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Microscopic Colitis: A Diagnostic Challenge in Patients with Irritable Bowel Syndrome

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ABSTRACT

Background & Aims: Irritable Bowel Syndrome (IBS) is one of the most frequently diagnosed gastrointestinal disease with a prevalence of 4.1% in the general population. It is diagnosed using the Rome IV criteria. Microscopic colitis (MC), collagenous/lymphocytic colitis is a cause of chronic, watery, non-bloody diarrhea. It is a real challenge to diagnose MC in patients with IBS. The aims of the study were to determine the prevalence of MC in patients initially diagnosed with IBS, as well as to correlate fecal calprotectin levels with the endoscopic findings and microscopic inflammation in MC.

Methods: This is a retrospective study conducted in a single tertiary center with over 89 IBS patients for a period of 4 years. The patients included were patients diagnosed with IBS predominant diarrhea (IBS-D) and mixed IBS (IBS-M) using the Rome IV criteria. Total colonoscopy was performed in these patients, multiple biopsies being taken and calprotectin levels were measured.

Results: Out of a total of 89 IBS-D patients, 58 patients (65.2%) had no microscopic lesions, 12 patients (13.5%) had diverticular disease, 9 patients (10.1%) had non-specific chronic inflammation of the colon mucosa and 10 patients (11.2%) were diagnosed with MC. The calprotectin levels ranged from 49 μg/g to 213 μg/g. Of a total of 10 patients diagnosed with MC, 6 (60%) of them had calprotectin levels <100 μg/g and 4 (40%) had calprotectin levels >100 μg/g. The fecal calprotectin levels were higher in patients diagnosed with MC compared to those who had no microscopic lesions at the histological exam and it was also correlated with the grade of colonic microscopic inflammation.

Conclusions: Microscopic colitis is less familiar to physicians and can be clinically misdiagnosed as IBS-D. An early and correct diagnosis is important for an accurate therapy.

Key words: collagenous colitis – lymphocytic colitis – irritable bowel syndrome – calprotectin -diagnosis.

Abbreviations: CC: collagenous colitis; IBS:: irritable bowel syndrome; IBS-D: IBS predominant diarrhea; IBS-M: mixed IBS; LC: lymphocytic colitis.

INTRODUCTION

Irritable bowel syndrome (IBS) is one of the most frequently diagnosed gastrointestinal disorders and is characterized by the presence of altered bowel habits and abdominal pain [1]. It has a prevalence of about 4.1% in the general population, often affecting younger individuals, predominantly women [2].

Microscopic colitis (MC) was first described in 1980 as a cause of chronic, watery, non-bloody diarrhea [3]. The histological exam is essential for diagnosing microscopic colitis [4, 5]. The classification of microscopic colitis includes collagenous colitis (CC) and lymphocytic colitis (LC). Inflammation in the lamina propria is present on the entire colon in both types of MC [6, 7]. Studies in North America and Europe reported the incidence of MC from 1 to 25/100.000 person-years, but recent studies reported a incidence up to 46-49/100.000 person-years [3]. Reporting higher incidence must be the consequence of the greater awareness and of the ageing population, being more frequent in older individuals (> 50 years) [4]. Almost 10% of the non-bloody diarrheas are caused by MC [8].

Microscopic colitis if often misdiagnosed as IBS. Around 1/3-1/2 of the patients diagnosed with MC have symptom criteria for IBS and around 10% have diagnostic criteria for IBS [9]. Clinical history may help to differentiate MC from IBS. Microscopic colitis is more frequent in patients over 50 years and the diarrhea is often watery and non-bloody, leading

to urgency and fecal incontinence. Moreover, weight loss and autoimmune diseases can be associated with MC [10]. It is expected that some of the patients diagnosed by Rome IV criteria for IBS may in fact have MC and making a prompt diagnosis of MC has important management implications because treatment options are quite different [11, 12]. Table I displays the clinical differences between IBS and MC.

Table I. Clinical differences between irritable bowel syndrome (IBS) and microscopic colitis (MC)

Clinical history	IBS	MC
Age of first occurrence	< 50 years	>50 years
Stool consistency	Variable	watery
Abdominal pain	Mandatory	variable
Nocturnal diarrhea	Unlikely	probable
Incomplete bowel evacuation	Common	unlikely
Weight loss	Rare	common
Faecal incontinence	Rare	Common
Bloating	Common	Rare
Autoimmune diseases	Rare	Common

The treatment for MC is focused on eliminating the risk factors, such as smoking, proton pumps inhibitors (PPIs), nonsteroidal anti-inflammatories (NSAIDs), H2 receptor antagonists, selective serotonin reuptake inhibitors (SSRI) and statins [13]. Treatment guidelines recommend using budesonide for symptomatic MC in order to induce and maintain the remission with a rate of clinical remission and histological improvement of 81% [14, 15].

Differential diagnosis of MC can be made with: IBS-D, inflammatory bowel disease (IBD), celiac disease, ischemic colitis, infectious colitis, small intestinal bacterial overgrowth, hyperthyroidism/thyreotoxicosis, laxative abuse, bile acids malabsorption [16]. Microscopic colitis is often associated with other conditions such as celiac disease, type 1 diabetes mellitus, autoimmune thyroiditis and oligoarticular arthritis [17], with a stronger correlation between autoimmune conditions and CC.

The objectives of our study were to evaluate the prevalence of MC in patients with an initial diagnosis of IBS and also the prevalence of LC or CC in patients diagnosed with MC. Our secondary aim was to measure calprotectin levels in patients diagnosed with MC, IBS-D and IBS-M that performed colonoscopy, in order to check if there is a correlation between fecal calprotectin levels, the existence and the grade of microscopic inflammation.

METHODS

This is a retrospective study conducted in a single tertiary center over a period of 4 years. The patients included were patients diagnosed with IBS using the Rome IV criteria. Patients with IBS-C, IBD, colon cancer or colonic diverticular disease were excluded. Colonoscopy was performed and multiple biopsies were taken from the entire colon, histological exams were performed and also calprotectin levels were measured. We reviewed the medical charts of the patients and recorded clinical, biological and endoscopic aspects and also demographic data. The data were processed using Microsoft Excel 2016 and for the statistical analysis of the data we used IBM SPSS Statistics v28. The statistical methods we used for data analysis are represented by the chi-square test and the Pearson correlation.

RESULTS

In the study were included 274 patients with IBS. 176 with IBS-C, 98 patients (IBS-D and IBS-M) remained included, 89 patients with IBS-D (IBS with diarrhea) and 9 with IBS-M (IBS mixed type). In the cohort of IBS patients (IBS-D and IBS-M) 34 (43%) were males and the average age was 57.9 years.

Colonoscopy was performed in 89 patients (9 patients refused the colonoscopy). Fifty-eight (65.2%) patients had no microscopic lesions, 12 (13.5%) patients had diverticular disease, 9 (10.1%) patients had non-specific chronic inflammation of the colon mucosa and 10 patients (11.2%) were diagnosed with microscopic colitis.

Ten of the patients had microscopic lesions that were suggestive for MC. In this cohort, the mean age was 65.6 years; 6 persons were females. Eight (80%) of them were diagnosed with LC and two (20%) of them were diagnosed with CC. All the patients diagnosed with MC were initially diagnosed with diarrhea predominant irritable bowel syndrome (IBS-D) and none of them with IBS-M. In our study, the levels of fecal calprotectin were measured in patients diagnosed with MC. The calprotectin levels ranged from 49 μg/g to 213 μg/g, with a mean of 124.1 μg/g and a median of 112.5 μg/g, 92.75 μg/g and 159 μg/g represent the 25th and 75th percentile values (Fig. 1). Of a total of 10 patients diagnosed with MC, 6 (60%) of them had calprotectin levels >100 μg/g and 4 (40%) had calprotectin levels <100 μg/g.

We randomly selected 10 patients diagnosed with IBS-D and IBS-M from the group of patients with no macroscopic or microscopic lesions detected at colonoscopy and measured the fecal calprotectin levels. The levels ranged from 15 μg/g to 56 μg/g with a mean of 32.2 μg/g and a median of 30.5 μg/g, 18.5 μg/g and 44.5 μg/g represent the 25th and 75th percentile values (Fig. 1). The standard deviation (SD) for the fecal calprotectin levels in the MC group was 47.83 μg/g and for the IBS group was 14.03 μg/g.

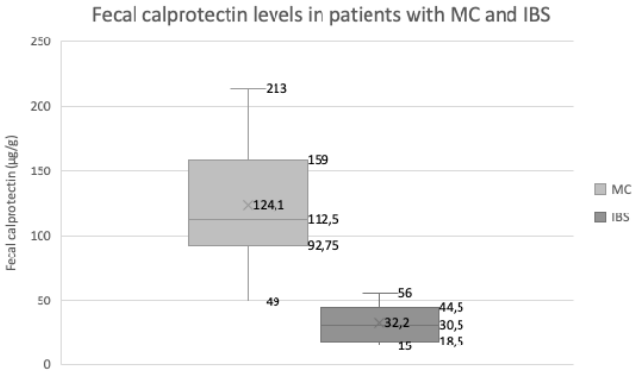

Fig. 1. Fecal calprotectin levels in patients with MC and IBS

We also wanted to check if there was any correlation between the levels of fecal calprotectin and the endoscopic findings (MC/IBS). We performed a Chi-square test using the fecal calprotectin levels of the patients diagnosed with MC and the group of 10 patients diagnosed with IBS-D or IBS-M with no endoscopic lesions.

The chi-square statistic with Yates correction was 9.8; the p-value was 0.0017. The correlation between the level of fecal calprotectin and the endoscopic findings (MC, no endoscopic lesions - IBS) was statistically significant.

We also correlated the fecal calprotectin levels with the grade of microscopic inflammation in patients diagnosed with MC using Pearson correlation. The Pearson correlation coefficient was 0.736. It showed a strong positive relationship between the two variables and the correlation was also statistically significant, the Sig (2-tailed) p-value was 0.015.

DISCUSSION

Diarrhea predominant IBS is a relatively widespread gastrointestinal disorder and frequently physicians miss the diagnosis of MC labelling it as IBS-D, because MC is rare. However, some studies report higher frequency of MC. In some European countries, the incidence rate of MC has surpassed the incidence rate of ulcerative colitis and Crohn's disease [18]. A meta-analysis calculated a pooled prevalence for MC in patients with IBS-D of 8.3% (95%CI: 3.5%–15.0%), but there was a significant heterogeneity between studies [19]. In our study the prevalence of MC in patients considered as having IBS-D was 11.2%, a value that is included in the 95%CI of the meta-analysis, so our results were concordant with the results found in literature.

A meta-analysis of 25 studies calculated the prevalence for lymphocytic colitis and collagenous colitis. The prevalence of LC was 63.05 cases per 100,000 person-years and the prevalence of CC was 49.21 cases per 100,000 person-years. The prevalence of LC surpasses the one of CC [20]. This aspect is also found in our study. Of a total of 10 patients diagnosed with MC, 8 (80%) of them were diagnosed with LC and only 2 (20%) of them were diagnosed with CC.

Fecal calprotectin is not considered to be useful as a marker of activity/inflammation in MC, but active MC is often associated with high levels of fecal calprotectin. A study conducted in Spain that included 94 patients, 30 of them diagnosed with MC had the purpose to quantify the usefulness of calprotectin as a biomarker in MC. The predefined cut-off value for calprotectin used in this study was 50 μg/g and the mean value of calprotectin was 175 μg/g. 67% of the patients had calprotectin levels over 100 μg/g [21]. In our study 9 patients diagnosed with MC had levels of fecal calprotectin over 50 μg/g, the mean value was 124.1 μg/g and also 60% of the patients diagnosed with MC had levels of calprotectin over 100 μg/g. The results of our study are similar with the ones found in the literature.

Despite the fact that in our study the grade of colonic inflammation was strongly correlated with fecal calprotectin levels, the studies that evaluated this correlation have been conflicting. There are studies that suggested that fecal calprotectin can be used in order to monitor the activity of MC [22] and some of them concluded that fecal calprotectin can be a potential marker in differentiating active MC from IBS-D but further research is needed [23].

In our study, there is a correlation between the level of fecal calprotectin and the microscopic findings. Normal fecal calprotectin levels were associated with IBS-D or IBS-M and no endoscopic lesions and higher calprotectin levels were associated with the presence of MC.

We used as a cut-off for fecal calprotectin the value of 50 μg/g. This confirms what previous studies have showed, that fecal calprotectin is associated with inflammation. A normal level is much more likely to suggest the presence of IBS [24], and as we have shown before higher levels of fecal calprotectin is associated with MC and moreover, also with the grade of microscopical inflammation in MC.

CONCLUSIONS

Microscopic colitis can be easily misdiagnosed as IBS. The prevalence of MC in patients initially diagnosed with IBS was 11.2% in our study. The prevalence of LC surpassed the prevalence of CC. Fecal calprotectin levels were elevated in patients with MC compared to patients diagnosed with IBS and it turned out to be useful for the differential diagnosis. The fecal calprotectin level was also correlated with the grade of microscopic inflammation, and it can also be used to monitor the activity of MC. Additional research is needed to study these conclusions on a larger group of patients.

Conflicts of interest: None to declare.

Authors' contribution: F.R. conceived the study. F.R., R.L.C, L.M. collected, analyzed the data and drafted the manuscript. D.C.L. performed the statistical analysis. D.L.D. thoroughly revised the manuscript. All authors read and approved the final version of the manuscript.

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