Clinical course of microscopic colitis in a single-center cohort study

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Lymphocytic colitis;
Collagenous colitis;
Clinical course

Abstract

Background and aims: The long-term natural history of collagenous (CC) and lymphocytic colitis (LC) is not well known. The aims of this study were to evaluate the clinical course of microscopic colitis (MC) and to describe the morbidity evolution of the disease.

Material and methods: This study is based on a cohort of 54 patients (35 LC/19 CC), previously included in a randomized trial treated with mesalazine with or without cholestyramine. Patients were followed-up closely during the subsequent 5 years, undergoing clinical, endoscopic and histologic evaluation at least yearly. After this period, they were encouraged to undergo periodical clinical evaluations.

Results: In a mean follow-up time of 104.9 ± 14.1 months (range 81–138 months) at the end of the therapy, 12 patients (7 LC and 5 CC) relapsed. Of these patients, 4 reported a mild clinical relapse self-treated with antidiarrheal medication. In total 49 patients are clinically free from diarrhea, to date. At multivariate analysis the only predictive factor of relapse seems to be a slow response to treatment.

Conclusions: Only a minority of patients with MC had diarrhea more than once a week in a long-term follow-up and the symptom pattern was similar between CC and LC patients.

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1. Introduction

Microscopic colitis (MC) has emerged as a new and common cause of chronic diarrhea in the general population. MC is an umbrella term for a group of inflammatory diseases of the colon where the colonic lining appears endoscopically normal, but histologic examination on biopsy reveals increased intraepithelial lymphocytes (IEL) in the colonic mucosa. MC includes collagenous colitis (CC) and lymphocytic colitis (LC), which differs from histopathological features. At histology, CC presents a subepithelial collagen band (10 μm or more) adjacent to the basal membrane. Both diseases display inflammatory changes in lamina propria and superficial epithelial damage. They are considered benign chronic inflammatory diseases of the colon with a possible relapsing course. MC is a disease that predominantly affects old patients with incidence rates anywhere from 5 to 10 times higher in those over 65. Frequency among patients with chronic diarrhea and normal colonoscopy is around 10–15% particularly in old female patients.

MC has a variable course, but overall, the long-term prognosis is good. Symptoms of diarrhea and abdominal pain may precede the diagnosis by a certain number of months. These symptoms are generally mild and in most patients they were resolved spontaneously or with symptomatic therapy. MC has not been associated with an increased risk of colorectal cancer—this information should be conveyed to the patients.

The long-term natural history of collagenous colitis (CC) and lymphocytic colitis (LC) is unknown. The few reports available that address these issues have a limited follow-up. Approximately 30% of patients relapsed with ~70% remaining symptom free. Prospective observational and clinical trials are warranted to specifically address the issue of prognosis and the durability of the response to initial therapy.

The aim of this study was to re-examine the cohort of MC patients previously described in order to assess the clinical course, morbidity, drug consumption and evolution of disease or its complications in our cohort of 54 patients.

2. Material and methods

Our patients were originally included in a randomized trial of which 64 (41 LC, 23 CC) patients were treated with mesalazine 2.4 g/die with or without cholestyramine 4 g/die for six months. Diagnosis of both CC and LC was based on clinical criteria including chronic or recurrent non-bloody diarrhea and well established objective histological criteria.

Histological criteria included increased chronic inflammatory infiltrate in the lamina propria (plasma cells, lymphocytes and eosinophils), increased number of intraepithelial lymphocytes (IEL) (normal, higher than seven per 100 epithelial cells), and damage of surface epithelium, with flattening of epithelial cells and/or epithelial loss, detachment and minimal crypt architecture distortion. To diagnose CC the additional presence of an abnormal surface subepithelial collagen layer with a thickness >10 μm was required, which entraps superficial capillaries, with an irregular lacy appearance at the lower edge of the basement membrane. Measurements of the subepithelial collagen layer and recounts of intraepithelial lymphocytes were performed on well-oriented biopsies (sections perpendicular to the mucosal surface). A number of IEL higher than 20 lymphocytes per 100 epithelial cells in the absence of a thickened subepithelial collagen layer (<10 μm) were necessary to diagnose LC.

After completion of the above study, 54 patients, with clinical and histological remission, agreed to undergo to a program of annual clinical, endoscopic and histologic follow-up during the subsequent 5 years. After this period they were encouraged to undergo periodical clinical evaluations without a fixed schedule.

At each colonoscopy 2 biopsy specimens were taken each from the ascending, transverse, descending, and sigmoid colon as well as from the rectum for histologic assessment. In addition, one biopsy was taken each from the 3 distal colon segments for microbiologic examinations.

Clinical evaluation was conducted by structured questionnaire aimed at evaluating symptoms, actual therapy, if any, and quality of life. Each patient was asked to give information on the above issues concerning the present time and the previous year.

Clinical response to treatment was considered complete if there was complete resolution of diarrhea, partial if there was improvement but not resolution, and none if there was no significant change. Histological response was defined as complete only with the normalization of the histological pattern. Relapse was defined as stool frequency greater than three soft or liquid stools per day and, if relapse was confirmed at histology, patients were retreated for another 6 months with the same primary therapy.

The demographic and clinical characteristics of the study group were compared statistically by the χ² test. All statistical analyses were two-tailed in which significance was accepted at a P-value <0.05 and were performed using the SPSS (SPSS, Chicago, IL, USA). Time to relapse was analyzed using Kaplan–Meier estimates and the Mantel–Haenszel log-rank test.

3. Results

Fifty-four patients (35 with LC and 19 with CC) in clinical and histological remission were evaluated. Patients in both groups had well matched demographic and baseline characteristics (Table 1). The majority of patients (76%) were woman and the mean age was 40 years. The median stool frequency was approximately 6 per day, and virtually all patients had watery or loose stools. Diarrhea was constant in 31% and intermittent in 69%. Of patients the mean time between onset of diarrhea and diagnosis was 13 and 24 months for LC and CC, respectively. Fecal incontinence was common (22%). No patients had family history of CC, LC or inflammatory bowel disease. None of the patients had a history of cholecystectomy, colonic or ileum resections, or abdominal radiation.

The latest follow-up check occurred after a mean duration of 104.9±14.1 (81–138) months. In total, 12 patients presented a relapse during the follow-up and the remission rate was 77.8%.

Seven patients (13%) (4 with LC and 3 with CC) relapsed after 24 months at the end of the therapy. Relapse was mild in five patients and substantial in two patients and was confirmed at histology. One patient with CC was treated with budesonide 9 mg/die for 8 weeks and gradual tapering and a complete clinical and histological recovery were achieved.
The six remaining patients were treated for further 6 months. Of these patients, 4 were treated with mesalazine 2.4 g/day plus cholestyramine 4 g/die and two only with mesalazine 2.4 g/die. A complete recovery of diarrhea was achieved.

After 10 years, 4 patients reported a mild clinical relapse self-treated with antidiarrheal medication (i.e. loperamide) and one patient with LC developed ulcerative colitis after 6 years of well-documented health maintenance.

The mean follow-up was 104.9 ± 14.1 months (range 81–138 months) and to date 49 patients are clinically free from diarrhea.

In multivariable modeling we observed no effect of age, sex, diagnosis, time between diarrhea and diagnosis and stool frequency on risk for clinical relapse. Only a slow response to treatment (>14 days) (11/54 patients) was a risk factor for clinical relapse (OR = 7.6, 95% CI: 1.87–15.78, P = 0.0001) (Table 2). The interaction between early response to treatment (<14 days) and number of relapses is illustrated by the Kaplan–Meier survival curve (Fig. 1).

### 4. Discussion

The natural history of microscopic colitis is variable. Many cases are self-limiting, with symptoms lasting a few weeks or months, others may be symptomatic for years in a relapsing or continuous pattern.

The present study describes the clinical course and the response to therapy of a cohort of 54 patients. These patients were included in a randomized trial in which they were treated with mesalazine with or without cholestyramine. Mean age at diagnosis was 40 years, little less than in other cohorts, while male/female ratio confirmed a female prevalence (70%). Duration of symptoms before diagnosis (18 months) was similar those reported by others, and it is important to underline that a large number of patients still referred to different centers before obtaining definitive diagnosis of MC. This delay was also related to previous colonoscopies in which a normal mucosa was found, and biopsies were not performed. The symptoms of both groups were similar and did not differ from what has been reported in the literature.

We found that within the first 2 weeks of treatment around 84% of patients with MC experienced a complete clinical remission.

### Table 1 Clinical characteristics of patients at baseline.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>LC</th>
<th>CC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (female/male)</td>
<td>26/9</td>
<td>15/4</td>
</tr>
<tr>
<td>Age (years), median (range)</td>
<td>39.7±12.2 (19–65)</td>
<td>40.7±11.6 (27–68)</td>
</tr>
<tr>
<td>Stool frequency/day median (range)</td>
<td>5.9 (4–10)</td>
<td>6.2 (5–11)</td>
</tr>
<tr>
<td>Time between onset of diarrhea and diagnosis (months) median (range)</td>
<td>13 (2–16)</td>
<td>24 (2–35)</td>
</tr>
<tr>
<td>Acute onset of diarrhea, n (%)</td>
<td>25 (71.4)</td>
<td>14 (73.7)</td>
</tr>
<tr>
<td>Abdominal pain, n (%)</td>
<td>9 (25.7)</td>
<td>6 (31.6)</td>
</tr>
<tr>
<td>Nocturnal stools, n (%)</td>
<td>11 (31.4)</td>
<td>7 (36.8)</td>
</tr>
<tr>
<td>Fecal urgency, n (%)</td>
<td>24 (68.6)</td>
<td>13 (68.4)</td>
</tr>
<tr>
<td>Nausea, n (%)</td>
<td>4 (11.4)</td>
<td>3 (15.8)</td>
</tr>
<tr>
<td>Celiac disease, n (%)</td>
<td>2 (5.7)</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Thyroid dysfunction, n (%)</td>
<td>4 (11.4)</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Autoimmune diseases, n (%)</td>
<td>1 (2.8)</td>
<td>1 (5.3)</td>
</tr>
</tbody>
</table>

### Table 2 Predictors of relapse.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative risk</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per year</td>
<td>1.00</td>
<td>0.95–1.72</td>
<td>0.827</td>
</tr>
<tr>
<td>Sex</td>
<td>0.78</td>
<td>0.22–2.8</td>
<td>0.708</td>
</tr>
<tr>
<td>Stool frequency/day</td>
<td>4.32</td>
<td>4.96–5.79</td>
<td>0.052</td>
</tr>
<tr>
<td>Time between onset of diarrhea and diagnosis/months</td>
<td>1.00</td>
<td>0.56–0.98</td>
<td>0.593</td>
</tr>
<tr>
<td>Early response to treatment (&lt;14 days)</td>
<td>7.6</td>
<td>1.87–15.78</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

![Figure 1](https://example.com/figure1.png)
During the follow-up period, 10 years after therapy, 12 of the 54 (22%) patients presented a relapse, whereas 49 patients had complete resolution of symptoms (90%). Five patients (9%) improve but never had complete symptomatic improvement, whereas 7 patients (13%) relapsed after achieving complete remission. Relapse was confirmed at histology. No differences were noted in regards to the relapse rate between patients affected by CC or LC with or without cholestyramine treatment.

The long-term prognosis of MC is generally good. In a follow-up study 63% of the patients with CC had lasting remission after 3.5 years, and in another cohort study all 25 patients’ condition improved 47 months after diagnosis and only 29% of them required on-going medication.9,10 A benign course was reported in 27 cases with LC with resolution of diarrhea and normalization of histology in over 80% of the patients within 38 months.11 Others reported that 63% of the patients with LC had a single attack of disease with a median duration from onset of symptoms to remission of 6 months.12

Studies in CC have shown considerable clinical relapse rates in the range of 60–80% after the end of budesonide treatment, underlining the chronic course of disease in most patients.13–15 There is less evidence for treating LC, budesonide 9 mg daily for 6 weeks was found to be effective in producing clinical and histological responses, and was well tolerated.16 After 6 weeks of treatment with budesonide, the clinical remission rate was 86% compared to 48% with placebo. Moreover, the utility of this therapy to maintain a long-term response is not known, and further studies are required. Bismuth seemed to be beneficial at producing a clinical response, although the number of patients was too small to make any meaningful conclusion.17

In the Cochrane revision17 after achieving clinical remission in CC with budesonide the relapse rate with placebo was 72% at 6 months. Likewise, the relapse rate after stopping budesonide administered as maintenance therapy during 6 months was 76% after a follow-up of 6 months. In our population the relapse rate was only of 22% after a long-term follow-up of almost 10 years.

Some limitations occurred in our study. The sample size in each patients group is small; however, it is similar to most prior reports; thus, a type II error is less likely. The cohort of MC patients described was previously included in a randomized unblinded trial, and there was no placebo group. Some of the measured effects in both groups may have been due to spontaneous improvement of the disease. However, despite the limitations described, our prospective study assesses the long-term average of 10 years and the clinical course of microscopic colitis after treatment.

In conclusion, MC must be considered in the differential diagnosis of patients with chronic watery non-bloody diarrhea, and adequate biopsy specimens should be obtained to give the pathologist a reasonable chance of making a clear diagnosis. Treatment with mesalazine is particularly effective in LC, while mesalazine and cholestyramine seem to be the best choices for the treatment of CC. Another available therapeutic strategy is the use of oral budesonide. The ideal long-term management of MC should be specifically addressed by further controlled clinical trials, but the only predictive factor of relapse seems to be a slow response to treatment.

References