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Warning to delay in diagnosing microscopic colitis in older adults. A series of cases

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HIGHLIGHTS

- Microscopic Colitis is a chronic inflammatory bowel disease causing non-bloody diarrhea.
- Several cases are undiagnosed and can be a hidden cause of chronic diarrhea.
- Treatment with budesonide MMX (Corament®, off label) was effective and safe.

ABSTRACT – Background – Microscopic colitis (MC) is a chronic inflammatory bowel disease causing non-bloody diarrhea, and several cases are undiagnosed as a hidden cause of chronic diarrhea. **Objective –** We aimed to report the symptoms, delay diagnosis and the treatment of MC in a case series. **Methods –** All patients were treated at a Gastroenterology reference office from May 2022 to June 2023. Personal history including preexisting disorders, use of medications and smoking habits were collected. The delay between the onset of symptoms and the correct diagnosis was informed. All patients consented to use budesonide MMX (Corament®) off label. **Results –** During the study period, six Caucasoid patients were diagnosed with MC, five females and one male, between the ages of 65 and 74. All patients had comorbities and were taking multiple prescription drugs. Laboratory findings showed negative serology for celiac disease for all patients, normal levels of albumin and vitamin B12. The delay between the symptoms and the MC diagnosis varied from 2 months to 6 years. All patients had a previous diagnosis of irritable bowel syndrome. All patients were in complete clinical remission during the treatment and referred no side effects of the drug. **Conclusion –** Older females using high-risk medications are suggestive of MC. Preventing delay in the diagnosis of MC is crucial to improvement in patients´ quality of life. Budesonide MMX appears to be effective, safe and well-tolerated.

Keywords – Microscopic colitis; chronic diarrhea; diagnosis, treatment.

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INTRODUCTION

Chronic diarrhea (CD) lasting over 4 weeks occurs in 6.6% of the population, and may be caused by a variety of disorders, making etiological diagnosis difficult in some cases, particularly in older adult patients due to atypical presentations of specific disorders that require an increased index of suspicion[1]. The diagnostic approach of CD in older individuals includes medical history, physical examination and complementary tests. If a diagnosis cannot be reached, colonoscopy with mucosal biopsies is recommended[1]. Endoscopically, macroscopic changes are inconsistent or absent, therefore histopathological evaluation is always required for the diagnosis of MC. Therefore, endoscopists alerted by physicians, should consider obtaining fragments even when mucosa shows normal appearance as in the case of suspected microscopic colitis (MC)[2,3].

MC is a chronic inflammatory bowel disease causing non-bloody diarrhea with variable or recurrent mild to severe course[4]. Up to 10–20% of CD cases are considered to be secondary to MC[4]. The disease is characterized by normal appearance of the colon along with pathognomonic histological abnormalities, that distinguish three subtypes of MC: collagenous colitis (CC), the lymphocytic colitis (LC) and the incomplete microscopic colitis (IC)[4]. The incidence of MC is estimated to be 11.4 cases per 100.000 person-years and the prevalence is 119.0 per 100.000 persons. Considering persons with chronic watery diarrhea the frequency reported was 12.8%[4]. MC has been reported in individuals from several continents, indicating that despite genetic and environmental differences, similar immunological evolution allowed the disease to evolve[4]. There are very few publications regarding this disorder in Brazil[5,6]. The etiology is unknown, and the pathogenesis is complex and multifactorial, including luminal factors, immune dysregulation and genetic predisposition[4,7]. The three determinants of the diagnosis are non-bloody diarrhea, normal endoscopic picture of the colon, and pathognomonic histological picture[7-9], but several cases are undiagnosed as a hidden cause of CD, resulting in missed treatment opportunities[7].

Physicians, particularly in primary care, are less familiar with MC than with other causes of CD[10]. Given the need to reduce costs in certain healthcare systems, the diagnosis of irritable bowel syndrome (IBS) is made without a colonoscopy, or biopsies are not performed if a colonoscopy is normal. As a result, MC is undetected and remain as a hidden cause of CD[7,10].

Herein, we described the symptoms, delayed diagnosis, and the treatment of MC in a case series of older Brazilian patients.

METHODS

This was a retrospective study conducted using a survey of clinical charts between April 2022 to August 2023. This study was approved by the Institution's Ethics Committee under protocol 5,302.175. All patients were treated in a Gastroenterology reference office in Curitiba, Brazil. The endoscopies were performed by the same endoscopists, and the biopsies were evaluated by the same pathologist. Personal history included preexisting disorders, use of medications and smoking habits. The delay between the onset of symptoms and the correct diagnosis was informed. The Short Health Scale (SHS) proposed by Stjermann et al. was used to assess quality of life (QoL)[11]. All patients performed upper gastrointestinal tract endoscopy and small bowel biopsies were performed according to the American College of Gastroenterology guidelines[12]. Colonoscopies with biopsies were performed according to guidelines recommended for the diagnosis of suspicious MC; two to three samples from the ascending colon, two to three from the transverse colon and two to three from the descending colon, were placed in separate labelled containers[4,13]. Microscopic results were reported according to Fiehn et al.[14].

All the patients consented to use budesonide MMX[15] (Corament®) off label. The treatment consisted of using 1 capsule of 9 mg per day for 8 weeks. Clinical remission was defined as having fewer than 3 stools per day and fewer than 1 water stool per day during one 1-week period of registration[16]. Periodic controls with budesonide MMX were performed at 4-week intervals. Response to treatment was defined as the early disappearance of symptomatology one week post treatment, with subsequent improvement in QoL and gradual weight gain.

All patients were tested for IgA serum levels and

anti-transglutaminase tissue antibody to exclude celiac disease (CeD)[17]. Other laboratory tests, such as serum albumin, vitamin B12, vitamin D, iron, fecal pancreatic elastase-1 levels and fecal calprotectin were performed.

RESULTS

During the study period, six Caucasoid patients were diagnosed with MC, five females and one male, with a minimum age of 65 and a maximum age of 74 years, with predominance of CC (5 cases) among females and LC among males (one case). All patients were referred due to CD with a previous diagnosis of IBS with no improvement and poor QoL. There were no reports of previous or current smoking habits.

The delay between the onset of symptoms and the correct diagnosis was referred to as follows: in two cases, less than 1 year; n two cases, between one and two years and in two cases, more than 4 years (varied from 2 months to 6 years).

TABLE 1 shows the main demographical and clinical data, and the prescription drugs used by the patients.

Laboratory findings showed that all patients had negative serology for CeD (with normal IgA concentrations), normal levels of albumin and vitamin B12. Five cases had low levels of vitamin D, four cases had low levels of iron and high levels of fecal calprotectin, three cases had low levels of fecal pancreatic elastase-1.

Endoscopies of the stomach were normal in 4/6 patients (one patient had gastritis and the other peptic ulcer). Duodenal macroscopy and microscopy were both normal in all cases. At ileocolonoscopy, macroscopy was normal in all cases (one patient had diverticular disease). Microscopy revealed collagenous colitis in five females and lymphocytic colitis in one male, as demonstrate in the TABLE 2. If no symptoms were reported after 6 to 8 weeks of oral therapy with budesonide 9 mg/day, the prescription drug was gradually discontinued[4]. Two patients, one with CC and the other with LC, achieved remission in 8 weeks of treatment and did not require treatment during the follow-up Two patients achieved remission in 8 weeks, and require drug maintenance in lower dose for fourth months. Two patients continued on with a lower dose of the drug for clinical remission due to symptom recurrence when the dose was reduced. After 1 year, all the studied patients were considered in complete clinical remission. They did not report side effects during the treatment.

DISCUSSION

There are no Brazilian reports on patients with microscopic colitis. The disease is undiagnosed, inadequately or insufficiently investigated and has a detrimental influence on the patient's quality of life due to diagnosis delay.

All the patients studied were older adults, which is consistent with previous findings. Female gender

TABLE 1. Clinical and demographical data from patients with microscopic colitis studied (n=6).

Case	Gender	Age at diagnosis (years)	Diagnosis delay (years)	N of bowel moviments/ day	Appearance of the stools	Abdominal Pain/ distension	Weight loss	Comorbidities	Drugs in use to treat Comorbidities
01	F	65	5	4	Watery	Yes	Yes	Depression	SSRIs
02	F	68	2	6	Watery	Yes	Yes	Depression, DM-2, previous bariatric surgery	SSRIs
03	F	73	6	7	Watery	Yes	Yes	HT, ASH, previous bariatric surgery	Levothyroxin, statins, beta-blockers
04	F	73	3	10	Watery	Yes	Yes	Depression, HT, Cronh's Disease	SSRIs, Levothyroxin, Steroid, PPIs
05	F	75	<1	3	Watery	Yes	Yes	HT, DM-2, ASH, gastric ulcer.	Levothyroxin, statins, beta-blockers
06	M	76	<1	4	Watery	Yes	Yes	ASH, onicomicosis	beta-blockers, terbinafine

F: female; M: male; DM-2: type 2 diabetes mellitus; HT: hypothyroidism; ASH: arterial systemic hypertension.

TABLE 2. Colonoscopy and biopsy findings, and response to treatment with oral budesonide in the patients with microscopic colitis studied (n=6).

Case	Previous diagnosis	Colonoscopy findings	Biopsy findings (right and left colon) diagnosis[1]	Response to treatment with oral budesonide	Duration of treatment
01	IBS	Normal	Collagenous colitis	Good	16 weeks
02	IBS	Normal plus diverticular disease	Collagenous colitis	Good	48 weeks
03	IBS	Normal	Collagenous colitis	Good	48 weeks
04	IBS	Normal	Collagenous colitis	Good	16 weeks
05	IBS	Normal	Collagenous colitis	Good	8 weeks
06	IBS	Normal	Lymphocytic colitis	Good	8 weeks

SSRIs: serotonina inhibitors; PPIs: proton pump inhibitors; NSAIDs: non-steroidal anti-inflammatory drugs; AAS: acid acethyl salicylic; IBS: irritable bowel syndrome. [1]Collagenous colitis defined by subepythelial collagen band >10 µm thickness plus inflammatory infiltrate in lamina propria more than 20 intraepithelial lymphocytes/100 epithelial cells.
Lymphocytic colitis defined by subepythelial collagen band <10 µm thickness plus inflammatory infiltrate in lamina propria more than 20 intraepithelial lymphocytes /100 epithelial cells.

is a risk factor for MC as evidenced in our case series, and supported by previous studies[2,4,7].

A delay in diagnosis was observed in our cases. This finding has also been reported by other authors as a result of a low index of suspicion by the professionals involved in diagnosis, as a forgotten disorder[10], or due to normal macroscopy at colonoscopy without biopsies[7]. Prior to the diagnosis of MC, IBS was reported by all patients, but it was a medical misdiagnosis. IBS commonly appears before the age of 50, with the consistency of stools varying from soft to hard, and abdominal pain accompanied by a sense of incomplete evacuation. However, fecal incontinence and weight loss may assist in distinguishing IBS from MC[4,8,9].

Celiac disease must be eliminated in the differential diagnosis of MC, as the link between these two disorders have been previously described[17] All cases in our study had normal IgA serum levels, negative serum autoantibodies and normal histopathology of duodenal mucosa, excluding CeD.

Both types of MC (CC or LC) present the same clinical pattern[9]. In general, the initial complaints started suddenly, and the distinguishing clinical sign is non-bloody diarrhea, which may be accompanied by nocturnal diarrhea and fecal incontinence. Bloating, flatulence with abdominal pain were frequently reported symptoms. All the studied patients referred these symptoms which are important for the differential diagnosis of IBS. Weight loss was observed in all of the patients, indicating the severity of the disorder[4]. (TABLE 1).

The concomitance with other diseases and the use of several medications, more than one at the same time, is very important. Depression, hypertension, hypothyroidism and type 2 diabetes are common diseases in this age group. (TABLE 1) Crohn's disease has been reported as a risk factor for MC[9], yet our patients was in remission for years without the use of prescription drugs. Bariatric surgery was reported in 2/6 cases and was performed 12 and 18 years before the onset of MC symptoms, but no relationship with MC was found in the literature. The drugs prescribed for the other comorbidities were the same as those documented in the literature for MC[18]. Some of them, but not all, might be avoided during MC treatment. The current recommendations suggest discontinuing any prescription drug that is suspected to have chronological relation to the onset of diarrhea, as was the case of the one of the patients in our case series who used oral terbinafine for the treatment of onychomycosis. Even after excluding the drug, severe diarrhea persisted and the final diagnosis was LC. Terbinafine is an antifungal medication with gastrointestinal symptoms side effects, but no reports about MC[19].

Fecal calprotectin is an unspecific biomarker for some inflammatory intestinal disorders[20], and it may be increased at the time of MC diagnosis and significantly decreased when in remission[21]. In our cases, fecal calprotectin was not shown to be useful in excluding or in assessing MC, as indicated in two cases of this study with severe symptoms and normal levels.

Due to the variable nature of MC, the therapeutic options should be tailored to each patient[22]. The diet

approach in each case was based on nutritional requirements[4]. In our cases, antidiarrhea medication was not used. The American Gastroenterological Association recommends budesonide as first-line therapy in patients with MC with moderate-severe symptoms[23], as well as the United European Gastroenterology and European Microscopic Colitis Group[4]. Budesonide is a synthetic glucocorticosteroid similar to prednisolone, but it has 15 times greater affinity for the glucocorticoid receptor and higher topical action[24]. Budesonide MMX® is a formulation that has been approved for the treatment of mild-to-moderate ulcerative colitis. The capsules are composed of lipophilic and hydrophilic excipients enclosed within a gastro-resistant pH-dependent coating[25]. This pharmaceutical formulation ensures that the drug is distributed uniformly over the colonic segments, particularly distal ones[25]. Pharmacokinetic studies have shown that the average absorption of budesonide MMX in the area between ascending and descending colon was 95.5%. As a result, the MMX delivery system ensures that active drugs play their therapeutic role directly on the colonic mucosa and minimizes the systemic absorption of the drug[24,25].

Since this delivery system has been used to treat conditions in which high colonic drug concentrations are advisable/required for treatment success, whereas absorption and systemic delivery of the compound is best avoided, why not recommend it for other diseases that affect the colon? Given that this technology has been developed and proven effective, many other possible colonic diseases might be targeted, potentially with similar efficacy, as in MC[15].

Despite the small number of patients in this study, our data suggest that 8 weeks of budesonide MMX (Corament®, off label) was effective and safe in the treatment of acute MC for the induction of clinical remission and as well as for long-term use of the drug[26].

The physician's suspicion of MC must be communicated to the endoscopist[27]. The incidence of MC is increasing worldwide, therefore primary care professionals and/or gastroenterologists must be aware of this overlooked condition. More colonoscopies with biopsies to distinguish MC from IBS are necessary to increase diagnosis[2,3,7,27].

CONCLUSION

Older adults using several medications were at higher risk of developing MC. Suspicion can prevent delay in diagnosis of MC and provide early treatment to improve patients' QoL. Off-label use of budesonide MMX (Corament®) appears to be effective, safe, and well tolerated.

Authors' contribution

Conception and design: Kotze LMS, Kotze LR, Souza RCA, Kotze PG and Nisihara R. Data collection were performed by Kotze LMS, Souza RCA and Kotze LR. All authors revised on previous versions of the manuscript. All authors read and approved the final manuscript.

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Kotze LMS, Kotze LR, Souza RCA, Kotze PG, Nisihara R. Alerta de atraso no diagnóstico de colite microscópica em idosos. Uma série de casos. Arq gastroenterol. 2024;61:e23114.

RESUMO – Contexto – A colite microscópica (CM) é uma doença inflamatória intestinal crônica que causa diarreia não sanguinolenta, e vários casos não são diagnosticados como uma causa oculta de diarreia crônica. **Objetivo –** Esse estudo visou relatar os sintomas, qual o atraso diagnóstico e o tratamento da CM em uma série de casos. **Métodos –** Todos os pacientes foram atendidos em um consultório de referência em Gastroenterologia no período de maio de 2022 a junho de 2023. Foram coletados antecedentes pessoais, incluindo distúrbios preexistentes, uso de medicamentos e tabagismo. Foi buscado o período entre o início dos sintomas e o diagnóstico correto. Todos os pacientes consentiram em usar budesonida MMX (Corament®) *off label*. **Resultados –** Durante o período do estudo, seis pacientes caucasóides foram diagnosticados com CM, cinco mulheres e um homem, com idades entre 65 e 74 anos. Todos os pacientes apresentavam comorbidades e faziam uso de vários medicamentos prescritos. Os achados laboratoriais mostraram sorologia negativa para doença celíaca em todos os pacientes, níveis normais de albumina e vitamina B12. O atraso entre os sintomas e o diagnóstico de CM variou de 2 meses a 6 anos. Todos os pacientes tinham diagnóstico prévio de síndrome do intestino irritável. Todos os pacientes apresentaram remissão clínica completa durante o tratamento e não referiram efeitos colaterais da droga. **Conclusão –** As mulheres mais velhas que usam medicamentos de alto risco são sugestivas de CM. Evitar o atraso no diagnóstico de CM é fundamental para melhorar a qualidade de vida dos pacientes. A budesonida MMX foi eficaz, segura e bem tolerada.

Palavras-chave – Colite microscópica; diarreia crônica; diagnóstico; tratamento.

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