ORIGINAL ARTICLE

Microscopic colitis: prevalence and distribution throughout the colon in patients with chronic diarrhoea

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ABSTRACT

Background: Microscopic colitis presents with chronic diarrhoea with or without abdominal pain. Microscopic colitis is an important cause of chronic diarrhoea. It can be distributed throughout the colon, as well as limited to the right colon. Microscopic colitis is associated with coeliac disease. We studied the prevalence and distribution of microscopic colitis in patients with diarrhoea and normal colonoscopy and we studied the association with coeliac disease.

Methods: Colonoscopy was performed. Biopsies were taken from every segment of the colon. Lymphocytic colitis was defined as the presence of more than 20 lymphocytes per 100 epithelial cells and collagenous colitis was defined as thickening of the basal membrane of more than 10 μm. Upper endoscopy was performed if upper intestinal symptoms were present. If this was the case, small bowel biopsies were taken.

Results: Microscopic colitis was found in 13 out of 103 patients. The distribution was diffuse throughout the colon in ten and restricted to the right colon in three patients. In seven patients, upper endoscopy was performed. Marsh I/II lesions were found in six out of seven patients.

Conclusion: Microscopic colitis was limited to the right colon in 23% of patients. Biopsies of macroscopically normal colonic mucosa in patients with diarrhoea is mandatory.

KEYWORDS

Colonoscopy, diarrhoea, distribution, microscopic colitis

INTRODUCTION

Microscopic colitis is an entity that presents with chronic, watery diarrhoea and with a macroscopically normal looking colonic mucosa.[1,2] In addition to diarrhoea, cramping abdominal pain and weight loss may occur. The peak incidence of microscopic colitis is in the fifth and sixth decade of life and the disorder has a female preponderance.[3] Three forms of microscopic colitis have been identified based on histopathology: lymphocytic colitis, characterised by the presence of a lymphocytic infiltrate in the epithelium; collagenous colitis, in which the subepithelial collagen layer is thickened (>10 μm), and a mixed form.[4-6] Microscopic colitis is recognised as an important cause of chronic diarrhoea. A large study found a frequency of 9.5 per 100 patients with chronic diarrhoea and normal-looking colonoscopies.[7] Shah *et al.* found microscopic colitis in 13 of 168 patients (7.7%) with chronic diarrhoea in a study, which also included patients with endoscopic abnormalities in the colon.[8]

The presence of histopathological changes diffusely throughout the colon has been described, but the microscopic abnormalities may be limited to the transverse and right colon.[9] The distribution of the histopathological abnormalities obviously has direct consequences for the diagnostic tool that should be used. Tanaka *et al.* found a 27% false-negative rate in a group of patients with collagenous colitis if only biopsies were taken within the reach of a 60 cm sigmoidoscope.[10] Another study reports that in even 40% of patients the diagnosis of microscopic colitis would not have been made if sigmoidoscopy were to have been performed instead of colonoscopy, implying that sigmoidoscopy is inferior to colonoscopy in diagnosing this disease.[11] However, others found a false-negative rate

of only 0.2% using sigmoidoscopy in a group of patients with a variety of colonic diseases presenting with chronic diarrhoea claiming sigmoidoscopy to be a suitable and cost-effective diagnostic tool in the evaluation of chronic diarrhoea.[12]

In patients with microscopic colitis, a high frequency of coeliac disease has been reported[13-15] and persisting diarrhoea in coeliac disease despite adherence to a gluten-free diet warrants a search for microscopic colitis.[16,17]

The goals of the present study were 1) to assess the prevalence of microscopic colitis in patients with chronic diarrhoea and normal looking colonic mucosa, 2) to determine the distribution of microscopic colitis in the colon to investigate whether sigmoidoscopy would suffice in these patients and 3) to investigate the association with coeliac disease.

MATERIALS AND METHODS

During a period of two years (1999-2000), all patients who presented with chronic diarrhoea underwent a total colonoscopy using a standard colonoscope after giving informed consent. The study took place in a large general hospital. Chronic diarrhoea was defined as loose, frequent bowel movements existing for more than three months. All patients were given midazolam intravenously for sedation and they were monitored with pulse oximetry during the procedure. If no endoscopic abnormalities were found, patients were included in the study. Two mucosal biopsies were taken from every segment of the colon (caecum, ascending colon, transverse colon, descending colon and sigmoid colon) and from the rectum. These biopsies were oriented on a methylcellulose strip paper (Sartorius AG, Germany) using two little wooden sticks. The biopsies were oriented on the strip in the same order as they were taken. Thus, the first biopsies on the strip were from the caecum and the last ones were from the rectum.

Histopathological examination was performed. The biopsies were fixed in 10% (v/v) neutral buffered formalin and embedded in paraplast. Thereafter, 2 μm thin sections were prepared, which were routinely stained, using haematoxylin and eosin. When an increase in intra-epithelial lymphocytes was suspected, the exact number of intra-epithelial lymphocytes per 100 surface epithelial cells was determined by histomorphometry, counting an area of maximally 400 epithelial cells, using a Leica Imaging System (Cambridge, United Kingdom; Software Qwin 2.1 with a locally designed programme) after immunohistochemical staining of the lymphocytes (CD3 clone F7.2.38, DAKO, Glostrup, Denmark; detection system Power Vision HRP-mono, Labvision, Fremont CA, USA). If there was suspicion of collagenous colitis, the basal membrane was also visualised using the AZAN

staining and measured using the Leica Imaging System. Lymphocytic colitis was defined as the presence of more than 20 lymphocytes per 100 epithelial cells and collagenous colitis was defined as thickening of the basal membrane of more than 10 μm. Mucosal biopsies from all segments of the colon as mentioned above were examined and the distribution of microscopic colitis along the colon was assessed. Duodenal biopsies were obtained in patients with an indication for upper endoscopy because of symptoms. In these duodenal biopsies histopathology and histomorphometry were performed. The exact number of intra-epithelial lymphocytes per 100 surface epithelial cells was determined by histomorphometry, counting an area of maximally 400 epithelial cells, after immuno-histochemical staining of the lymphocytes as described above. Histopathology of duodenal biopsies was expressed according to the Marsh classification.[18]

An increased number of intraepithelial lymphocytes of >30 per 100 epithelial cells with otherwise normal histology was defined as Marsh I.[19,20] An increased number of intraepithelial lymphocytes in combination with crypt hyperplasia was defined a Marsh II lesion and partial/total villous atrophy as Marsh III.

RESULTS

In a two-year period, 103 patients (66 female, mean age 45 years, range 17-82 years) with chronic diarrhoea and normal colonoscopy were studied. The caecum was reached in all patients. No complications due to the procedure or sedation occurred. Microscopic colitis was diagnosed in 13 (11 female) patients in total (13%); lymphocytic colitis was diagnosed in 12 patients and collagenous colitis in one patient. The mean age of these patients was 52 years (range 17-82). The presenting symptoms were diarrhoea in all patients, abdominal cramps in 11 (85%) and weight loss in 8 (62%) patients.

The distribution of histopathological abnormalities was diffuse throughout the colon in ten (77%) patients with lymphocytic colitis while the inflammatory changes were located only in the transverse colon and ascending colon in three patients, among whom the patient with collagenous colitis. In these three patients (23%) the diagnosis would have been missed if only sigmoidoscopy had been performed. Seven patients had upper intestinal symptoms. Upper endoscopy was performed in these patients and small bowel biopsies were obtained. In six of these patients (86%) histopathological investigation was abnormal. In three patients, biopsies showed an increased number of intraepithelial lymphocytes with normal villous architecture (Marsh I), and in three patients an increased number of intraepithelial lymphocytes and crypt hyperplasia was seen (Marsh II). Partial or total villous atrophy (Marsh III) was not found in any of the patients.

DISCUSSION

Microscopic colitis is an important cause of chronic, watery diarrhoea. The pathogenesis of microscopic colitis is not completely understood. An autoimmune basis has been suggested. Also, microscopic colitis may be caused by several drugs. PPIs may cause microscopic colitis,[21] as well as NSAIDs.[22]

Several studies found a prevalence of 5 to 10% in populations with chronic diarrhoea and normal looking mucosa.[7,23] In our study we investigated 103 patients with total colonoscopy. All patients had normal looking mucosa. In 13 patients (13%) microscopic colitis was diagnosed. Some reports have suggested that in microscopic colitis the histopathological abnormalities are not distributed evenly throughout the colon, but may be located mainly in the right and transverse colon.[10,11] Our results show that in our group of patients the distribution of the disease was diffuse throughout the colon in most of the patients. However, in a considerable proportion of patients the histopathological abnormalities were located solely in the right and transverse colon, not within reach of a sigmoidoscope. In these patients the diagnosis microscopic colitis would not have been made if a sigmoidoscopy had been performed instead of a total colonoscopy. This finding is in line with other studies.[9-11] Our results imply that a diagnosis of microscopic colitis cannot be excluded without a total colonoscopy being performed. To orient our biopsies, we used a simple and reliable method using a methylcellulose strip paper and two little wooden sticks. This simple method allows good orientation of biopsies. Optimal orientation of biopsies is advocated in the diagnosis of coeliac disease[24,25] and we hypothesised that also in microscopic colitis it may facilitate pathological examination, especially in collagenous colitis, where the measurement of the thickness of the basal membrane may depend on the quality of the orientation.

The association of microscopic colitis, lymphocytic as well as collagenous colitis, with coeliac disease is well established.[13,14,26] In our study, we also found abnormal duodenal histology in a high percentage of patients.

It should be mentioned that not all patients with microscopic colitis underwent upper endoscopy, but only those patients with upper abdominal symptoms. We found an increased number of intraepithelial lymphocytes (Marsh I) in three patients and increased intraepithelial lymphocytes with crypt hyperplasia (Marsh II) in another three. The significance of Marsh I-II lesions has not yet been fully elucidated. Currently it may be regarded as latent coeliac disease and is usually not treated with a gluten-free diet.[27] However, some recent studies indicate that a significant proportion of these patients may indeed respond to a gluten-free diet.[28-30] However, these studies were small and uncontrolled and the clinical relevance of Marsh I lesions needs to be further clarified.

Nevertheless, if a patient with microscopic colitis does not respond to treatment, one should be suspicious of coexisting coeliac disease. Alternatively, a patient with coeliac disease and persisting diarrhoea despite strict adherence to a gluten-free diet should undergo evaluation for microscopic colitis.[16,17]

In conclusion, our study confirms that microscopic colitis is an important cause of chronic diarrhoea. The distribution of this disease throughout the colon can be diffuse but the histopathological abnormalities are located mainly in the ascending colon in a considerable proportion of patients. Therefore, patients with chronic diarrhoea should undergo a total colonoscopy with biopsy sampling from both right and left colon.

NOTE

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