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Alimentary Tract

Prevalence and incidence of microscopic colitis in patients with diarrhoea of unknown aetiology in a region in central Spain

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ABSTRACT

Background: Often previously overlooked, microscopic colitis, including collagenous colitis and lymphocytic colitis, has now emerged as a common cause of chronic diarrhoea.
Aims: To evaluate the prevalence and incidence of microscopic colitis in patients with diarrhoea of unknown aetiology.
Methods: 271 consecutive patients who were referred to the General Hospital of Tomelloso from April 2008 to December 2010 for diarrhoea of unknown aetiology underwent a full colonoscopy to obtain biopsy samples to diagnose microscopic colitis on the basis of commonly accepted histological criteria. All patients were classified according to the Roma III criteria for diarrhoea-dominant irritable bowel syndrome.
Results: In 234/271 consecutive patients with normal endoscopic appearance we observed 32/234 patients with microscopic colitis (30 lymphocytic colitis and 2 collagenous colitis) with a prevalence of microscopic colitis of 48 cases/100,000 inhabitants (95%CI: 30–65) and mean annual standardised incidence of 18 cases/100,000 inhabitants (95%CI: 16.0–20.0). Analysing only the patients that met the Roma III criteria (84/271), we observed 10.7% microscopic colitis diagnosis, with higher risk in the presence of autoimmune disease, seronegative celiac disease and intake of non-steroidal anti-inflammatory drugs.
Conclusions: Microscopic colitis was found in 13.7% of patients with chronic diarrhoea. Microscopic colitis is present in a relevant proportion of symptomatic patients meeting diagnostic criteria for irritable bowel syndrome (10.7%).

1. Introduction

The term microscopic colitis (MC) may be now considered as an umbrella term [1] for two conditions (lymphocytic colitis (LC) and collagenous colitis (CC)), both characterised by chronic or recurrent watery diarrhoea, normal radiological examinations, normal or near-normal endoscopic appearance and specific microscopic abnormalities in colonic biopsies [2,3]. CC differs from LC in that it presents a sub-epithelial collagen band adjacent to the basal membrane whereas the hallmark of LC is a dense lymphocytic infiltration into the epithelium [4,5]. Several variants of these two conditions have been reported but these are probably not specific entities [1].

The epidemiology of CC and LC is not completely known, with studies on the condition being scarce. Nevertheless, CC and LC seem to be a common finding amongst patients undergoing colonoscopy with biopsy analysis to evaluate chronic or recurrent watery diarrhoea. The prevalence observed is about 9.5%, which increases to 20% in patients over the age of 70 [6]. Population-based studies have shown an incidence rate varying between 1 and 12 per 100,000 people per year [6–10]. In Europe, the incidence of CC has been estimated as being 1.1–5.2 per 100,000 inhabitants per year, whilst the incidence of LC is 3.1–4.0 per 100,000 inhabitants per year, taking into account differences between various geographic areas [7–9]. Incidence rates in North America are similar to those reported for Europe, although several studies have found prevalence as high as 103 per 100,000 inhabitants [10,11]. In any event, the past few years have witnessed similar increases in incidence rates of CC and LC in both North America and Europe [12]. The reason for this apparent increase in the prevalence of the disease remains unclear, but may be due to the fact that diagnostic colonic biopsies are performed more frequently, even in the absence of endoscopic alterations.

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Other possibilities include the increased use of medications that may cause CC and LC and increased exposure to different risk factors in different geographical areas.

The aims of this study are to evaluate the prevalence and incidence of CC and LC in patients with chronic diarrhoea of unknown origin, its subtypes over time and the prevalence of CC and LC in patients with symptoms of diarrhoea-dominant irritable bowel syndrome (IBS) in a specific geographic area in a central region of Spain.

2. Methods

2.1. Study setting

The recruitment area of General Hospital of Tomelloso is located in the centre of Spain in the autonomous region of Castilla-La Mancha. The study area is predominantly rural, with a reference population of roughly 67,360 inhabitants (based on data from the year 2009). There is only one hospital in the area that offers universal coverage for specialist services. The hospital's Department of Gastroenterology is considered a referral centre for chronic diarrhoeal diseases in the area.

2.2. Patients

All consecutive adult patients with watery chronic diarrhoea (defined by persistent symptoms lasting for more than 1 month) who were referred to the Department of Gastroenterology at the General Hospital of Tomelloso between April 2008 and December 2010 underwent a full colonoscopy. All patients with stool examinations positive for ova, parasites, *Clostridium difficile toxin*, *Salmonella* spp., Shigella spp., *Campylobacter* or *Yersinia* were excluded, as were those with a previous diagnosis of celiac disease, inflammatory bowel disease or any other known intestinal disease. Patients with a positive serology for human immunodeficiency virus were also excluded. Furthermore, patients who had undergone previous gastrointestinal or colonic surgery (except appendicectomy or cholecystectomy) were also excluded. In addition we excluded women who were pregnant or breast-feeding at the moment of clinical evaluation.

In patients diagnosed with MC, we studied the prevalence of celiac disease by determining the genetic markers (haplotype HLA), serological CD-related antibodies (Immunoglobulin A (IgA) tissue transglutaminase antibodies and total IgA) and by assessing histopathological features in duodenal biopsies (on at least six biopsy samples from the duodenal bulb and second/third duodenum segments), according to the Marsh classification [13] and the new simplify classification [14].

2.3. Clinical data

The medical records of each patient were scrutinised for clinical data and complete chronic or frequent drugs intake (defined as more than 3 days weekly) up to 3 months before the carrying out of colonoscopy [15]. All drugs were recorded separately and analysed. The date of diagnosis was defined as the date of colonoscopy when biopsies led to a diagnosis of CC or LC. The type of symptoms and the appearance of anaemia and/or increased inflammatory markers associated with chronic diarrhoea were also defined. All patients included in the study were classified into two groups: patients who met the Roma III criteria [16] for the diagnosis of diarrhoea-dominant irritable bowel syndrome (IBS) without the appearance of "alarm symptoms" (Group 1) and patients who did not meet the Roma III criteria for the diagnosis of diarrhoea-dominant IBS (Group 2), but who presented at least one of the "alarm symptoms" or were aged 50 and over. The "alarm symptoms" were defined as: unexplained weight loss (>10 lbs over 6 months), fever, significant gastrointestinal bleeding (a spotting of red blood on the toilet tissue after a bowel movement was not considered to be an alarm symptom), increased inflammatory markers, presence of iron deficiency anaemia and/or those patients who reported a family history of a first degree relative with colon cancer, celiac disease or inflammatory bowel disease.

2.4. Colonoscopy and biopsy sampling procedure

A complete colonoscopy carried out under conscious sedation was performed on all patients, reaching the cecum in all of them. At least two biopsy samples were obtained with the aid of a standard, open-type endoscopic biopsy forceps in each one of the following locations: (a) cecum and/or ascending colon, (b) transverse colon and (c) descending and sigmoid colon. Biopsies were fixed separately in 4% formalin and routinely processed.

The colonic biopsy specimens were stained with haematoxylin-eosin. Cases of CC were identified by measuring the sub-epithelial collagen layer after van Gieson staining with the aid of an ocular micrometre in a representative and well-orientated section of the mucosa, where three adjacent crypts were cut in a vertical manner extending all the way down to the muscularis mucosa. In those doubtful cases a Masson Trichrome staining was done to optimally assess the existence of a collagen layer.

2.5. Histopathology

Diagnoses of CC vs. LC were based on histopathological criteria assessed by an expert pathologist. CC was defined by: a diffusely distributed and thickened sub-epithelial collagen layer (>10 μm), epithelial damage such as flattening and detachment, inflammation in the lamina propria with mainly mononuclear cells and an increased number of intraepithelial lymphocytes (IEL). LC was defined by: IEL >20 per 100 surface epithelial cells, epithelial damage such as flattening and mucin depletion, inflammation in the lamina propria with mainly mononuclear cells and a sub-epithelial collagen layer <10 μm.

LC cases were identified by counting IEL. The number of IEL per 100 epithelial cells was calculated by counting the number per 300 epithelial cells divided by three. Only the surface epithelium was examined, avoiding areas overlying lymph follicles in the lamina propria. Counting was performed on at least two biopsy samples from different parts of the colon and the mean number for each patient was recorded. Counting of IEL was performed in sections stained with haematoxylin-eosin, and after CD3 immunohistochemistry staining in those cases in which IEL count was close to the cut-off criteria for LC. The severity of both epithelial cell damage and lamina propria inflammation were estimated. Occasional crypt abscesses, cryptitis, crypt distortions or neutrophil leucocytes in the lamina propria were allowed [17,18].

2.6. Data analysis and ethics

The results were expressed as mean and standard deviation (quantitative variables) or as percentages (qualitative variables). The differences in clinical characteristics depending on age group were explored using the chi-square test (categorical variables) and an analysis of variance (quantitative variables). When appropriate, nonparametric tests were used, namely Fisher's exact test and the Mann–Whitney test. Values of $p < 0.05$ were considered to be statistically significant. Incidence calculations were based on the date of diagnosis. Incidence was calculated as a crude rate as well as age-adjusted to the 2009 population of the recruitment area of General Hospital of Tomelloso and standardised to a 2009 Spanish reference population.

Table 1
Characteristics of study subjects with a diagnosis of microscopic colitis and other patients with diarrhoea.

Characteristics	Microscopic colitis ($n=32$)	Diarrhoea without microscopic colitis ($n=253$)	p
Age	50.1 ± 21.8	48.5 ± 19.1	0.68
Sex (males)	15 (46.9%)	145 (57.5%)	0.34
Abdominal pain	4 (12.5%)	29 (11.5%)	0.75
Weight loss	5 (15.6%)	27 (10.7%)	0.54
Fever	0	3 (1.2%)	1
Increased inflammatory markers	1 (3.1%)	15 (6%)	1
Anaemia	0	13 (5.2%)	0.21
Fulfilled Roma III criteria for irritable bowel syndrome	9 (28.1%)	78 (30.8%)	0.98

Table 2
Characteristics of patients fulfilling the Roma III criteria for irritable bowel syndrome with and without a diagnosis of microscopic colitis.

Characteristics	Irritable bowel syndrome ($n=71$)	Irritable bowel syndrome like microscopic colitis ($n=9$)	p
Sex (males)	35 (49.3%)	5 (55.6%)	1
Autoimmune disease	1 (1.4%)	3 (33.3%)	0.004*
Coeliac disease	2 (2.8%)	3 (33.3%)	0.009*
Other diseases	23 (32.4%)	4 (44.4%)	0.48
Drug intake	37 (52.1%)	7 (77.8%)	0.18
NSAID	4 (5.6%)	3 (33.3%)	0.028*
PPIs	23 (32.4%)	3 (33.3%)	1
Psychiatric treatment	13 (18.3%)	2 (22.2%)	0.67

PPIs: proton pump inhibitors; NSAID: nonsteroidal anti-inflammatory drugs.
* Significant.

The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the institutional review board of our hospital. Informed consent was obtained from all patients.

3. Results

3.1. Microscopic colitis prevalence and incidence

During the study period, 271 consecutive patients (154 female and 117 male; median age: 48.3 ± 19.2 years) underwent colonoscopy and microscopic evaluation of colonic mucosal biopsies for watery chronic non-bloody diarrhoea of unknown origin. In the minority of cases (13.7%), the colonoscopy presented an abnormal endoscopic appearance with a different level of colonic mucosal inflammation. Of these patients, 51.4% (19/37) had a subsequently confirmed diagnosis of inflammatory bowel disease, 8.1% (3/37) had a diagnosis of pseudomembranous colitis, 24.3% (9/37) had a histopathological diagnosis of undefined chronic inflammation without the specific features of MC or other types of colitis and 13.5% (6/37) exhibited normal histopathological findings.

Mucosal appearance in colonoscopies was normal in the majority of patients studied (86.3%). Amongst these patients, 13.7% (32/234) fulfilled the criteria of MC; 30 with a diagnosis of LC and 2 with a diagnosis of CC. We found no significant differences between patients with water chronic diarrhoea with or without an MC diagnosis with regard to symptoms at the time of diagnosis, age or gender (Table 1). The annual number of colonoscopies in patients with non-bloody diarrhoea in relation to the total number of colonoscopies was stable during the period between 2008 and 2010 (13.7–11.6%).

The overall prevalence of MC calculated in the recruitment area during the study period was 48 cases/100,000 inhabitants (95%CI: 30–65 cases per 100,000 inhabitants). The mean annual standardised incidence rate of MC was 18 cases/100,000 inhabitants (95%CI: 16.0–20.0 cases per 100,000 inhabitants). Considering separately the two variant of MC, the prevalence of LC was 45 cases/100,000 inhabitants (95%CI: 30–64 cases per 100,000 inhabitants) and the annual standardised incidence rate was 16 cases/100,000 inhabitants (95%CI: 8–29 cases per 100,000 inhabitants). The prevalence of CC was 3 cases/100,000 inhabitants (95%CI: 0.4–11 cases per 100,000 inhabitants) and the annual incidence rate of CC was <1 cases/100,000 inhabitants (95%CI: no determined).

3.2. Microscopic colitis features

We evaluated the characteristics of patients with MC considering them as a single group because the number of patients with CC (2 patients) and CL (30 patients) was too small to be compared. The median age at diagnosis of MC was 48.1 ± 19.4 years, with 21.9% of the subjects being over 70 and 18.8% under the age of 30. No statistically significant differences were observed in the different age groups analysed with respect to gender, clinical symptoms, drug intake or presence of autoimmune or other diseases.

Taking all MC patients into consideration, no statistically significant differences in either prevalence or incidence were observed with regard to gender (17 female and 15 male). Mucosal appearance in colonoscopies was normal in all patients with a diagnosis of MC. Regarding to the extent of colonic involvement, 28% of MC patients (9/32) had a unique location in the right colon and the remaining had diffuse location affecting to all colonic segments.

Associated symptoms were observed only in 25% of MC patients, with a higher prevalence of abdominal pain and weight loss. Increasing values for inflammatory markers were present in only 6.3% of MC patients whereas iron deficiency anaemia was present in only 3.2%. The median duration of symptoms was 16.1 months (range 1–120 months).

The prevalence of autoimmune disease was 21.9% (7/32), with thyroiditis, celiac disease and psoriasis being the most common. In particular, the prevalence of celiac disease in the patients diagnosed with MC was 15.6% (5/32), being in all cases a LC type. All celiac patients showed the presence of HLA-DQ2 and/or HLA-DQ8 and negative IgA tissue transglutaminase antibodies serum levels without IgA deficiency. All patients normalised duodenal mucosal biopsies after 6 months following a gluten-free diet and subsequent reappearance of the lesions in the duodenal mucosa after 6 months of reintroduction of a diet containing gluten. According to the Marsh classification and a new simplify classification, we found two patients with Stage A (three patients with Marsh 1 and one with Marsh 2) and one patient with Stage B1 (Marsh 3a).

3.3. Microscopic colitis and irritable bowel syndrome

During the study period, 84 patients (31%) undergoing a full colonoscopy for diarrhoea of unknown origin fulfilled the Roma III criteria for the diagnosis of diarrhoea-dominant IBS (Table 2). The median age was 35.5 ± 8.7 years with no statistically significant difference with regard to gender. The overall prevalence of MC in suspected diarrhoea-dominant IBS patients was 10.7% (9/84); all were under 50 years of age. It is worth highlighting that in the subgroup of patients that met the Roma III criteria for diarrhoea-dominant IBS, 4.8% (4/84) of them presented inflammatory bowel disease (IBD) in the early stages. Analysing the whole number of patients with an organic intestinal pathology, we found that 15.5% of cases (MC and IBD) occurred in the sub-group of patients that met the Roma III criteria for diarrhoea-dominant IBS. With respect to MC patients, 28.1% consisted of patients fulfilling the Roma III

criteria for diarrhoea-dominant IBS diagnosis at the moment of the endoscopic evaluation.

We found that the presence of autoimmune diseases (33.3% vs. 1.4%, $p = 0.004$), particularly celiac disease, was significantly more frequent in patients diagnosed with MC as compared to patients without an MC diagnosis (33.3% vs. 2.8%, $p = 0.009$). Moreover, MC patients presented a significantly higher intake of non-steroidal anti-inflammatory drugs (NSAID) compared to patients without a diagnosis of MC (33.3% vs. 5.6%, $p = 0.028$). No statistically significant differences with regard to gender, age, clinical symptoms, presence of other diseases or intake of other drugs were observed.

4. Discussion

This study demonstrates that MC, mainly LC, is a relatively common cause of chronic diarrhoea of unknown origin in central Spain. A previous study conducted in northern Spain found lower incidence rates for the disease as compared to North America and Northern Europe, suggesting the existence of a north–south difference in the incidence of MC [8,12]. Our study, which found a higher prevalence of MC in a central region of Spain, suggests a different pattern of distribution of this disease within the same country. The aetiology of MC is still unknown, but leading models of pathogenesis point to autoimmunity, an immune or inflammatory response to luminal factors and medications and, in the case of CC, myofibroblast dysfunction as probable factors [3,19]. Several potential mechanisms have been proposed to explain the pathophysiology of MC, although no dominant mechanism has emerged. The distribution differences for various geographic areas could be justified by exposure to different risk factors.

In our study, MC patients showed an equal ratio of women to men. Previously published data regarding the gender distribution of MC are inconclusive. Some studies have found a consistently high female to male ratio, ranging from 3:1 to 9:1, especially in patients with CC, whereas the ratio in patients with LC is lower, with some studies finding no significant differences [6–8,20,21]. Our results may be due to the higher prevalence of LC as compared to CC in our sample population. However, a review of all published cases of LC and CC showed no difference with regard to gender in MC patients [4].

Although MC can be diagnosed in patients of any age, previously published studies seem to show that it is more common amongst older patients [7–9,21,22]. The median age at diagnosis in our study was lower in comparison to other studies (48.1 years vs. 53–69 years); although this result needs to be confirmed in larger sample size studies, direct comparisons of these findings may be misleading. We examined two different age groups for the appearance of MC (older and younger). MC was diagnosed in about 22% of the patients over 70, as found in previous studies. However, we found that about 19% of patients diagnosed with MC were under 30. This is new data, and suggests that although MC seems to be a disease mainly of late middle age, it should not be discounted in younger patients. Indeed, several other studies have shown that 25% of all MC patients are under the age of 45 and even some paediatric cases have been reported [22–24]. It is important to highlight that MC may represent a new, emerging disease in young patients, especially because the lack of clinical awareness of the prevalence of MC in this age group could reduce the likelihood of carrying out colonoscopies with biopsies to make a subsequent diagnosis.

MC and diarrhoea-dominant IBS share similar symptoms and endoscopic appearance; in fact, there are no markers which predict a differential diagnosis between the two. Currently, the general view is that a patient with chronic watery non-bloody diarrhoea who fulfils the criteria for diarrhoea-predominant IBS should be given only a limited number of tests if there are neither alarm symptoms nor abnormalities in standard blood analyses [15]. Unfortunately, little research has been devoted to the diagnostic overlap between MC and diarrhoea-dominant IBS. A systematic review of the studies published to date shows that an organic disease in patients fulfilling the diarrhoea-dominant IBS Roma III criteria is seldom identified [25]. The usefulness of routinely obtaining colonic biopsies was evaluated in only one study that we reviewed and focused only on rectal biopsies. However, it is well-known that rectal biopsies may be normal in up to 40% of CC cases and that MC is limited to the right colon in 23% of patients [26–29], as well as we observed in our study. It seems clear, then, that the need for obtaining multiple colonic biopsies in diarrhoea-dominant IBS has not been properly evaluated. The fact that there is considerable overlap between symptoms of diarrhoea-dominant IBS and those of MC was demonstrated in a recent retrospective study performed on a population-based cohort of MC patients using the "Rochester Epidemiological Project" database, which showed that 56% of patients fulfilled the Roma II criteria for diarrhoea-dominant IBS [30]. Our data likewise showed that the prevalence of MC in patients fulfilling the diarrhoea-dominant IBS diagnostic criteria is not insignificant, reaching 10.7% of all cases. This is especially important considering the difference in patient management and follow-up. We therefore feel that the clinical symptom-based criteria for diarrhoea-dominant IBS are not specific enough to rule out MC, especially in patients with associated autoimmune diseases and NSAID intake.

In summary, we found a relatively high prevalence and incidence of MC in a central region of Spain, which contrasts with the results of another study carried out in the northern part of the country. This discrepancy probably reflects different rates of exposure to MC-inducing agents. Additionally, our results reinforce the idea that MC should be suspected not only in older patients, but also in a younger population. Finally, we confirmed that patients with suspected diarrhoea-dominant IBS should undergo biopsies of the colon to rule out the possibility of MC. To gain further insight into this subject, prospective studies are needed to identify predictor factors to better distinguish between diarrhoea-dominant IBS and MC.

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