considerations for gastroenterologists, endoscopists, and pathologists

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HIGLIGHTS

- Diagnosis of microscopic colitis necessitates effective communication among gastroenterologists, endoscopists, and pathologists.
- The gastroenterologist should refer every patient with chronic watery diarrhea to perform a colonoscopy in spite of the benign course of the disease and the absence of alarm symptoms.
- The endoscopist should take 2 or 3 biopsy samples of the colonic mucosa from the right and left colon, put in separate recipients, despite that the mucosa looked macroscopically normal.
- The pathologist should be encouraged to use objective histological criteria to make the diagnosis.

ABSTRACT – Microscopic colitis is a chronic inflammatory bowel disease characterized by non-bloody diarrhea that can range from mild to severe. It is difficult to attribute up to 10–20% of chronic diarrhea to microscopic colitis. The three determinants factors of the diagnosis are characteristic clinical symptoms, normal endoscopic picture of the colon, and pathognomonic histological picture. This manuscript aimed to update considerations and recommendations for professionals involved (gastroenterologist, endoscopists and pathologist) in the diagnosis of MC. In addition, a short recommendation about treatment.

Keywords – Microscopic colitis; diagnosis; pathology; colonoscopy.

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INTRODUCTION

Microscopic colitis (MC) is a chronic inflammatory bowel disease characterized by non-bloody diarrhea that can range from mild to severe. It is difficult to attribute up to 10–20% of chronic diarrhea to MC. The disorder is characterized by normal (or almost normal) appearance of the colon and distinct histological abnormalities that detect three subtypes: collagenous colitis (CC), lymphocytic colitis (LC), and incomplete microscopic colitis (IC)[1-3].The incidence of MC is estimated to be 11.4 cases per 100,000 person-years, with a prevalence of 119.0 per 100.000 persons. In the case of chronic watery diarrhea, the reported frequency was 12.8%[1,4]. Moreover, geographical differences can exist.

MC has been reported in diverse populations from various continents, demonstrating that, despite genetic and environmental differences, similar immunological evolution allowed the disorder to emerge[5]. In Brazil, there are few publications on this disorder[6,7], and the etiology is unknown[1,8]. The pathogenesis of MC is complex and multifactorial, with luminal factors, immune dysregulation, and genetic predisposition all playing a role[1,9,10]. MC is a disease that is becoming more widely recognized, with a symptom burden that impairs health-related quality of life and that significantly increases after treatment[1-3].

The three determinants of the diagnosis are characteristic clinical symptoms, normal endoscopic picture of the colon, and pathognomonic histological picture[8,10,11]. This manuscript aimed to update considerations and recommendations for professionals involved in the diagnosis of MC.

Considerations for gastroenterologists

MC can affect people of all ages, but the risk of developing CC or LC is higher in middle-aged patients, who are more likely to be female than male. There are no significant differences in clinical presentation between CC and LC; however, women outnumber men in CC[1,2,12]. Moreover, chronic watery non-bloody diarrhea (84–100%), acute onset or persisting for 6 months prior to MC diagnosis (43%), six to seven movements per day, and nocturnal stools are the most common clinical symptoms. Further, fecal urgency (55%), nocturnal stools (35.3%), and fecal incontinence (26.3%) are common concomitant symptoms. Abdominal pain, bloating, and weight loss can all be symptoms. Depending on the severity of the disease or concomitant comorbidities, patients with MC have a lower health-related quality of life[1,11].

The main associated risk factors and differential diagnosis in MC were shown in TABLE 1. Smoking is a risk factor for both LC and CC[13] as is the chronic or frequent use of drugs such as proton pump inhibitors (omeprazole, lansoprazole, rabeprazole), nonsteroidal anti-inflammatory drugs (diclofenac is more common), serotonin receptor blockers (duloxetine, sertraline), carbamazepine, statins, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers (olmesartan), and acarbose[1,3,10,14]. It is important to understand the interactions between medications, the onset of symptoms, and new medications. In addition, there is a strong association with autoimmune diseases, including polyarthritis, thyroid disorders, celiac disease, and type 1 diabetes mellitus: 60% in LC and 17–40% in CC[14]. Fedor et al.[15] discovered a link between allergic diseases and alimentary hypersensitivities. Due to the higher prevalence of CD in both types of MC (MC in patients with celiac disease is 6.7% and celiac disease in patients with MC is 7.7%), screening for CD is recommended[1,5,8,14]. The underlying mechanism of the link between MC and celiac disease remains unknown. Further, similar HLA complexes have been found to be involved in the development of both diseases, with an improves in the prevalence of HLA-DR3DQ2[5].

TABLE 1. Associated risk factors and differential diagnosis in patients with microscopic colitis.

Associated risk factors	
Demographic features	Middle-aged to older, female
Immunomediated diseases	Celiac disease, thyroid disorders, type 1 diabetes, rheumatoid arthritis, Sjogren syndrome, SLE
Drugs	NSAIs, serotonin reuptake inhibitors, statins, beta-blockers, proton pump inhibitors, beta-blockers
Lyfe style	Smoking
Differential diagnosis	
Infections	*Clostridioides*
Functional disorders	Irritable bowel syndrome with diarrhea
Inflammatory bowel disease	Crohn's disease, ulcerative colitis
Alimentary hypersensitivities	Peanut, soy, tomatoes, milk, egg, bananas, peach, oats

NSAIDs: nonsteroids anti-inflammatory drugs.

Given the overlap in symptoms between irritable bowel syndrome (IBS) and MC, differences in clinical history between patients with IBS and those with MC are extremely important. In IBS, the first occurrence is usually before the age of 50, with stool consistency varying from soft to hard, abdominal pain that is always present, discomfort, bloating, a sense of incomplete bowel evacuation, no fecal incontinence, and no weight loss[8]. In MC, on the other hand, the first occurrence is usually after the age of 50, with watery and soft stools during the day or at night, variable discomfort or abdominal pain, common incontinence, common weight loss, and concomitant autoimmune disease[8,11].

Specific tests can rule out conditions such as medication-induced diarrhea, intestinal malabsorptive disorders, small intestinal bacterial overgrowth, infection by *Clostridium difficile*, and inflammatory bowel disease (IBD)[3,14]. Fecal calprotectin, a biomarker for some intestinal disorders, is ineffective for excluding or monitoring MC unless other diseases with similar symptoms are ruled out[1,8,16].

In summary, the awareness of the involved physician in the diagnosis of MC is essential in order to avoid delay.

Recommendation: the physician, being aware of the differences between MC and other diseases, recommends colonoscopy and instructs the endoscopist to perform biopsies even if the mucosa appears normal macroscopically.

Considerations for endoscopists

Normal endoscopic findings are common in MC, as they are in other disorders, but clinical information and a suspected diagnosis are required[17]. In MC, macroscopically visible lesions or alterations were reported in 38.8% of cases, as in CC and LC, including isolated linear ulcerations, pseudo membrane, irregular vascular pattern, mucosal lacerations, and irregularities such as erythema, edema, and nodularity, but they are not specific[18]. Biopsies from the right and left colon are recommended for the diagnosis of MC, with 95–98% of cases demonstrating characteristic histologic changes of MC on both sides. Virine et al.[19] recommended taking two biopsies from the ascending and descending colons. On the other hand, Malik et al.[20] proposed three ascending colon biopsies and three descending colon biopsies. This method of collecting biopsy specimens has the potential to reduce endoscopy and histologic time examination without compromising diagnostic sensitivity[19]. Only biopsies from the left colon revealed a lower number of MC diagnoses. Moreover, biopsies taken solely from the rectum are insufficient[3].

Because the number of inflammatory cells in normal surface epithelium and lamina propria is higher in the right colon, these specimens should be sent in separate labeled containers[8,11]. Similarly, the normal collagenous band has been reported to be thicker in the sigmoid colon and rectum, with lower cellularity. This is especially important in borderline cases to assist the pathologist. If specimens from different sites of the colon are combined for putative cost-effectiveness, minor degrees of CC and LC might be overlooked[11].

Suzuki et al.[21] reported that colonoscopic examination with indigo carmine was useful in diagnosing MC. They found a diffuse mosaic pattern in five of ten cases of CC and three cases of LC. The chromoendoscopic findings were almost entirely consistent with the microscopic findings. The authors emphasized that biopsies could be limited to cases where chromoendoscopy shows clear mucosa changes, saving money and limiting the number of biopsies[21]. Koulaouzidis and Toth[22] proposed using advanced endoscopy to magnify white-light images with or without carmine spraying. Biopsies could be performed not only in areas of the colon that appear abnormal but as a standard one-sample per colonic segment[22]. In Brazil, Funari et al.[7] reported a case of CC with endoscopic changes enhanced by indigo carmine chromoendoscopy.

Recommendation: the endoscopists, detecting normal or mild abnormalities in the mucosa, takes biopsies and alerts the pathologist to the possibility of MC.

Considerations for pathologists

In hematoxylin-eosin (HE) slides, LC is defined by an increased number of intraepithelial lymphocytes (IELs) ≥20 per 100 surface epithelial cells, as well as an increased inflammatory infiltrate in the lamina propria and a collagenous band of normal thickness (<10 **µm**). For CC, in addition, a thickened subepithelial collagenous band ≥10 **µm** and ≥20 IELs, observed in HE, is required[17-19].

Patients with appropriate clinical presentation and borderline histology (collagen band of 5–10 **µm** and 10–20 IELS)[1,11,23] can be diagnosed with incomplete MC. MC incomplete has previously been described as "colonic epithelial lymphocytosis" or "MC, not otherwise specified". These patients have similar clinical presentation as MC, but show less prominent mucosal injury and only mild lymphoplasmacytic infiltrates in the lamina propria[23]. In borderline cases, Masson's trichome or immunohistochemical staining procedures can be used in addition to routine HE stains. However, the use of immunostaining may require a higher IEL count in order to avoid overdiagnosis[3]. There is no recommendation to follow MC patients with post-diagnosis biopsies because there is no correlation between clinical activity and histologic features, disease progression, or remission of the histological aspects, regardless of clinical picture. Histology can return to normal in 10% of patients and can also last longer than the first year or treatment[1].

Diagnosis of MC necessitates effective communication among gastroenterologists, endoscopists, and pathologists. It is critical to mention the suspicion of MC when requesting the workup and referring the biopsy. This metric guides the pathologist's evaluation of the biopsy.

Recommendation: if the gastroenterologist has a strong clinical suspicion of MC and the biopsy result is inconclusive, the slides should be reviewed by a pathologist who specializes in gastrointestinal disorders.

Considerations about the treatment of MC

It is crucial to stop smoking and withdraw from offending drugs[13]. Oral budesonide is the drug of choice for treating MC because it can induce and maintain remission in patients with CC or LC, improving their quality of life[1,10,14,24].

Budesonide 9 mg/day for 4 weeks, 6 mg/day for 2 weeks, and 6×3 mg alternated per 2 weeks promote remission in 84.5% of cases in 10 days[10,25]. Although nasopharyngitis, headache, and dyspepsia have been reported as side effects of budesonide in MC, none have been linked to an increased risk of severe adverse events. Although this medication is considered safe and effective, relapses can occur in 70–80% of cases after discontinuation. The majority of these patients will respond to a new therapeutic schedule, budesonide can be used in maintenance at low doses if there are more relapses[1,26].

The risk of osteoporotic bone fractures does not appear to be increased in patients treated with budesonide, but long-term use may be associated with a decrease in bone mineral density[27]. During prolonged treatment, attention must also be paid to hypertension, hyperglycemia, glaucoma, and cataracts[14]. Before concluding that the patient is not responsive to budesonide, other causes of diarrhea must be ruled out[26]. Patients with chronic diarrhea who do not respond well to first-line therapy should be evaluated for a secondary cause[5]. Prednisolone and other corticosteroids are not recommended because they are ineffective[1,10].

Mesalazine is no more effective than placebo in the treatment of MC, and bismuth subsalicylate is not recommended[1,8,25]. Loperamide may be used in mild disease due to its antidiarrheal effect[25]. If there is bile acid diarrhea, bile acid blockers (colestyramine) could be used: 4 g two or three times/day[25]. Thiopurines are not recommended, but azathioprine 2 mg/kg/day can provide 89% complete response and 33% partial response in cases of refractory MC or steroid dependence[8,24]. There is no evidence that antibiotics should be used[1,24]. Probiotics are not mentioned, but the role of microbiome and dysbiosis is being researched[24]. Moreover, the indication for stool transplantation remains unknown[10,24]. In selected patients with MC who do not respond to budesonide, anti-TNF or other biologics, considered second-line agents, can be used to induce and/or maintain clinical remission[1,8,24,25].

If all medical treatment fail, surgery may be considered as a last resort in certain MC patients[1].

Prognosis

The natural course of MC is marked by periods of asymptomatic and diarrheal episodes[10]. Despite the recurrence of symptoms, the disease is treatable, the disorder does not worsen, and it is not associated with an increased risk of mortality and colon cancer[28]. However, depending on the activity and severity of the disease, as well as concomitant comorbidities, patients with MC have a lower health-related quality of life. It is crucial to consider how to improve this outcome with appropriate treatment[1,24].

CONCLUSION

Given the increase in life expectancy and the use of numerous drugs by elderly people suffering from chronic diseases, it is expected that MC will be diagnosed more frequently.

It is necessary to make efforts to educate professionals about the key aspects of MC, particularly in primary care settings where MC is less familiar to physicians and may be diagnosed as IBS and not referred to colonoscopy for biopsies.

A good relationship between the physicians involved is required for the diagnosis of MC. Nowadays, with the facilities presented by digital media, this proposal can be reached more easily, avoiding delays in diagnosis and providing early improvement in patient's quality of life.

Authors' contribution

All authors contributed to the study conception and design. Data collection were performed by Kotze LMS, Kotze PG, Kotze LR and Nisihara R. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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RESUMO – A colite microscópica é uma doença intestinal inflamatória crônica caracterizada por diarreia não sanguinolenta que pode variar de leve a grave. Atribui-se que cerca de 10–20% das diarreias crônicas são devidas à colite microscópica. Os três fatores determinantes para o diagnóstico são sintomas clínicos característicos, quadro endoscópico normal do cólon e quadro histológico patognomônico. Este manuscrito tem como objetivo atualizar e trazer recomendações para os profissionais envolvidos (gastroenterologista, endoscopista e patologista) no diagnóstico de colite microscópica. Adicionalmente, uma breve recomendação sobre o tratamento.

Palavras-chave – Colite microscópica; diagnóstico; patologia; colonoscopia.

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