Received: 23.8.2007 **Accepted: 15.6.2008**

Original Article

Is microscopic colitis a missed diagnosis in diarrhea-predominant Irritable Bowel Syndrome?

Hamid Tavakkoli, Farshad Sheikh Esmaeili**, Mohammad Hasan Emami***, Parvin Mahzouni****, Saeid Haghdani******

Abstract

BACKGROUND: There are controversies about the importance of biopsies of normal colon mucosa in the investigation of patients with diarrhea predominant irritable bowel syndrome (IBS). On the other hand, microscopic colitis may be missed based on normal colonoscopy and laboratory examination in this group of patients

METHODS: The study took place in Alzahra and Noor hospitals and Poursina Hakim Research Institute, from 2002 to 2004. Eligible patients were those suffering from diarrhea for at least 4 weeks. A total of 138 patients were included in the study after meeting Rome criteria (II) with normal CBC, ESR, stool examination and no endoscopic abnormality.

RESULTS: The histologic findings in 138 patients with diarrhea predominant IBS with mean age of 34.7 years (female 55.1% and male 44.9%) were as follows: 10 patients (7.2%) had collagenous colitis and 3 patients (2.2%) were compatible with lymphocytic colitis. No significant diagnostic histologic findings were seen in the rest of patients. Collagenous colitis was detected in 13% of right colon biopsies and in 10% of sigmoid and transverse colon biopsies. Nocturnal diarrhea was found in 30% of collagenous colitis patients.

CONCLUSIONS: Total colonoscopy and multiple biopsies in diarrhea predominant IBS patients are necessary for early diagnosis of microscopic colitis.

KEY WORDS: Irritable bowel syndrome, microscopic colitis, colonoscopy, biopsy, diarrhea.

JRMS 2008; 13(4): 202-206

Irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal medical problems in clinical practice, affecting between 10-20% of general population.[1] It is characterized by clinical symptoms such as abdominal discomfort or pain, change in defecation habit, and abnormal stool. Clinically, IBS is classified into three types: diarrhea-predominant IBS, constipation-predominant IBS and alternating diarrhea and constipation IBS. In barium enema or colonoscopy, IBS usually presents no structural changes or evidence of systemic diseases.[2,3] Microscopic colitis is a term that includes two idiopathic forms of inflammatory bowel disease: lymphocytic colitis and collagenous colitis. The cardinal clinical manifestation of microscopic colitis is a watery, non-bloody diarrhea.[4] Collagenous colitis is not common, with an annual incidence reported to be 0.6-2.5/100,000 and a prevalence of 15.7 cases/100,000.[5] However, this may well be an

*Assistant Professor, Department of Gastroenterology, Alzahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran.
e-mail: h_tavakoli@med.mui.ac.ir (Corresponding Author)
**Fellow of Gastroenterology, Digestive Disease Research Center (DDRC), Tehran University of Medical Sciences, Tehran, Iran.
***Associate Professor, Department of Gastroenterology, Alzahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran.
****Associate Professor, Department of Pathology, Alzahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran.
*****Medical Student and Research Assistant, Isfahan University of Medical Sciences and Poursina Hakim Research Institute, Isfahan, Iran.

underestimate given the increasing importance of performing colonic biopsies on patients with chronic diarrhea, even when the mucosa appears normal.[6] Indeed, up to 5% of patients with chronic diarrhea may have collagenous colitis.[7] The diagnosis of these conditions is dependent on well-defined histological criteria in association with a clinical picture of chronic diarrhea and normal macroscopic findings at endoscopy.[8] Thus, differentiating patients with functional bowel disorders from those with microscopic colitis can be difficult. Our study, evaluated patients with diarrhea type IBS for microscopic colitis.

Methods

The study involved patients suffering from diarrhea for at least 4 weeks and IBS according to the Rome criteria (II) in two general hospitals, Alzahra and Noor and Poursina Hakim Research Institute, during a period of two years (2002-2004). All patients were interviewed by a resident of internal medicine to fill out a detailed clinical questionnaire. Exclusion criteria included patients with abnormal laboratory tests. Patients underwent colonoscopy by a gastroenterologist using a standard video colonoscope (Olympus CV-145). If no endoscopic abnormalities were found, patients were included in the study. At least three mucosal biopsies were taken from the sigmoid colon and/or the transverse and ascending colon. The biopsies were fixed in 10% (v/v) neutral buffered formalin and embedded in paraplast. Histopathological examination was performed thereafter; thin sections were prepared, which were routinely stained, using hematoxylin and eosin and Masson's trichrome staining. All histopathological examinations were carried out by one pathologist. The number of intraepithelial lymphocytes per 100 surface epithelial cells was determined in an area of maximally 400 epithelial cells. Diarrhea was defined as having frequent, loose stool for more than four weeks. Collagenous colitis was defined as thickening of the sub-epithelial collagenous band more than 10 µm with surface epithelial damage, increased plasma cells, eosinophil in lamina propria, and increased intraepithelial lymphocytes. Lymphocytic colitis was defined as the presence of more than 20 lymphocytes per 100 epithelial cells without thickened collagen band. The following variables were examined: age, sex, smoking habits, detailed drug history (use of aspirin, non-steroidal anti-inflammatory drugs (NSAIDs)), diarrhea (duration, type and frequency), the presence of associated "autoimmune conditions" including rheumatoid arthritis, thyroid disorders, diabetes, systemic diseases (systemic lupus erythematosis, polymyalgia, Sjögren's disease, Raynaud's phenomenon), asthma/allergy, psoriasis and history of previous surgery. CBC, ESR and stool smear were also checked. Statistical analyses were carried out with SPSS 13 software.

Results

Sixty-two men and seventy-six women met Rome criteria (II) and were enrolled in the study. The characteristics of IBS patients are listed in table 1. Laboratory examinations of IBS patients revealed normal findings. No number of patients with IBS, experienced improvement with symptoms by avoiding lactose foods for at least two weeks. According to our findings, diagnoses of patients were as follows: 125 (95.5%) mild-reactive pattern, 10 (7.2%) collagenous colitis and 3 (2.2%) lymphocytic colitis. In addition to diarrhea as a prominent clinical manifestation, patients also suffered from the following symptoms: 104 (75.4%) inadequate evacuation, 98 (71%) abdominal pain, 92 (66.7%) urgency, 88 (63.8%) bloating and abdominal distention and 76 (55.1%) patients from mucous discharge. The mean age of collagenous colitis patients was 41 years. Nocturnal diarrhea was significantly more frequent in patients with collagenous colitis (30% versus 10%). None of the patients had a past history of NSAIDs usage, smoking, or drinking alcohol. Collagenous colitis was detected in 13% of right colon biopsies and in 10% of patients with sigmoid and transverse colon biopsies.

Table 1. Characteristics of IBS patients.

Patient Characteristics	Results (percent)
Mean age	34.7 years
Education level	
Illiterate	21 (15.2%)
High school	39 (28.3%)
Diploma	39 (28.3%)
More than diploma	12 (8.7%)
Bachelor and more	27 (19.6%)
Disease duration >1 year	93 (67.4%)
NSAIDs usage	15 (10.9%)
Nocturnal diarrhea	15 (10.9%)
Smoking	20 (14.5%)
Alcohol	19 (13.7%)
Stress-exacerbation	129 (93.5%)
Relief with defecation	132 (95.7%)
Past medical history	
Negative	98 (71%)
Diabetes mellitus	1 (0.7%)
Cardiovascular disease	4 (2.9%)
Hypertension	3 (2.2%)
Duodenal ulcer	6 (4.3%)
Site of biopsy	
Sigmoid colon	24 (17.4%)
Transverse colon	42 (30.4%)
Transverse sigmoid colon	51 (37%)
Right colon	21 (15.2%)

Discussion

In a colonoscopic assessment of 1018 patients with chronic non-bloody diarrhea in Sweden, 5% and 4.5% had collagenous colitis and lymphocytic colitis, respectively. About 88% and 67% of these patients were females, respectively. Median age at diagnosis was 64 years in collagenous colitis and 59 years in lymphocytic colitis. Frequency of microscopic colitis was found in 10% of all patients with non-bloody diarrhea referred for colonoscopy and in almost 20% of those older than 70 years.[9] MacIntosh et al obtained rectal biopsy from patients with IBS and found no significant pathologic findings. They concluded that patients with normal colonoscopy and diagnosis of IBS are unlikely to have histologic abnormalities in the rectum and rectal biopsies are unnecessary in the investigation of IBS.[10] In another study consisted of 30 IBS patients, 23.3% lymphocytic colitis was reported and none had collagenous colitis. Investigators recommended that functional disorders of the bowel should be evaluated for possible lymphocytic colitis.[11] Based on the results of our study, the incidence of collagenous colitis was 7.2%, which shows the importance of colonoscopy and biopsy in patients with diarrhea predominant IBS. The mean age of collagenous colitis patients was 41 years, which is lower than that in other studies. This difference may be due to the lower age of IBS patients. Other features of microscopic colitis that are occasionally present include abdominal cramping, anorexia, nausea, mild weight loss, urgency and incontinence.[12] In reviewing 104 patients with microscopic colitis by Chande et al, 66 had collagenous colitis, 35 had lymphocytic colitis and 3 were diagnosed with both disorders at different times. The most common clinical presentations were diarrhea, weight loss, abdominal pain, fecal urgency and nocturnal stools.[13] The presence of nocturnal diarrhea is a distinguishing feature in irritable bowel syndrome, which is often a differential diagnosis.[8] In our study, the frequency of nocturnal diarrhea in patients with collagenous colitis was 30% versus 10% in IBS patients. An association between NSAIDs and collagenous colitis has been described, as has remission on their withdrawal.[14] NSAIDs use was not seen in collagenous colitis patients in our study. However, in another study the use of drugs such as NSAIDs were reported in 34% of patients.[13] There was a high incidence of arthritis and NSAIDs use in Goff et al study too.[15] The unusual associations of lansoprazole with development of collagenous colitis and, ticlopidine with lymphocytic colitis were reported.[16,17] These findings show the importance of evaluation of drug use in patients with microscopic colitis. Coffee consumption has been noted to be excessive in some patients with collagenous colitis. Although this is unlikely to be the cause of the disorder, it may be a contributing factor to the diarrhea, as it is known to induce small bowel hypersecretion. Smoking is also more prevalent among those with collagenous colitis,[18] even though none of those studied with collagenous colitis in our

study smoked or drank alcohol. Concomitant diseases occur in up to half of all patients with collagenous colitis.[4,19] Most commonly associated autoimmune disorders are rheumatoid arthritis, celiac disease, thyroid dysfunction and diabetes mellitus. Other diseases associated include pernicious anemia, CREST syndrome, scleroderma, Sjogren's syndrome and primary biliary cirrhosis. In addition, arthritis affects approximately 10% of patients. This is typically a peripheral monoarthritis or polyarthritis, which involves hands and wrists. The rheumatoid factor is negative.[13,20] Our study showed no significant association of collagenous colitis with concomitant diseases in patients past histories. However, the number of patients is less than that we can show any association between these variables. Recent studies discuss a less invasive method. Rectal luminal level of nitric oxide is greatly increased in inflammatory bowel disease and collagenous colitis and it is correlated with disease activity. This is minimally invasive and a rapid tool for differentiating between patients with active bowel inflammation and IBS. It may be useful for monitoring the patient's response to treatment [21] and possibly conducting primary screening of IBS patients who need colonoscopy and biopsy. In our study, detection of collagenous colitis in right colon biopsy was higher than that in left colon, which is compatible with previous investigations. In conclusion, helpful symptoms such as nocturnal diarrhea can be noted to distinguish microscopic colitis from diarrhea type. IBS patients should be told that total colonoscopy and multiple biopsies are necessary for early diagnosis of this subgroup of patients.

References

1. Tillisch K, Chang L. **Diagnosis and treatment of irritable bowel syndrome: state of the art.** *Curr Gastroenterol Rep* 2005; 7: 249-256.
2. Camilleri M. **Management of the irritable bowel syndrome.** *Gastroenterology* 2001; 120: 652-668.
3. Longstreth GF. **Definition and classification of irritable bowel syndrome: current consensus and controversies.** *Gastroenterol Clin North Am* 2005; 34: 173-187.
4. Bohr J, Tysk C, Eriksson S, Abrahamsson H, Jarnerot G. **Collagenous colitis: a retrospective study of clinical presentation and treatment in 163 patients.** *Gut* 1996; 39: 846-851.
5. Bohr J, Tysk C, Eriksson S, Jarnerot G. **Collagenous colitis in Orebro, Sweden, an epidemiological study 1984-1993.** *Gut* 1995; 37: 394-397.
6. Shah RJ, Fenoglio-Preiser C, Bleau BL, Giannella RA. **Usefulness of colonoscopy with biopsy in the evaluation of patients with chronic diarrhea.** *Am J Gastroenterol* 2001; 96: 1091-95.
7. Giardiello FM, Lazenby AJ. **The atypical colitides.** *Gastroenterol Clin North Am* 1999; 28: 479-90.
8. Tagkalidis P, Bhathal P, Gibson P. **Microscopic colitis.** *J Gastroenterol Hepatol* 2002; 17: 236-248.
9. Olesen M, Eriksson S, Bohr J, Jarnerot G, Tysk C. **Microscopic colitis: a common diarrhoeal disease. An epidemiological study in Orebro, Sweden, 1993-1998.** *Gut* 2004; 53: 346-350.
10. MacIntosh DG, Thompson WG, Patel DG, Barr R, Guindi M. **Is rectal biopsy necessary in irritable bowel syndrome?** *Am J Gastroenterol* 1992; 87: 1407-09.
11. Tuncer C, Cindoruk M, Dursun A, Karakan T. **Prevalence of microscopic colitis in patients with symptoms suggesting irritable bowel syndrome.** *Acta Gastroenterol Belg* 2003; 66: 133-136.
12. Pokorny CS, Selby WS. **Microscopic colitis: an underdiagnosed cause of chronic diarrhoea--the clue is in the biopsies.** *Intern Med J* 2003; 33: 305-309.
13. Chande N, Driman DK, Reynolds RP. **Collagenous colitis and lymphocytic colitis: patient characteristics and clinical presentation.** *Scand J Gastroenterol* 2005; 40: 343-347.
14. Bohr J. **A review of collagenous colitis.** *Scand J Gastroenterol* 1998; 33: 2-9.
15. Goff JS, Barnett JL, Pelke T, Appelman HD. **Collagenous colitis: histopathology and clinical course.** *Am J Gastroenterol* 1997; 92: 57-60.
16. Rosa I, Nahon S, Cohen C, Abd A, I, Flejou JF, Hagege H *et al.* **[Ticlopidine-induced lymphocytic colitis].** *Ann Med Interne (Paris)* 1999; 150: 437-439.

17. Tremaine WJ. **Diagnosing collagenous colitis: does it make a difference?** *Eur J Gastroenterol Hepatol* 1999; 11: 477-479.
18. Baert F, Wouters K, D'Haens G, Hoang P, Naegels S, D'Heygere F *et al.* **Lymphocytic colitis: a distinct clinical entity? A clinicopathological confrontation of lymphocytic and collagenous colitis.** *Gut* 1999; 45: 375-381.
19. Jawhari A, Talbot IC. **Microscopic, lymphocytic and collagenous colitis.** *Histopathology* 1996; 29: 101-110.
20. Zins BJ, Sandborn WJ, Tremaine WJ. **Collagenous and lymphocytic colitis: subject review and therapeutic alternatives.** *Am J Gastroenterol* 1995; 90: 1394-1400.
21. Reinders CI, Herulf M, Ljung T, Hollenberg J, Weitzberg E, Lundberg JO *et al.* **Rectal mucosal nitric oxide in differentiation of inflammatory bowel disease and irritable bowel syndrome.** *Clin Gastroenterol Hepatol* 2005; 3: 777-783.