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• *BASIC RESEARCH* •

Lymphocytic colitis: A clue to bacterial etiology

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Abstract

AIM: To find out the role of bacteria as a possible etiological factor in lymphocytic colitis.

METHODS: Twenty patients with histopathological diagnosis of lymphocytic colitis and 10 normal controls were included in this study. Colonoscopic biopsies were obtained from three sites (hepatic and splenic flexures and rectosigmoid region). Each biopsy was divided into two parts. A fresh part was incubated on special cultures for bacterial growth. The other part was used for the preparation of histologic tissue sections that were examined for the presence of bacteria with the help of Giemsa stain.

RESULTS: Culture of tissue biopsies revealed bacterial growth in 18 out of 20 patients with lymphocytic colitis mostly *Escherichia coli* (14/18), which was found in all rectosigmoid specimens (14/14), but only in 8/14 and 6/14 of splenic and hepatic flexure specimens respectively. In two of these cases, *E coli* was associated with proteus. Proteus was found only in one case, Klebsiella in two cases, and *Staphylococcus aureus* in one case. In the control group, only 2 out of 10 controls showed the growth of *E coli* in their biopsy cultures. Histopathology showed rod-shaped bacilli in the tissue sections of 12 out of 14 cases with positive *E coli* in their specimen's culture. None of the controls showed these bacteria in histopathological sections.

CONCLUSION: This preliminary study reports an association between *E coli* and lymphocytic colitis, based on histological and culture observations. Serotyping and molecular studies are in process to assess the role of *E coli* in the pathogenesis of lymphocytic colitis.

Key words: Lymphocytic colitis; *E coli*; Histopathology; Culture

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INTRODUCTION

Microscopic colitis is a syndrome consisting of chronic watery diarrhea, a normal or near normal gross appearance of the colonic mucosa, and a specific histological picture described as either lymphocytic or collagenous colitis[1]. The term microscopic colitis was first introduced by Read *et al*[2] that was found in eight patients who were having idiopathic chronic diarrhea and normal colonoscopic findings. The diagnosis of microscopic colitis in such patients was based on the presence of excess amount of chronic inflammatory cells in the lamina propria of colorectal mucosa. A closely related term "lymphocytic colitis" was introduced by Lazenby *et al*[3], who reported that the most distinctive histological feature of microscopic colitis is the presence of an excess amount of intraepithelial lymphocytes, and renamed microscopic colitis as "lymphocytic colitis". Recently, the histopathology of lymphocytic colitis has been more specified by Lamps and Lazenby[4].

The etiology of lymphocytic colitis is still unclear, and several factors have been claimed. First, it is induced by drugs especially non-steroidal-anti-inflammatory drugs (NSAIDs)[5]. However, subsequent studies found that there is no association between NSAID consumption and microscopic colitis[6]. Vascular tonics have also been suspected to play a part in the pathogenesis of lymphocytic colitis via chronic activation of the mucosal immune system by one or several components of such drugs[7]. Other drugs that claimed to be a cause of lymphocytic colitis include Lansoprazole[8] and Modopar[9]. The second concept is the reported association of microscopic colitis with celiac disease, which may indicate a common pathogenesis[1,10,11]. Nevertheless, many patients with celiac disease do not show colonic lymphocytosis[12]. Lastly it is the possible role of pathogenic organisms. Some investigators have found spirochetes in some patients with microscopic colitis, and suggested that these microorganisms are capable of inducing the disease[13]. Conversely, earlier studies reported that spirochetes have no clinical significance[14]. In a search for infectious causes, Afzalpurkar *et al*[15] investigated 14 patients with chronic idiopathic diarrhea by stool examination and stool culture as well as a culture of the jejunal fluid. Although stool examination and culture were negative, abnormal growth

of bacteria in the jejunal fluid was noted in four patients. Similarly, the culture of the jejunal aspirate in 14 patients having chronic idiopathic diarrhea has revealed bacterial growth in one patient who was successfully treated with antibiotics[2].

The aim of the current preliminary study was to search for a possible role of the pathogenic bacteria in lymphocytic colitis. This has been achieved by thorough histologic examination as well as culture of the colonic tissue specimens, which is to the best of our knowledge not previously reported in the literature.

MATERIALS AND METHODS

Patients

The present study consisted of 20 patients fulfilling the classic definition of lymphocytic colitis, which is described as a triad of idiopathic chronic, watery diarrhea, normal or nearly normal colonoscopic findings, and colonic epithelial lymphocytosis without a thickened subepithelial collagen band[16]. The patients were chosen from the in- and outpatients of Ain-Shams University Hospital during the period between 1999 and 2001, after excluding all other causes of diarrhea by a thorough clinical examination, radiologic, endoscopic, and laboratory investigations. The exclusion criteria were autoimmune diseases, any systemic disease that could cause diarrhea as diabetes, history of food sensitivity, use of laxatives or other drugs that could cause diarrhea, presence of ova and parasites or occult blood in stools.

Ten age- and sex-matched healthy volunteers with no diarrhea or any other gastrointestinal diseases were used as negative controls. The endoscopic and histologic pictures of their colonic mucosae were normal. All patients and controls were not allowed to take antibiotics for 3 wk before the biopsy, since antibiotic treatment may affect the bowel microbial flora. Informed written consent was obtained from all the patients and volunteers.

Stool analysis

Microscopic examination of fresh unstained smears was done to exclude parasitic infestation.

Colonoscopic examination and biopsy

Using lower CF 100 L video colonoscope (Olympus), the whole colon was examined for any pathological lesions including the inspection of the terminal ileum if possible. Patients were selected on the basis of having normal or nearly normal colonoscopic findings. From each patient and control, four tissue samples were taken from each of the following sites: hepatic flexure (HF), splenic flexure (SF), and rectosigmoid region (RS). These biopsy specimens were collected separately, then each specimen was divided into two parts, the first part was put in normal saline and sent for culture, the other part was fixed in 10% buffered formalin and sent for histopathology.

Culture studies of biopsy samples

For all subjects, fresh colonic tissue specimens obtained from HF, SF, and RS regions were incubated separately on the media listed in Table 1 to detect bacterial flora. Specimens were crushed before incubation. The isolated intestinal bacteria were identified by colony morphology, microscopic examination of gram stained smears, conventional biochemical reactions and API20 E identification system (BioMerieux) for the identification of Gram-negative bacteria.

Histopathology

Formalin-fixed colonic tissue specimens obtained from the 20 patients and 10 controls (3 specimens from each subject) were processed separately for the preparation of paraffin blocks. The latter were sectioned at 5 μm and stained with hematoxylin and eosin (H&E) for routine examination, Masson trichrome for the demonstration of subepithelial collagen band, and modified Giemsa stain to search for bacteria (as followed in the cases of chronic gastritis) to detect *Helicobacter pylori*[17]. One pathologist (T.E.H.) examined all the tissue sections without the knowledge of the clinical or endoscopic findings. All 60 specimens were examined for the histologic criteria of lymphocytic colitis, which were modified by Lazenby *et al*[3]. These criteria were simplified as follows. (1) Surface epithelial damage, which was seen as flattened or syncytial appearance of surface cells instead of the tall columnar cells that are normally observed. (2) Crypt distortion. Each of these two findings was graded according to severity into 1-3 scales (1+: mild, 2+: moderate, and 3+: marked). (3) Mononuclear cellular infiltrate in the lamina propria. This was graded into 1-4 scales (1+: normal, 2+: mild, 3+: moderate, and 4+: marked). (4) Intraepithelial lymphocytes. It was scored as the number of lymphocytes per 100 surface epithelial cells. It is worth mentioning that any case showing histologic features other than lymphocytic colitis was excluded from the study. These histologic exclusion criteria included features suggestive of inflammatory bowel disease[18], features of collagenous colitis[19], presence of ova or parasites, presence of viral inclusions, and melanosis coli.

Statistical analysis

Fisher's exact test was used to compare the patients and controls regarding the frequency of the bacterial growth.

Chi-square test was used to assess the association between the presence of bacteria and the severity of the histopathological features.

RESULTS

Clinical data

Patients with lymphocytic colitis included in the study consisted of 15 males and 5 females with a male to female ratio of 3:1. Ages ranged 20-67 years, with a mean of 36 ±10.3 years. All patients presented with chronic watery diarrhea of unknown cause for a period of 1-4.5 years with a mean of 2.5±0.76 years. The daily motions ranged 3-7 times (mean 4.5±1.3 times). All patients had associated mild to moderate abdominal discomfort. Five patients

Table 1 Culture media used for the detection of bacterial flora in colonic biopsies

Medium	Temperature	Incubation time (h)	Organism
MacConkey's agar	37 ℃	48-72	Coliform bacilli (*E coli* and Klebsiella) and Proteus
Aerobic blood agar	37 ℃	24-48	*Staphylococcus aureus*
Anaerobic blood agar	37 ℃	24-48	Anaerobic bacteria as Bacteroides spp.
Microaerophilic Campy-blood agar	42 ℃	24-48	*Campylobacter jejuni*
MacConkey's selective medium	25 ℃	24-48	*Yersinia Enterocolitica*
Selenite broth enrichment medium and Salmonella-Shigella agar	37 ℃	24	*Salmonella* and *Shigella*

Table 2 Culture results of 60 colonic tissue specimens from 20 patients with lymphocytic colitis

Organism	Patients (n = 20)	RS specimens (n = 20)	SF specimens (n = 20)	HF specimens (n = 20)
E coli	12	12	8	6
E coli + Proteus	2	2	0	0
Proteus	1	1	1	0
Klebsiella	2	2	2	1
Staphylococcus aureus	1	1	1	1
Total number	18	18	12	20

RS: rectosigmoid, SF: splenic flexure, HF: hepatic flexure.

Table 3 Histopathologic data of 60 colonic biopsies from 20 patients with lymphocytic colitis

Feature	RS	SF	HF
1 Surface epithelial damage			
1+	8	10	8
2+	6	6	6
3+	6	4	6
2 Crypt distortion			
1+	17	16	17
2+	3	4	3
3+	0	0	0
3 LP Inflammation			
2+	5	6	2
3+	11	10	12
4+	4	4	6
4 Mean % of IEL	23	22	28

RS: rectosigmoid, SF: splenic flexure, HF: hepatic flexure, LP: lamina propria, IEL: intraepithelial lymphocytes.

had significant weight loss. No other gastrointestinal manifestations were found.

Culture results

Bacterial growth was observed in the colonic tissue specimens of 18 out of the 20 patients (90%). The most frequent isolated organism was *E coli*, which was demonstrated in 14 out of 18 culture positive cases (77.8%). These organisms were seen in the rectosigmoid specimens in all the 14 cases, splenic flexure growth was found in 8 of them, and hepatic flexure growth in 6 cases only. In 2 out of the 14 cases, *E coli* was associated with the growth of Proteus. Other isolated bacteria were Klebsiella (two cases) and *Staphylococcus* aureus (one case). Other organisms such as *Shigella, Salmonella, Campylobacter, Yersinia* did not grow on their specific media. In the controls, *E coli* was obtained from the rectosigmoid samples of two cases (20%). The frequency of the bacterial growth was significantly higher in the patients than in the controls (P = 0.0003) (Table 2).

Histopathological results

The most prominent feature in all 60 colonic biopsies obtained from the 20 patients was the increased number of mononuclear cells in the lamina propria (Figure 1A) observed in all the three regions examined (rectosigmoid, splenic, and hepatic flexures), indicating total colitis. The inflammatory cells were mainly lymphocytes with less number of plasma cells and histiocytes; few polymorphonuclear cells were present in two cases with no crypt abscess formation. A small number of eosinophils were seen in three patients. Epithelial damage was mild to moderate in the majority of colonic biopsies (Figure 1A). The average crypt distortion was mild to moderate in all colonic biopsies. Few lymphocytes could be seen between the crypt epithelial cells, but not in the crypt lumen (Figure 1B). No other inflammatory cells were present in the lumen or epithelial cells of the crypts.

The percentage of the inflammatory cells in the surface epithelium ranged 15-50% with a mean of 23%, 22%, and 28% in the rectosigmoid, splenic flexure and hepatic flexure, respectively. The intraepithelial inflammatory cells were lymphocytes only (Table 3 and Figure 1C).

In 12 out of 18 patients with bacterial overgrowth in their colonic tissue specimens, rod-shaped bacilli were seen in the histologic tissue sections obtained from various colonic sites. These bacilli were visible on H&E-stained sections, but were more easily demonstrated by Giemsa stain. They were closely applied to the surface epithelium (Figure 1D), or within the lumen of the crypts which showed destruction of their lining cells (Figure 1E). It is important to note that the intercellular and intracellular localization of the organisms could not be assessed because these modes of colonization could not be definitely identified by light microscopy alone. The presence of bacteria was significantly associated with the degree of epithelial damage (χ^2 = 9.9, P = 0.007) and the degree of the cellular infiltrate in the lamina propria

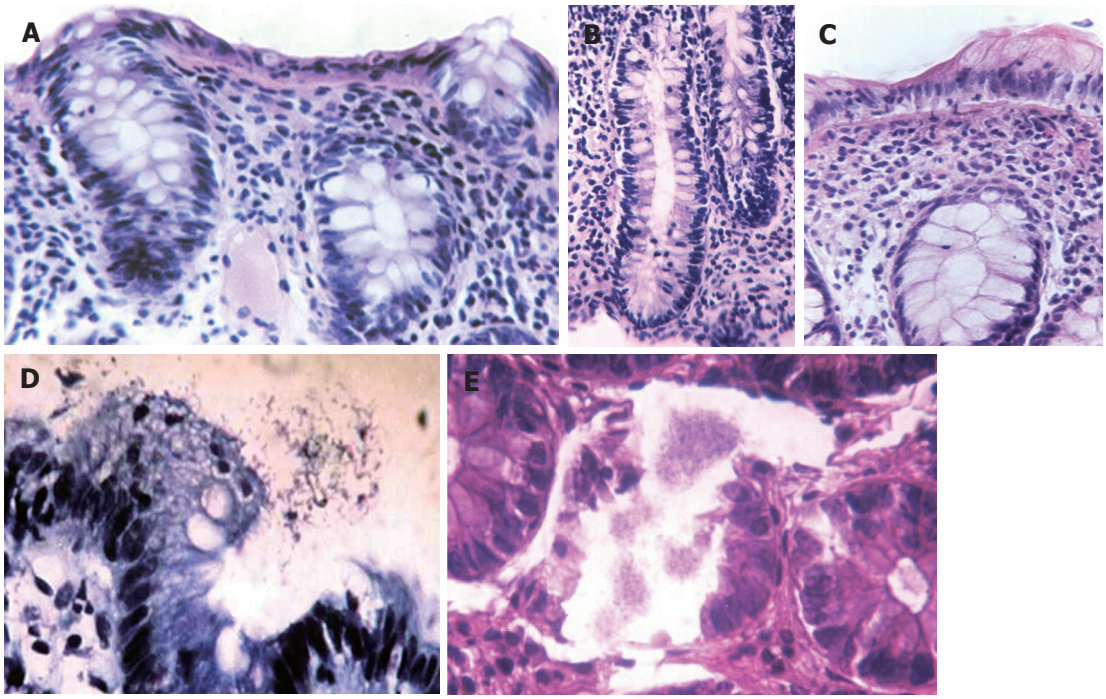

Figure 1 Cases of lymphocytic colitis showing respectively the damage of surface epithelium and increased mononuclear cells in lamina propria (H&E ×250) (**A**), few lymphocytes between crypt epithelial cells (H&E ×250) (**B**), intraepithelial lymphocytes (H&E ×250) (**C**), rod-shaped bacilli adherent to the surface epithelium (Giemsa stain ×400) (**D**), and bacilli within the lumen of transverse section of crypt (H&E ×400) (**E**).

(χ^2 = 6.0, P = 0.05). No significant relationship could be obtained between the presence of bacteria and the degree of crypt distortion (Table 4).

In all 30 colonic biopsies obtained from the 10 healthy controls, the colonic mucosa was nearly normal with no visible bacilli by H&E and Giemsa staining.

Table 4 Correlation between bacteria in tissue sections and histopathologic features in 60 colonic biopsies from 20 patients with lymphocytic colitis

Feature	Bacteria		χ^2	P
	+	−		
1 Epithelial damage				
1+	1	25	9.9	0.007
2+	4	14		
3+	7	9		
2 Crypt distortion				
1+	10	40	0.4	NS
2+	2	8		
3+	0	0		
3 LP Inflammation				
2+	2	11	6.0	0.05
3+	4	29		
4+	6	8		

LP: lamina propria, NS: not significant.

DISCUSSION

The main purpose of the present preliminary study was to investigate the possible role of bacteria in the pathogenesis of lymphocytic colitis. To achieve this aim, patients with definite diagnosis of lymphocytic colitis and normal controls were subjected to colonoscopy and biopsy. Specimens were examined in two ways. First, histopathological examination, including a thorough search for bacteria, similar to that for *H pylori* in gastric biopsies. Second, culture of colonic tissue specimens on specific media to isolate bacterial growth. Although some authors have investigated the possible role of infection in lymphocytic colitis or chronic idiopathic diarrhea, their methodology is limited to stool culture and/or culture of the jejunal fluid[2,15,19,20]. To the best of our knowledge, this is the first study, which attempted to search for bacteria in the colonic biopsies in cases of lymphocytic colitis by histologic examination of tissue sections as well as culture of the colonic tissue.

Microscopically, we could identify small or large number of rod-shaped bacilli closely related to the surface of the colonic mucosa and within the lumen of the crypts in 12 out of 14 patients with positive *E coli* in biopsy culture. It seems that *E coli* was most likely seen in the histologic sections of our tissue specimens, because these bacilli were seen in patients with positive *E coli* in biopsy culture.

The demonstration of these bacilli in the colonic mucosa of our patients with lymphocytic colitis raises several questions. The first question is why they have not been seen before in colonic tissue sections of such cases? We think that these bacteria have not been previously demonstrated because Giemsa stain is not routinely applied for colonic mucosal biopsy specimens and bacteria are easily overlooked on H&E-stained sections. The second question to be raised is whether these bacteria

are pathogenic or merely commensals in the colonic mucosa. From our point of view, we suggest that these bacilli, which have been demonstrated histologically, are pathogenic rather than commensals, since they are closely related to the mucosal surface and within the lumen of crypts, and not within the tissue debris. Moreover, they are always associated with prominent colonic pathology. It is worthy of notion that we could not demonstrate such bacteria in all colonic biopsies obtained from the healthy controls.

The relation between lymphocytic colitis and bacterial infection is still controversial. Gebbers and Laissue[13] reported the presence of spirochetes in some patients with microscopic colitis, and suggested that these microorganisms are capable of inducing the disease. On the other hand, earlier studies reported that spirochetes have no clinical significance[14]. Perk *et al*[21] presented a patient who had chronic watery diarrhea and showed stool culture positive for *Campylobacter jejuni*. Examination of her colonic biopsies led to the diagnosis of lymphocytic colitis. The authors believed that the patient's disease is due to an infectious process. Also, Tremaine[22] reported that bismuth subsalicylate is effective in the treatment of some patients with lymphocytic colitis, a finding that supports the concept of infectious etiology in such disease.

It is interesting to note that the search for bacterial etiology in cases of chronic watery diarrhea has been expanded to include the type of bacteria responsible for this disease. The most common organism investigated in this regard is *E coli*[23-25].

Diarrheagenic *E coli* (*E coli* causing diarrhea) is divided into four groups: enteropathogenic (causing acute diarrhea in infants and children), enteroinvasive (causing Shigella-like dysentery), enterohemorrhagic (causing hemorrhagic colitis and bloody diarrhea) and enterotoxigenic (causing travelers' diarrhea)[26]. In addition to these groups, two other types, which were previously classified as enteropathogenic, have been recently identified. The first is enteroaggregative *E coli* (EaggEC), which is now considered as a cause of prolonged diarrhea[27]. Another recently described type of *E coli* is the diffusely adherent type which has been found to be significantly associated with chronic diarrhea[28]. It is important to note that many strains of *E coli* belonging to the classic enteropathogenic type are now found to be enteroaggregative by DNA hybridization or PCR. This indicates that routine culture studies and even serotyping are of limited value for the identification of various groups of diarrheagenic *E coli*[29].

These new types of *E coli* may be more likely the types seen in the tissue sections and biopsy culture of our patients, being associated with chronic diarrhea as mentioned above, and may be related to the pathogenesis of lymphocytic colitis, since it can colonize both in large and in small intestines. In a study by Kang *et al*[30], strains of enteroaggregative *E coli* isolated from patients with diarrhea resulted in the colonization of both small and large intestines. In support to this suggestion is the study of Afzalpurkar *et al*[15], who found that 4 out of 14 patients with chronic idiopathic diarrhea have abnormal growth of bacteria in aspirated jejunal fluid and the results of quantitative cultures are consistent with contamination. In addition, one of the four patients had steatorrhea, which is one of the hallmarks of bacterial overgrowth syndrome. These data have led the authors to speculate that *E coli* or other bacteria not identified by routine culture methods are involved in the etiology of chronic idiopathic diarrhea. It is worth mentioning that the lack of response to antibiotics in the four patients with bacterial overgrowth reported in the previous study should not be considered as evidence against bacterial etiology, since multiple drug resistance in EaggEC has been reported by some studies recommending quinolone treatment for EaggEC-associated diarrhea[31].

In conclusion, bacteria play a possible role in lymphocytic colitis in which rod-shaped bacilli adherent to the colonic mucosa can be seen as in cases of *Helicobacter* gastritis. Further studies are now in process to investigate the pathogenicity of these organisms in case of lymphocytic colitis.

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