A retrospective study on a cohort of patients with lymphocytic colitis

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ABSTRACT

Objective: the term “microscopic colitis” includes lymphocytic colitis (LC) and collagenous colitis, bearing common clinical presentation distinguishable only by histopathological examination of colonic biopsies. This study reports on demographic and clinical characteristics, and outcome of a cohort of patients with LC.

Methods: demographic, clinical and histopathological data were reviewed. Every patient underwent total colonoscopy with multiple biopsies examined by an expert pathologist. Diagnosis of LC was confirmed if histopathological criteria were present. Routine laboratory tests were collected to rule out other diagnosis.

Results: we included 80 patients (28 males; mean age: 46.4 years). At diagnosis, 71 patients (88%) reported diarrhea, 46 (58%) abdominal pain, 21 (36%) weight loss, 10 (13%) nausea. Regarding autoimmune or inflammatory diseases accompanying LC, thyroid disorders and celiac disease (CD) ranked first. Moreover, in over 10% of patients who underwent esophagogastroduodenoscopy, duodenal biopsies showed villi alterations classified as Marsh I damage, without clinical and serological data for diagnosis of CD. Mesalazine and oral topical steroids (budesonide or beclomethasone) were used to treat LC in 34 (43%) and 32 (39%) of patients, respectively, with similar percentages of clinical response (approximately 80%).

Conclusions: the need for total colonoscopy with multiple biopsies in all patients with chronic watery diarrhea was confirmed. Since the association between CD and LC exists, additional tests should be performed in patients not responding to gluten-free diet or to LC specific therapy to exclude the other condition. Mesalazine obtained a similar outcome than oral steroids in this cohort.

Key words: Lymphocytic colitis. Microscopic colitis. Diarrhea. Mesalazine. Budesonide.

Simondi D, Pellicano R, Reggiani S, Pallavicino F, David E, Sguazzini C, Bonagura AG, La Terra A, Pizzetto M, Astegiano M. A retrospective study on a cohort of patients with lymphocytic colitis. *Rev Esp Enferm Dig* 2010; 102: 381-384.

INTRODUCTION

Lymphocytic colitis (LC), first described in 1989 (1), has been characterized as a condition associated to chronic watery diarrhea, especially in females and older patients. Together with collagenous colitis (CC), it is included under the umbrella term “microscopic colitis” (MC), in which chronic gastrointestinal symptoms (diarrhea, abdominal pain, fecal urgency, incontinence, nausea) are not associated to endoscopic or radiological alterations. It is not known whether LC and CC are two different diseases or distinct manifestations of the same clinical condition (2). Data on pathophysiology are conflicting, and different hypotheses refer to genetic predisposition (3), immune dysregulation, autoimmunity (4), bile acid malabsorption (5), infection (6), and drugs effect (7). The central role of an altered immune system in MC pathogenesis is supported by the association with several conditions in which an immune dysregulation is involved, such as celiac disease (CD), rheumatoid arthritis, hypo- and hyperthyroidism. Diagnosis can only be established by colonic biopsies and subsequent histopathological examination, when an increase in inflammatory infiltration and/or a thickening of the collagen layer are found (8). Among different drugs used to treat MC, budesonide have proved to be effective (9). However, the encouraging results obtained need to be confirmed on large samples.

Since the first report on LC, some retrospective studies have been published (10-21), focusing on clinical behaviors and therapeutic approaches. Our retrospective study reports

Received: 14-12-09.

Accepted: 25-02-10.

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on the demographic and clinical characteristics, together with diagnostic and therapeutic management, in everyday clinical practice, of a cohort of patients with LC.

PATIENTS AND METHODS

We reviewed clinical and histopathological data from patients diagnosed as LC between June 1994 and July 2008, in the outpatient unit of the Gastroenterology Department, Molinette Hospital, Turin, Italy. This facility carries out around 12,000 consultations/year (22) and is the main one in the Northwestern Italy.

Every patient underwent total colonoscopy with multiple biopsies, in most cases from both right and left colon. Macroscopic appearance observed during endoscopy was also registered. Diagnosis of LC was established after histopathological examination by an expert pathologist, who indicated if accepted diagnostic criteria for LC (9) were present (intraepithelial lymphocytes ≥ 20 per 100 surface epithelial cells, subepithelial collagen layer $< 10 \mu\text{m}$, lamina propria with inflammatory infiltration dominated by lymphocytes and plasmacells). Counting of intraepithelial cells was performed in hematoxylin-eosin stained samples, while subepithelial collagen layer was evaluated by an ocular micrometre in well-oriented sections, perpendicular to the mucosa, avoiding tangential sections that might give a false impression of thickening.

Routine laboratory tests were collected, and patients were excluded if a diagnosis other than LC was obtained. These included: full blood count, erythrocyte sedimentation rate (ESR), anti-endomysium (EMA) and/or anti-transglutaminase (t-TG) antibodies with total IgA determination, antinuclear antibodies (ANA) and routine tests to exclude pancreopathy and thyroid diseases.

The date of the diagnosis was defined when definitive histopathological report was assessed by the gastroenterologist, who stated the condition LC and undertook a therapeutic strategy. We defined as diagnostic delay the period between symptoms onset and diagnosis, and as follow-up the period between the diagnosis and the last visit of the patient in our unit. Three or more watery stools per day were considered as sign of diarrhea, and the presence of nocturnal stools, incontinence or abdominal pain was registered. Weight loss was signaled if the patient reported a decrease of at least 5% in his usual weight in the last 3 months. Clinical course of the disease was assessed on the basis of patients' history: continuous symptoms for at least 6 months were present in chronic continuous course, a symptom free period of at least 6 months between relapses was present in chronic intermittent course and an initial symptomatic period followed by continuous remission (with or without therapy) in single attack course.

Every continuative (more than 3 months) therapy at diagnosis was registered, focusing particularly on medications previously reported as involved in LC pathogenesis. After diagnosis, we recorded LC-related drugs assumed by

Table I. Demographic data and clinical features

Features	Patients n (%)
n (%)	80 (100)
Age at diagnosis, years (mean)	46.4
Sex, male/female	28/52
M:F ratio	1:1.86
Duration of symptoms before diagnosis, months (mean)	27.0
Follow up, months (mean)	25
Symptoms at diagnosis	
Daily stool number, n (mean)	5.4
Diarrhea at diagnosis, n (%)	71 (88)
Nocturnal stools, n (%)	7 (9)
Incontinence, n (%)	2 (3)
Abdominal pain, n (%)	46 (58)
Weight loss, n (%)	21 (26)
Nausea, n (%)	10 (13)
Weakness, n (%)	5 (6)
Endoscopic features (colonoscopy)	
Edema, n (%)	5 (6)
Hyperemia, n (%)	3 (4)
Diverticulosis, n (%)	4 (5)
Poliposis, n (%)	3 (4)
Clinical course	
Single attack, n (%)	28 (35)
Chronic intermittent, n (%)	44 (55)
Chronic continuous, n (%)	8 (10)
ESR elevation, n (%)	8 (10)
ANA positivity, n (%)	2 (9)

Fig. 1. Distribution of patients by age at diagnosis.

patients for at least 3 consecutive months, defining as “clinical response” the disappearance for at least 3 months of the symptoms reported at presentation. Follow-up visits were performed every 6 months. Drugs were switched if clinical response was not obtained after 3 months of therapy.

RESULTS

Eighty patients were included, 28 males and 52 females (M:F ratio 1:1.86). Demographic data and clinical features are reported in table I. Mean age at diagnosis was 46.4 years (range: 17-86), with a mean diagnostic delay of 27.0 months. Distribution of patients by age at diagnosis is shown in figure 1. The mean follow-up after diagnosis was 25 months. Colonoscopy described non-specific alterations (edema, hyperemia, diverticulosis or poliposis) in 15 cases (18.7%). At diagnosis, 71 patients (88%) reported diarrhea, 46 (58%) abdominal pain, 21 (36%) weight loss, 10 (13%) nausea. Only few patients presented with fecal incontinence, nocturnal stools or weakness. In 9 subjects not reporting diarrhea, the most frequent symptom was abdominal pain. Clinical course was chronic intermittent in most of cases (55%), while 28 (35%) presented a single attack and 8 (10%) a chronic continuous course. Among routine laboratory tests, ESR resulted increased in 8 patients (10%). In 23 subjects, the presence of ANA was assessed, with an elevated title in 2 (8.7%).

Of the LC-associated drugs reported, proton pump inhibitors (PPIs) were the most frequently used (7 patients, 9%), followed by aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) (5 patients, 7%), ticlopidin (3 patients, 4%), selective serotonin reuptake inhibitors (SSRIs) (3 patient, 4%), valproic acid, metformin, amitriptyline (1 patient for each one, 1%).

Regarding autoimmune or inflammatory diseases accompanying LC, thyroid disorders were found in 4 cases (5%), CD in 4 (5%), type 2 diabetes mellitus in 2 (3%) and rheumatoid arthritis in 2 (3%). Crohn's disease, systemic lupus erythematosus (ESL), autoimmune gastritis, lymphocytic gastritis were each reported in 1 patient only. In subjects undergoing esophagogastroduodenoscopy (EGDS) to investigate dyspeptic symptoms or to exclude CD (33 patients, 41%), duodenal biopsies showed villi alterations classified as Marsh I damage in 4 cases, without clinical and serological data for a definitive diagnosis of CD (23). Other conditions frequently found were gastritis (in 10 patients negative and in 5 positive for *Helicobacter pylori* infection) and peptic ulcer (1 case).

Medications used to treat LC are presented in table II with relative percentages of clinical response. Mesalazine

(2,400 mg/day per os) and steroids (budesonide 9 mg/day or beclomethasone 10 mg/day per os) were the most prescribed, in 34 (43%) and 32 (39%) of patients, respectively, with similar percentages of clinical response (approximately 80%). Probiotics, used in 16 (20%) cases, accompanied other medications. In most patients with associated arthritis, salazopyrine was used. Systemic steroids (prednisone, 1 mg/kg/day per os) were given to only 4 patients with associated aggressive autoimmune conditions (Crohn's disease, rheumatoid arthritis, ESL, ANCA positive vasculitis).

DISCUSSION

Our study reports on clinical characteristics of a population of patients with LC in a "real world clinical setting", focusing on symptoms at presentation, diagnosis and therapy. The clinical features of this cohort are quite similar to those previously reported (11-21,24). Mean age at diagnosis was 46.4 years, little less than in other cohorts, while male/female ratio confirmed a female prevalence. Duration of symptoms before diagnosis (27 months) was significantly longer than reported by others (17,18), and it is important to underline that a large number of patients still referred to different centers before obtaining definitive diagnosis of LC. This delay was also related to previous colonoscopies, in which a normal mucosa was found and biopsies were not performed (almost in 25-30% of patients –data not shown). Mean follow-up was 25 months and patients were usually lost in the case of clinical improvement. Among symptoms, chronic watery diarrhea was present in almost all cases (88%), and abdominal pain was the most frequent problem in subjects not reporting diarrhea. Symptoms as nocturnal stools and fecal incontinence were present but rarer, suggesting differential diagnosis with inflammatory bowel disease. The clinical course was benign, even if in 55% of cases, patients referred chronic intermittent condition, requiring periodical therapeutical intervention.

Many drugs are reported to be associated with LC (8). By registering all medications taken at diagnosis, we found 9 patients taking PPIs and 7 taking aspirin or NSAIDs. Since we did not find either disease onset in correspondence of drug introduction, or disease remission at drug withdrawal, these cases were defined as "possibly" drug-related LC, because criteria for "drug-induced microscopic colitis" were not satisfied (25,26).

The reported link between LC and autoimmune diseases is a very intriguing issue (24,27). In our cohort, 34% presented an autoimmune condition (most frequently CD and thyroid disorders). CD prevalence was 5%, significantly higher than in the general population, supporting an association between these two conditions. Similar data were reported in recent studies on larger cohorts (28-30). Hence, in the case of CD not responding to gluten-free diet, a diagnosis of LC should be ruled out.

Table II. Treatment responses

Medication	Patients treated, n (%)	Response (%)
Mesalazine	34 (43)	79
Budesonide / Beclomethasone	31 (39)	81
Probiotics	16 (20)	81
Salazopyrine	12 (15)	100
Prednisone	4 (5)	75
Antibiotics	4 (5)	50

Conversely, potential CD diagnosis should be evaluated in MC patient not responding to drug therapy.

There is weak evidence that mesalazine with or without cholestyramine may be effective in LC treatment, while more proof has been provided to budesonide efficacy (9,31). In spite of this, several patients in our cohort (43%) continued to be treated with oral mesalazine, with good response (79%), as confirmed by previous studies (32). Thirty-nine percent of patients were treated with budesonide or beclomethasone, with a response rate similar to mesalazine. Probiotics and anti-diarrheal agents (such as loperamide) were often used before definitive diagnosis. When these were given simultaneously with mesalazine or budesonide, no improvement was reported.

In conclusion, the present experience confirms the need of a total colonoscopy with multiple biopsies in all patients with chronic watery diarrhea, putting emphasis on the necessity of the multiple biopsies in different colonic segments, in order to avoid useless procedures. Since the potential association between CD and LC is confirmed, all patients not responding to gluten-free diet or to LC specific therapy should undergo colonoscopy and EGDS, respectively, to exclude the other condition. In this cohort of patients, mesalazine induced a similar outcome as oral steroids.

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