Lymphocytic colitis: a distinct clinical entity? A clinicopathological confrontation of lymphocytic and collagenous colitis

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Abstract

Background and aims—It is not known whether lymphocytic colitis and collagenous colitis represent different clinical entities or constitute part of a spectrum of disease.

Methods—Detailed clinical features and histological findings were compared in a large series of patients with confirmed lymphocytic and collagenous colitis.

Results—Histological diagnosis was confirmed in 96 patients with collagenous colitis and 80 with lymphocytic colitis. Twenty eight per cent of patients with collagenous colitis and 26% of patients with lymphocytic colitis had overlapping but less pronounced histological features. Both groups were equal in terms of age, use of aspirin and non-steroidal anti-inflammatory drugs, associated autoimmune conditions, arthritis, diarrhoea, and abdominal pain. The male:female ratio was 27:73 for collagenous colitis and 45:55 for lymphocytic colitis (p=0.013). Twenty five per cent of patients with collagenous colitis compared with 14% of patients with lymphocytic colitis were active smokers; only 8.3% of patients with collagenous colitis had stopped smoking compared with 23% of patients with lymphocytic colitis (p=0.013). Drug induced disease was suspected for ticlopidine (two collagenous colitis, four lymphocytic colitis) and flutamide (four lymphocytic colitis). Mean duration of symptoms before diagnosis was two months for lymphocytic colitis and four months for collagenous colitis. Overall prognosis was generally mild; 84% of patients with lymphocytic colitis and 74% of patients with collagenous colitis reported resolution or significant improvement (p=0.033).

Conclusions—Collagenous and lymphocytic colitis are similar but not identical. Patients with lymphocytic colitis present somewhat earlier and are less likely to be active smokers. Symptoms are milder and more likely to disappear in lymphocytic colitis. Ticlopidine and flutamide should be added to the list of drugs inducing colitis.

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Patients with chronic watery diarrhoea of no obvious aetiology with macroscopic normal colonoscopy may show clear histological abnormalities on colonic biopsy. Collagenous colitis and lymphocytic colitis are two related although distinct histological entities that have been implicated in these conditions.

It is unknown whether they are both manifestations of a single disease or whether they represent separate albeit related clinical conditions. A large retrospective series of collagenous colitis has been published.[1] Reports on lymphocytic colitis are scarce.[2 3] A series of 27 patients was recently published in this journal.[4] Furthermore, except for anecdotal reports on drug induced cases no clues about the aetiology are available. The clinical features and treatment of these diseases are mainly based on case reports and small uncontrolled series.

To describe further and elucidate the clinical, laboratory, and histopathological features of lymphocytic colitis the Belgian Inflammatory Bowel Disease (IBD) Research group set up a registry of both collagenous colitis and patients with lymphocytic colitis, collecting a large and representative sample of cases from both academic and community hospitals. In addition, collagenous colitis was compared with lymphocytic colitis to look for statistically significant differences in risk factors, clinical presentation, response to treatment, and prognosis.

Materials and methods

PATIENTS

We set up a registry of patients with a presumed diagnosis of lymphocytic and collagenous colitis. All members of the Belgian IBD Research Group were asked to perform a search in their clinical files and/or the pathological database at their hospitals from January 1994 to December 1996. Eight university centres and seven larger regional hospitals randomly distributed throughout the country participated in this study.

DIAGNOSTIC CRITERIA

The original paraffin wax embedded biopsy blocks were collected for all patients and new sections were made and stained with haematoxylin and eosin. All slides were blindly reviewed by two expert pathologists according

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Abbreviations used in this paper: IEL, intraepithelial lymphocytes; IBD, inflammatory bowel disease; NSAID, non-steroidal anti-inflammatory drug.
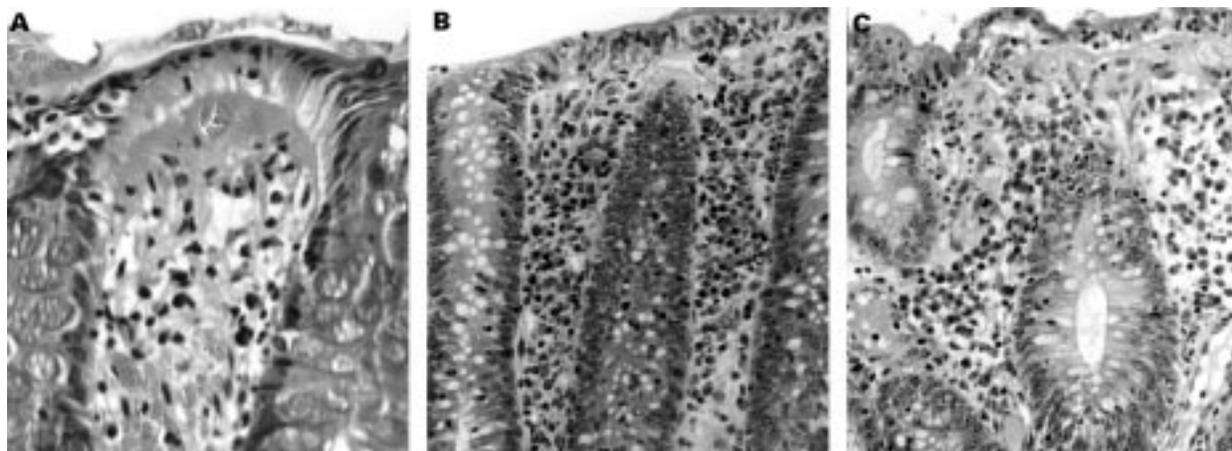
Figure 1   (A) Microphotograph of collagenous colitis showing clear thickening of the subepithelial collagen table, mild lamina propria inflammation, and no increase in intraepithelial lymphocytes (IELs) (haematoxylin and eosin; original magnification × 500). (B) Microphotograph of lymphocytic colitis with increase in IELs (haematoxylin and eosin; original magnification × 300). © Microphotograph of overlap form (collagenous and lymphocytic colitis) with thickening of the subepithelial collagen table, epithelial damage, and increase in IELs (haematoxylin and eosin; original magnification × 300).

to stringent histological criteria. Only cases with at least three different biopsy specimens available, obtained at the same colonoscopy, were included. Three specimens were considered necessary in order to assess the diffuse nature of the disease and to allow more accurate measurements of the collagen table and counting of the intraepithelial lymphocytes (IELs). Patients were either rejected or classified as having collagenous colitis or lymphocytic colitis. Histological diagnosis of lymphocytic colitis was confirmed when the number of IELs exceeded 20 per 100 epithelial cells (fig 1B). The diagnosis of collagenous colitis was made when the subepithelial collagen band on a well oriented section of the mucosa had the typical features and exceeded 10 μm (fig 1A). In addition an increased mixed inflammatory cell infiltrate in the lamina propria, predominantly mononuclear, was present in both entities. Other findings including regenerative epithelial changes with mucin depletion, surface epithelial damage and sloughing, rare infiltration of neutrophils and eosinophils, both in the epithelium and the lamina propria, were sometimes noted but not required for the diagnosis. Cases with overlapping histological features for both diseases were classified according to the most predominant findings (fig 1C). The biopsy specimens were obtained from various sites of the colon in all patients. All specimens were assessed by two independent observers (KW and KG) but quantifications were performed by one observer. Measurements were performed using an ocular micrometer, on well oriented sections of the mucosa—that is, a section where at least three adjacent crypts are cut in their vertical plane. For all cases three measurements were performed (on specimens from different sites). Results are expressed as mean (SD).

In addition to histological features, the following clinical criteria were required for inclusion in the study: a well documented clinical history of chronic watery diarrhoea with no obvious other cause as documented by stool examinations for ova, parasites and pathogens, and endoscopic or radiological study. In particular all patients underwent a complete colonoscopy with random biopsies from different segments. Except for diverticulosis all (ileo)colonoscopies showed no obvious signs of macroscopic inflammation or other significant abnormalities. Biopsy specimens could not be obtained in the vicinity of a tumour or a significant polyp.

Only patients fulfilling all the above criteria were selected for this study. If the initial histological diagnosis was not confirmed by review of the biopsy samples, patients were rejected.

DATA
Collaborating physicians were asked to fill out a detailed clinical questionnaire through a retrospective review of their clinical files. When data were missing the patients or their local physicians were contacted by telephone. All data were centralised anonymously and entered into a computer database for further statistical analysis. The following data were collected.

Clinical data
Age at diagnosis, sex, smoking habits (never, former, current, unknown), use of coffee (excessive, normal, unknown). Detailed drug history (specific reference to the use of aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), H_2 receptor antagonists, and phlebotropic drugs). Diarrhoea (duration, type, and frequency). The presence of meteorism, abdominal pain, weight loss, and extraintestinal symptoms. The presence of associated "autoimmune conditions" including rheumatoid arthritis, thyroid disorders, coeliac disease or dermatitis herpetiformis, lymphocytic gastritis, diabetes, systemic diseases (systemic lupus erythematosus, polymyalgia, Sjögren's disease, Raynaud's phenomenon, sarcoidosis), asthma/allergy, psoriasis was recorded as well as previous cholecystectomy. Type of treatment initiated initially and follow up data were recorded including duration, type of treatment, improvement or resolution of symptoms, and follow up biopsies if available.

Table 1 Histopathological features

	Collagenous colitis (n=96)	Lymphocytic colitis (n=80)
Thickness of collagen band (µm)		
Mean	11.4 (3)	5.5 (2.4)
Range		3–10
Number of IELs/100 epithelial cells		
Mean	13.6	29.4 (9)
Range	5–27	
Overlap forms with LC/CC	27 (28%)	21 (26%)

Number of cases with biopsies examined = 210.
Number of cases with confirmed diagnosis: CC = 96; LC = 80; total = 176 (83.8% of cases confirmed).
LC, lymphocytic colitis; CC, collagenous colitis; IEL, intraepithelial lymphocytes.

Endoscopy data

A detailed colonoscopy report was included: mucosal appearance, absence of significant polyps or colorectal cancer, ileoscopy (with or without biopsies) performed or not.

Laboratory data

Data from blood samples obtained within one week prior to diagnosis were recorded for erythrocyte sedimentation rate (mm/first hour), C-reactive protein (mg/dl), K^+ (mEq/l), leucocyte count $(10^9/l)$, percentage eosinophils, and antinuclear factor if available.

Histopathology data

Sample quality and orientation. The number and the locations (taken from different areas) were recorded. Samples that were difficult to interpret due to poor orientation or quality were excluded from the study. Microscopic evaluation included: (1) the epithelial component (surface irregularity, crypt architecture, surface epithelial cell and crypt epithelial cell abnormalities, presence of ulcerations or erosions); (2) the subepithelial collagen table (mean thickness and aspect) measured in five fields using a calibrated eye piece; (3) the presence of an inflammatory infiltrate (number of IELs/100 surface epithelial cells counted in five different high power fields; presence, distribution, and composition of the infiltrate in the lamina propria).

STATISTICS

Non-parametric statistical analysis was performed using the Wilcoxon and the χ^2 test in the SAS program.

Table 2 Demographic features and risk factors

	Collagenous colitis (n=96)	Lymphocytic colitis (n=80)	p Value*
Sex: M/F (%)	27/73	45/50	0.013
Age (y) at diagnosis			NS
Mean	64.3	63.6	
SD	14.5	15.8	
Range	23–87	22–91	
Smoking			0.013
Active smoker	24 (25%)	11 (14%)	
Former smoker	8 (8.3%)	18 (23%)	
Never smoked	37 (38.5%)	25 (31%)	
Unknown	31 (32.3%)	26 (33%)	
Coffee use			NS
Excessive	5 (5%)	1 (1.2%)	
Normal	28 (29%)	30 (37.5%)	
Unknown	63 (66%)	49 (61.2%)	
Aspirin	11 (11.4%)	17 (21.2%)	NS
NSAID	16 (16.6%)	12 (15%)	NS

*χ^2 test.
NSAID, non-steroidal anti-inflammatory drug.

Results

HISTOPATHOLOGY

Colonic biopsy specimens taken at the moment of diagnosis of 210 patients from 15 different centres identified as having collagenous or lymphocytic colitis were reviewed. Histological confirmation by two expert blinded pathologists was the first and paramount criterion for inclusion in this study. The diagnosis of either of the forms was confirmed in 176 patients (83.8%). Agreement between the two pathologists was reached in all cases. In four cases consensus was reached after a discussion using the multiheaded microscope. The patients were classified according to the predominant histological finding as having collagenous (96 patients) or lymphocytic colitis (80 patients). Twenty three cases were rejected because of poor quality of the biopsy specimens and 12 because only one specimen was available. Eight remaining patients had very suggestive clinical and histological findings but did not meet the stringent histological criteria. Table 1 presents the main histopathological features. The thickness of the collagen band was heterogeneous when biopsy specimens from different sites were compared. Overall it varied between 5 and 20 µm in the 69 cases with pure collagenous colitis (no increase in IELs above 20/100 epithelial cells). There was a small, non-significant tendency for a more increased thickness in the right colon. For the 59 patients with pure lymphocytic colitis (with a collagen band less than 10 µm) the number of IELs/100 epithelial cells varied between 10 and 65. There was no tendency for a more prominent increase in a particular area of the colon. Twenty eight per cent of patients with collagenous colitis had overlapping features with lymphocytic colitis and 26% patients with lymphocytic colitis had an increase in their collagen band. The mean thickness of the collagen band was 11.4 µm in collagenous patients and 5.5 µm in the overlap syndromes. The mean number of IELs per 100 epithelial cells was 29.4 in the patients with lymphocytic colitis and 13.6 in the overlap patients. All patients showed a chronic polymorphic inflammatory infiltrate in the lamina propria. A clear erosion was present in only one patient. A striking high number of macrophages–histiocytes was present in one and an equally high number of giant cells in another patient, both in a subepithelial position.

DEMOGRAPHIC FEATURES AND POTENTIAL RISK FACTORS

Table 2 presents the demographic features and potential risk factors. The mean age of the patients with collagenous colitis and lymphocytic colitis was 64.3 years (range 23–87) and 63.6 years (range 22–91) respectively. As fig 2B shows, however, the male patients with collagenous colitis had a widespread age distribution at diagnosis whereas for the females there was a pronounced peak incidence in the sixth and seventh decade. For the patients with lymphocytic colitis there seemed to be a more normal distribution for both sexes with a peak incidence between 60 and 70. Almost three
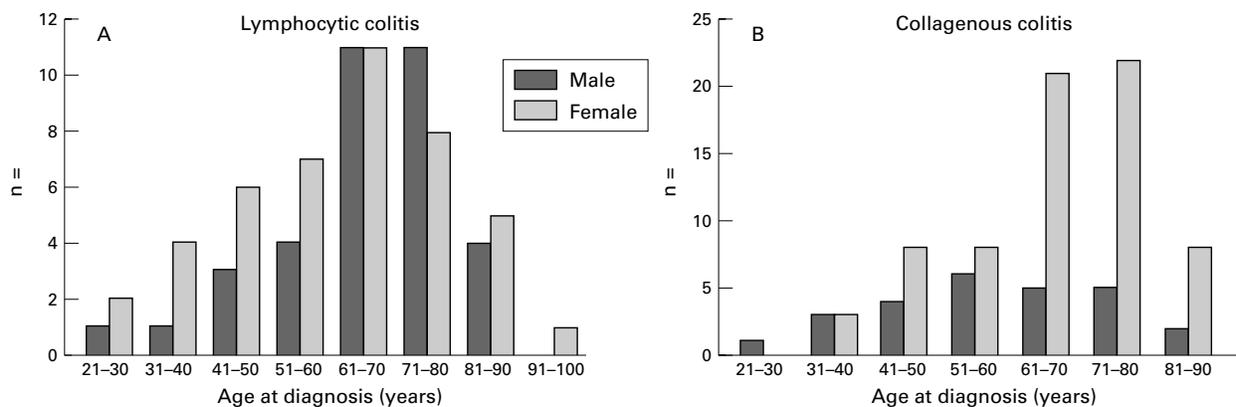
Figure 2   Age and sex distribution for lymphocytic colitis (A) and collagenous colitis (B).

quarters of the patients with collagenous colitis were women; in the lymphocytic colitis group the male/female distribution was almost equal (p=0.013). In terms of the suggested risk factors there were no significant differences in the use of aspirin or NSAIDs. There was, however, a statistical significant difference in the smoking behaviour of both patient groups. Twenty five per cent of patients with collagenous colitis compared with 14% of patients with lymphocytic colitis were active smokers, whereas only 8.3% of patients with collagenous colitis had stopped smoking compared with 23% of patients with lymphocytic colitis (p=0.013).

A detailed list of the medications used by the patients in both groups was recorded and compared. Eleven of 96 patients with collagenous colitis and 15 of 70 patients with lymphocytic colitis were taking aspirin (NS). Fourteen of 96 collagenous colitis and 11 of 70 patients with lymphocytic colitis were taking an NSAID on a more or less regular basis before diagnosis. A high number of patients in this series (14 collagenous colitis and 19 patients with lymphocytic colitis) were taking antidepressants, both tricyclics and selective serotonin reuptake inhibitors. Only four collagenous colitis and two

patients with lymphocytic colitis used venotropic drugs. In none of the few patients taking H_2 receptor blockers (three collagenous colitis and four lymphocytic colitis) was an association with the use of ranitidine or cimetidine suspected. However, for ticlopidine (two collagenous colitis and four lymphocytic colitis), flutamide (four lymphocytic colitis), and herbal preparations (two collagenous colitis) there was a strong suspicion (independently by different physicians and the patients themselves) that the symptoms were related to these drugs. In all of these patients there was a temporal association between onset of symptoms and start of the drugs. For flutamide the diagnosis was made after a median of two months (range 1–3); for ticlopidine after a median of three months (range 1.5–12). The symptoms resolved quickly in all patients without any anti-inflammatory treatment on discontinuation of these drugs. For all other medicines no associations with the development of diarrhoea or colitis were suspected by the patients or their physicians.

SYMPTOMS AND ASSOCIATIONS
The symptoms of both patient groups were similar and did not differ from what has been described in the literature (table 3). The diarrhoea was mostly chronic and watery with more than five bowel movements per 24 hours in nearly 50% of the patients. There was a tendency towards a shorter onset of symptoms before diagnosis in the lymphocytic colitis group (median two months compared with four months in the collagenous colitis group, p=0.06). The diarrhoea was accompanied by meteorism and slight abdominal pain in about 20% of patients in both groups. Slight weight loss was reported in 42% of collagenous colitis and 48% of lymphocytic colitis cases. Joint pain was reported in 11% and 13% respectively. No other extraintestinal manifestations were noted.

No significant laboratory abnormalities were noted except for hypokalaemia in 12 patients, usually with more severe diarrhoea. Three patients with ticlopidine induced colitis had a moderate eosinophilia (7.2%, 11.6%, and 16.5%). Associated diseases of both conditions were recorded with particular attention to autoimmune conditions and if cholecystec-

Table 3   Symptoms

	Collagenous colitis (n=96)	Lymphocytic colitis (n=80)	p Value*
Diarrhoea			NS
Acute	10 (10%)	15 (19%)	
Intermittent	15 (16%)	11 (14%)	
Chronic	70 (74%)	54 (67%)	
Duration of symptoms before diagnosis (months)			0.06
Median	4	2	
p25–p75	1–24	0–6.5	
Range	0–600	0–240	
Frequency (no of bowel movements per day)			NS
<2	11 (12%)	14 (17%)	
3–5	40 (41%)	30 (38%)	
>5	45 (47%)	36 (45%)	
Stool consistency			NS
Watery	66 (69%)	59 (73%)	
Mucous	9 (94%)	6 (7.5%)	
Bloody	1 (1%)	2 (3%)	
Meteorism	20 (21%)	14 (18%)	NS
Abdominal pain			NS
Severe	5 (5%)	0 (0%)	
Slight	17 (18%)	17 (21%)	
Intermittent cramps	28 (29%)	7 (9%)	
Weight loss	41 (42%)	38.4 (48%)	NS
Extraintestinal manifestations			NS
Arthritis	10 (11%)	10 (13%)	

*χ^2 test.

Table 4 Associated conditions

	Collagenous colitis (n=96)	Lymphocytic colitis (n=80)
Rheumatoid arthritis	2	3
Thyroid disorders	13	9
Coeliac disease	3	7
Diabetes		
Insulin dependent	2	2
Non-insulin dependent	6	6
Systemic diseases		
SLE	–	1
Sjögren's disease	1	–
Raynaud's phenomenon	2	1
Sarcoidosis	1	–
Multiple sclerosis	–	–
Asthma/allergy	7	5
Lymphocytic gastritis	–	1
Psoriasis	1	1
Total autoimmune	38	36
Cholecystectomy	7	6

SLE, systemic lupus erythematosus.

Table 5 Treatment and follow up data

	Collagenous colitis (n=96)	Lymphocytic colitis (n=80)
Treatment initiated	58%	45%
Type of treatment		
Diet + discontinue medication	5%	8%
Loperamide	13%	8%
Cholestyramine	2%	–
Sulphasalazine	25%	11%
5-ASA	4%	3%
Metronidazole	2%	6%
Corticosteroids	6%	3%
Duration of treatment (months)		
Mean	22.1	8.8
Median	5	3
p25–p75	3–18	1–6.7
Range	0–240	0–52
Follow up available	n=69 (72%)	n=39 (49%)
Prognosis		
Symptoms gone	24 (34%)	23 (59%)
On treatment	7	7
No treatment	17	16
Symptoms improved	28 (40%)	10 (25%)
On treatment	17	9
No treatment	11	1
No change	17 (26%)	6 (15%)
On treatment	15	4
No treatment	2	2

5-ASA, 5-aminosalicylic acid.

tomy was performed. A high number of associated autoimmune conditions was noted for both collagenous colitis and lymphocytic colitis (table 4). Seven patients with lymphocytic colitis and three patients with collagenous colitis had a longstanding diagnosis of coeliac disease. They presented with diarrhoea despite no obvious gluten ingestion. There were no significant differences in the number of cholecystectomies for both conditions.

TREATMENT AND PROGNOSIS

About half of the patients in this series from different centres were treated with a variety of non-specific or anti-inflammatory agents (table 5). Patients were treated for a median of three (for lymphocytic colitis) to five (for collagenous colitis) months. Overall the prognosis of both conditions was relatively good. Follow up was available in 72% of patients with collagenous colitis and 49% of patients with lymphocytic colitis. Prognosis for lymphocytic colitis was better than for collagenous colitis. After a median follow up of six months 59% of patients with lymphocytic colitis compared with 34% of patients with collagenous colitis

reported a resolution of symptoms. Only 15% of patients with lymphocytic colitis compared with 26% of patients with collagenous colitis had persistent important symptoms (p=0.033).

Discussion

The disease processes referred to as collagenous colitis, microscopic colitis, and lymphocytic colitis have many clinical, endoscopic, and histological similarities; however, their precise interrelation remains controversial.[5] As recently argued by authorities in the field we prefer not to use the confusing term microscopic colitis.[6]

Recently a large collagenous colitis series has been reported.[7] Our study is by far the largest series of patients with lymphocytic colitis reported. Detailed comparison of histological and clinical data in these two conditions reveals several important observations.

Colonic biopsy specimens of all our patients were independently reviewed by two expert pathologists. Diagnosis was confirmed in all cases included in this study. The high rate of agreement between the two pathologists can probably be explained by the strict nature of the diagnostic criteria. In eight patients with equal or very similar symptoms biopsies were very suggestive of a mild collagenous colitis or lymphocytic colitis but did not meet the stringent histological criteria. Although they were not included in this study they probably represent mild forms of the same condition. Whereas the diagnosis of collagenous colitis is relatively easy, lymphocytic colitis is a less well known condition and was clearly underreported in some centres.

In both groups cases with overlapping features were observed. The precise meaning of this is not clear. While this microscopic finding might indicate a relation between lymphocytic colitis and collagenous colitis the clinical data seem to indicate that both conditions are different. The microscopic relation between collagenous colitis and lymphocytic colitis is however limited. A mild thickening of the collagen table can be seen in some cases of lymphocytic colitis but this feature is not consistent in all biopsy specimens from the same patient. The same is true for the increase in IELs in collagenous colitis. The overlap can probably be explained by the limited morphological repertoire of the inflammatory reaction of the colonic mucosa. Microscopic review of all sections also revealed a few special features. Extensive superficial damage in the form of an erosion was present in one patient. A peculiar form of colitis was observed in two other patients: a subepithelial accumulation of histiocytes and giant cells. Other alternative aetiologies such as infections and systemic diseases were excluded in these two patients.

As reported in other smaller groups we found a clear sex difference between the two conditions.[3] A peak incidence around the sixth decade is noted mainly for female patients with collagenous colitis and to a lesser extent for patients with lymphocytic colitis, but the diagnosis should be suspected as early as age 20.

We found interesting data for tobacco use in both patients groups. Patients with collagenous colitis are more likely to be active smokers and patients with lymphocytic colitis are significantly more likely to be ex-smokers. These data are even more convincing if one considers the sex differences and median age group of these patients. In analogy with ulcerative colitis it is possible that tobacco use may have an important influence on the colonic mucosa and its antigen handling. These data on smoking behaviour of both patient groups may also explain the higher incidence of lung cancer reported for collagenous colitis compared with patients with lymphocytic colitis.[7]

Non-steroidal anti-inflammatory drugs have been associated with collagenous colitis. Despite special attention to this matter only 15% of patients in both groups were using NSAIDs in our series. These figures are lower then the 18/31 patients in a reported case control study.[8] A high percentage of our patients were using a variety of antidepressant drugs. It is unknown whether this reflects a causal relation or if these drugs are prescribed for presumed functional diarrhoea. Clear causal relations are however suspected for ticlopidine and flutamide (an antiandrogenic drug). Although diarrhoea is a well known side effect of both drugs the pathogenesis is unexplained. A few cases of ticlopidine and no cases of flutamide induced lymphocytic colitis have been reported.[9–11] Because no patient in this series underwent a rechallenge with either of these drugs we realise that there is no hard evidence. But we believe that the temporal association and the quick resolution of symptoms on discontinuation are suggestive of a causal relation.

No cases in this series were thought to be associated with the use of ranitidine or phlebotomic drugs as previously reported.[11–13] Two patients started using herbal preparations shortly before the onset of symptoms. In these patients symptoms disappeared spontaneously after discontinuing use of these preparations. The incidence of cholecystectomy was equal for lymphocytic colitis and collagenous colitis, and did not seem to differ from an age and sex matched control population.

The high incidence of the associated autoimmune conditions and joint symptoms suggests a possible underlying autoimmune pathogenic mechanism. In particular the association of lymphocytic colitis with coeliac disease is striking. The observed histological colonic changes in these patients may be due to a toxic luminal agent other than gluten. Lymphocytic colitis seems to be non-responsive to a gluten free diet, but a detailed histological study with follow up colonic biopsies has not been reported to our knowledge. Coeliac patients presenting with diarrhoea while strictly adhering to their gluten free diet should therefore undergo colonoscopy with biopsies to look for colonic abnormalities. Other studies found differences in HLA patterns for lymphocytic colitis and not for collagenous colitis.[13–15]

In general lymphocytic colitis seems to have a somewhat milder presentation and a better prognosis. Overall both conditions are less chronic than initially reported. If one considers the bias from patients lost to follow up the overall prognosis is likely to be even better than the figures reported. In this large series no cases with life threatening diarrhoea were encountered. Patients received a variety of medical treatments; no diverting ileostomies or colectomies were performed.[15–17] The numerous drugs used in an uncontrolled way do not allow conclusions to be drawn on efficacy from these retrospective data.

In summary, lymphocytic and collagenous colitis are related but not identical clinical conditions. Although overlap syndromes seem to exist, their particular histological presentation, difference in sex, smoking behaviour, and prognosis suggest two distinct clinical syndromes. The precise pathogenic mechanism remains obscure but is likely to be multifactorial. As in patients with chronic idiopathic IBD there may be an underlying immune dysregulation causing an inappropriate inflammatory reaction of the colonic mucosa, possibly modified by smoking and NSAID use, to a rather common luminal antigen. Among unknown triggering factors different classes of drugs and possibly herbal preparations can be involved. Ticlopidine and flutamide should be added to the list of known causes. Controlled prospective data on the efficacy of different anti-inflammatory drugs are urgently needed. These trials should be placebo controlled and focus on true refractory cases excluding all possible drug induced cases.

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