Collagenous and lymphocytic colitis: A clinical and histopathological review

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J Bohr, M Olesen, C Tysk, G Järnerot. Collagenous and lymphocytic colitis: A clinical and histopathological review. *Can J Gastroenterol* 2000;14(11):943-947. Collagenous colitis and lymphocytic colitis are newly described colitides that are only diagnosable microscopically; therefore, both are known under the umbrella term 'microscopic colitis'. This is a short review of the clinical findings, and epidemiological and basic observations of these relatively little described colitides belonging to the group of inflammatory bowel diseases.

Key Words: *Collagenous colitis; Inflammatory bowel disease; Lymphocytic colitis; Microscopic colitis*

Colite collagénique et lymphocytaire : revue clinique et histopathologique

RÉSUMÉ : La colite collagénique et la colite lymphocytaire sont des colites nouvellement décrites qui ne sont diagnostiquables qu'au microscope. Par conséquent, les deux se retrouvent sous le terme « colite microscopique ». Voici une brève synthèse des signes cliniques et des observations épidémiologiques et fondamentales associés à ces colites relativement peu décrites, appartenant au groupe des maladies inflammatoires de l'intestin.

The term 'microscopic colitis' (MC) generally refers to two forms of colonic inflammation: collagenous colitis (CC) and lymphocytic colitis (LC). CC was first described by Lindström (1) in 1976, and in an abstract the same year, Freeman et al (2) reported two patients with a similar histopathological picture. The term 'LC' was suggested by Lazenby et al (3) in 1989. The predominant clinical symptom in both diseases is chronic watery diarrhea. In both cases, the colonic mucosa appears normal endoscopically and radiologically. Microscopic examination of colonic mucosal biopsies, however, reveals specific histopathological features.

COLLAGENOUS COLITIS

Epidemiology: Patients with CC are typically middle-aged women. The female to male ratio varies in the literature from six to one, to nine to one (4,5). Only four children with

this disease below the age of 12 years have been reported. However, CC was diagnosed in 25% of 163 patients before the age of 45 years, so it must be considered in younger subjects with chronic watery diarrhea (6).

CC was regarded as a very rare disease, but the first epidemiological study showed an incidence of 1.8 in 10⁵ people per year and a prevalence of 15.7 in 10⁵ people (4). The annual incidence reached a maximum of 14.6 in 10⁵ inhabitants in women aged 70 to 79 years, which is similar to that of ulcerative colitis (Figure 1). In a recent epidemiological study, the incidence of CC was 1.1 in 10⁵ people per year (5); new preliminary data (Olesen, unpublished data) show an even higher incidence of around four in 10⁵ people per year.

Histopathology: CC is diagnosed based on the following histopathological features in the colorectal mucosa.

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Figure 1) Age- and sex-specific incidence of collagenous colitis. Reprinted with permission from reference 4

- A diffuse noncontinuous thickening of a subepithelial collagen layer beneath the basement membrane throughout the colon. The thickness of the subepithelial layer must be 10 μ m or more on a well orientated section of the mucosa, compared with 0 to 3 μ m in healthy individuals.
- The inflammation in the lamina propria is dominated by lymphocytes and plasma cells. Eosinophils and mast cells can be found, but neutrophils are very rarely seen.
- Flattening and vacuolization of the epithelial cells and detachment of the surface epithelium are seen. Intraepithelial lymphocyte infiltration is present, though not as prominent as in LC (3,7) (Figure 2).

The disease is mainly located in the colon and the rectum. Deposit of subepithelial collagen has infrequently been reported in the duodenum and stomach, as well as in the terminal ileum in some patients with CC. Within the colon and rectum, the collagenous layer is most prominent in the proximal part of the colon and may be absent in the rectal mucosa in 18% to 73% of biopsy specimens (5,8,9).

Etiology and pathophysiology: The etiology of CC is unknown. Based on the finding of an increased number of T lymphocytes in the epithelium, several authors have proposed and supported the theory that CC may be caused by an abnormal immunological reaction to a luminal agent in predisposed individuals (7,10,11). Diversion of the fecal stream normalizes or reduces the characteristic histopathological changes in CC (12), which supports the theory that an exogenous agent can trigger the disease. The effect of various antibiotics and the sudden onset of the disease in a proportion of the patients (6) suggest that such an agent may be of microbiological origin. This view is further supported by a recent study in which *Yersinia enterocolitica* was detected in three of six patients before diagnosis of CC (13), and a serological study that showed that *Yersinia* species were more common in CC patients than in healthy controls (14).

Due to the frequent occurrence of arthritis in patients

Figure 2) Biopsy from colon showing typical findings of collagenous colitis – increased subepithelial collagen layer, inflammation of lamina propria and epithelial lesions with intraepithelial lymphocytes

with CC, these patients often use nonsteroidal anti-inflammatory drugs (NSAIDs). In one study, the use of NSAIDs was significantly more common in CC patients than in a control group, and discontinuation of NSAIDs was followed by improvement of the diarrhea in some patients (15). Most patients with CC, however, do not use NSAIDs; therefore, it can only be one of several possible etiological factors (6).

The thickened subepithelial collagen layer may cause diarrhea in patients with CC by reducing the permeability for electrolytes and water. However, fasting reduced the stool weight and sodium output in patients with CC, which implies that an osmotic mechanism is important (Bohr, unpublished data). The inflammatory cell infiltrate in the lamina propria may also have a pathophysiological role; a correlation between the degree of inflammation in the lamina propria and the stool frequency has been noted (16).

Nitric oxide is increased in patients with MC (17,18) and seems to be correlated with the histopathological findings in patients with CC (19) rather than with clinical symptoms. Nitric oxide is known to be increased in other forms of inflammatory bowel disease as well (20). It functions as an inflammatory mediator, but its role is unclear (21).

CLINICAL FEATURES AND DIAGNOSIS

In a study of 163 CC patients, 40% of the patients described the onset as sudden (6). Some patients could even recall the exact date of onset, just as in an infectious gastroenteritis. Watery diarrhea is the primary symptom in CC and may be accompanied by nocturnal diarrhea, crampy abdominal pain and distension. Initial weight loss is common and occasionally pronounced. Serious dehydration is rare, although daily stool volumes up to 5 L have been reported. Mucus or blood in the stools is uncommon (6).

In patients with CC, the relative risk of developing colorectal cancer does not appear to be increased (22). The course in the majority of cases seems to be chronic relapsing and benign (23). In a follow-up study, 63% of patients had lasting remission after 3.5 years (24). For a number of CC patients, however, remission is difficult to achieve, and such

patients have often tried many different treatments in vain (6).

Patients with CC often have concomitant diseases. Up to 40% have one or more associated autoimmune diseases. The most common are rheumatoid arthritis, thyroid disorders, celiac disease, asthma/allergy and diabetes mellitus (6). Co-existence of Crohn's disease or ulcerative colitis with CC has occasionally been reported (6).

There is no single parameter in the blood tests that makes screening for patients with CC possible. The erythrocyte sedimentation rate may be mildly elevated (6). Analyses of perinuclear antineutrophil cytoplasmic antibodies (25) or serum procollagen III propeptide are not of diagnostic value (26). Stool examinations reveal no pathological organisms, though increased excretions of fecal leukocytes have been reported in more than half of the CC patients (27).

The results of a barium enema and endoscopy are usually normal (28), although subtle endoscopic changes such as mucosal edema, granularity and erythema may be seen in up to 30% of cases (6). Pancolonoscopy must be preferred to sigmoidoscopy because a thickened collagenous layer may be absent in 18% to 73% of rectal biopsy specimens, as mentioned above.

Therapy: Loperamide and cholestyramine drugs have been reported to be of benefit in the majority of CC patients and are recommended as primary treatment (6,29,30).

Sulphasalazine is often the second choice if treatment with loperamide or cholestyramine fails. It is of benefit in about 60% of cases (6,29). Mesalazine and olsalazine have been tried in small series and case reports with effect in 50% and 40%, respectively (6).

Metronidazole and erythromycin were the most frequently prescribed antibiotic drugs for the treatment of CC, and approximately 60% of patients responded temporarily to one of these treatments (6).

Prednisolone is the most effective therapy, and up to 80% of patients respond. The effect, however, is usually not sustained after withdrawal, and the dose required to maintain remission is often unacceptably high – more than 20 mg/day (6,31). Budesonide has been tried in several patients with a similar response rate as for prednisolone (6,32,33,34), even in patients who are refractory to prednisone (35). As for prednisolone, the effect of budesonide is often not sustained after withdrawal, but in some patients it can be tapered to 3 mg/day (32-35).

A positive effect of bismuth subsalicylate and bismuth subnitrate in the treatment of CC has been reported (36,37). In two recent reports (38,39), one of which was placebo controlled (39), patients with CC and LC responded both clinically and histopathologically to bismuth subsalicylate, and the effect was mostly sustained after the treatment was withdrawn. One study of the use of bismuth subnitrate in seven CC patients and one LC patient showed a good immediate clinical effect, but the diarrhea relapsed shortly after withdrawal (34).

There are case reports on therapy with azathioprine, methotrexate and octreotide, but the data are very limited.

Surgery is an alternative for patients with severe, unresponsive CC (12), but the increasing success of medical treatment in these patients makes it important to consider carefully whether all other options have been tried.

LYMPHOCYTIC COLITIS

The term 'MC' was introduced in 1980 by Read et al (40) as a name for a mild form of colonic inflammation in patients with chronic watery diarrhea but normal results on endoscopy and barium enema. In 1989, Lazenby et al (3) proposed changing the name of MC to LC based on comparative morphological studies because the major distinguishing feature of MC was an increased number of intraepithelial lymphocytes. MC has evolved as an umbrella term that includes both CC and LC. There is less scientific and clinical knowledge of LC than of CC.

Epidemiology: In the only published, population-based, epidemiological study of LC, an annual incidence of 3.1 cases per 10⁵ population was found (5). There was a peak incidence in older women. The mean age at onset of symptoms was 64 years, and the female to male ratio was 2.7 to one. Preliminary unpublished data gave similar epidemiological results (Olesen, unpublished data).

Etiology: The cause of LC is unknown. There have been reports on drug-induced disease, particularly in association with Cyclo 3 Fort (Laboratoires Pierre Fabre Cardiovasculaire, France) and ticlopidine, and occasionally with ranitidine, carbamazepine, vinburnine or tardyferon treatment (41-53). The onset of LC after an infection with *Campylobacter jejuni* has been reported (54). Of special interest in this context is the condition known as 'Brainerd diarrhea', a term that has been applied to outbreaks of chronic watery diarrhea characterized by acute onset and prolonged duration (55). Colonic biopsies in these patients show epithelial lymphocytosis similar to CC and LC but not the surface epithelial changes. Furthermore, abnormalities of colonic histology resembling LC have been reported in patients with untreated celiac disease (56). From these observations, it may be hypothesized that LC arises in predisposed individuals as a specific mucosal reaction to different mucosal insults.

Clinical features, diagnosis and histopathology: The clinical picture of LC is similar to that of CC, and the predominant symptom is chronic watery diarrhea, but a recent report found that symptoms associated with LC were milder and more likely to disappear than those associated with CC (57). The colonic mucosa is macroscopically normal, and the diagnosis can only be made histopathologically. The major histopathological features are epithelial lesions, an increase in intraepithelial lymphocytes (more than 20 lymphocytes per 100 epithelial cells), and an infiltration of the lamina propria with lymphocytes and plasma cells (Figure 3). The intraepithelial lymphocytes are predominantly CD8⁺ lymphocytes expressing the alpha-beta T-cell receptor, whereas the lymphocytes in the lamina propria are mostly of the CD4⁺ haplotype (58).

Because the histopathological features of CC and LC are similar, with the exception of the subepithelial collagen

Figure 3 Biopsy from colon showing typical findings of lymphocytic colitis – epithelial lesions with intraepithelial lymphocytes and inflammation in the lamina propria

band found only in the former condition, it has been proposed that CC is a later stage of LC. Indeed, a few reports have described the conversion of colitis from lymphocytic to

collagenous. However, most cases of LC remained unchanged. In addition, there seems to be differences in the sex ratio and in the distribution of human leukocyte haplotypes between CC and LC, so that they are considered to be two separate but similar diseases. The importance of genetics in MC is unknown. Familial occurrence of CC has been reported in two families (59), and in one MC register, there were five families in which two sisters in each family had some form of MC (Järnerot, unpublished data).

Similar to CC, LC has been reported in association with autoimmune diseases. The occurrence of collagenous gastritis and LC (60), and primary ileal villous atrophy and LC have occasionally been reported (61).

Prognosis and therapy: The prognosis of LC seems to be good. There is no increased mortality and no increased risk of subsequent bowel malignancy reported. Mullhaupt et al (62) reported a benign course in 27 cases with resolution of diarrhea and normalization of histology in more than 80% of patients within 38 months. Although no controlled data on the treatment of LC exist, the guidelines mentioned above for CC can be followed.

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