Clinical presentation, diagnosis, pathogenesis and treatment options for lymphocytic colitis (Review)

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Abstract. Lymphocytic colitis (LC) is characterized by chronic or relapsing non-bloody watery diarrhea and a macroscopically normal colon. However, histopathological examination of colonic biopsy samples reveals an increased intraepithelial infiltration of lymphocytes (≥20/100 enterocytes), and increased inflammatory cells within the lamina propria, but with a normal mucosal architecture. The reported prevalence of LC varies from 14.2 to 45 per 100,000 individuals, while its reported incidence is between 0.6 and 16 per 100,000 individuals. LC has a high rate of spontaneous symptomatic remission and is not associated with an increased risk of colon cancer or inflammatory bowel disease. The diagnosis is based on the histopathological findings. The density of colonic chromogranin A-positive cells provides an effective diagnostic tool with high sensitivity and specificity in both the right and left colon. Gastrointestinal infections, drugs, and/or autoimmunity may trigger chronic colonic low-grade inflammation. Colonic nitric oxide, serotonin and peptide YY (PYY) cell densities are markedly increased in patients with LC. It has been hypothesized that the low-grade inflammation in LC through the endocrine-immune axis causes this increase. It has been postulated further that these abnormalities in the neuroendocrine system of the colon are responsible for the diarrhea observed in patients with LC. The benign course and rate of spontaneous remission of LC denotes that drugs with severe side-effects should be avoided if possible. The drug cost and drug coverage may also be limiting factors for some patients. These aspects should be taken into account when making decisions regarding treatment options.

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Contents

1. Introduction

Read *et al* (1) introduced the term lymphocytic colitis (LC) in 1980 to describe patients with chronic or relapsing non-bloody watery diarrhea and an endoscopically and/or radiologically normal colon. However, a histopathological examination of colonic biopsy samples from these patients shows increased intraepithelial infiltration of lymphocytes and increased inflammatory cells within the lamina propria (1). The reported prevalence of LC in population-based investigations has varied from 14.2 to 45 per 100,000 individuals (2-8), while its incidence has been reported to be between 0.6 and 16 per 100,000 individuals (7-13). Although LC can occur at all ages, its incidence peak occurs at approximately 60 years of age, and females constitute 68% of patients with LC (14). Analysis of the prevalence and incidence of LC in different populations should, therefore, consider the age structure of these population pyramids (15).

Long-term epidemiological studies have found that the incidence of LC is increasing (14,16); this could be a real increase or the result of an increased awareness of the necessity of examining colonic biopsy samples in patients with diarrhea without obvious etiology (14). In Örebro county (Sweden) and Olmsted county (MN, USA) where these studies were conducted, the awareness of LC has been high and constant during all of the investigation period, making it unlikely that this factor played a role in the observed increase in LC incidence. However, change in the age distribution during the long observation periods (>15 years) may have an effect on this increase, since official Swedish statistics indicate a considerable increase in the proportion of individuals >60 years of age in Örebro county.

There have been several recent comprehensive reviews on LC (5,14,17-21). The present review takes a different approach

from the others by aiming not merely to present an updated account of LC, but also to highlight the debated issues of clinical presentation, diagnosis, pathogenesis and treatment options.

2. Clinical presentation and course

The cardinal symptom for LC is chronic or recurrent non-bloody diarrhea (22,23). The diarrhea is chronic in 33% and intermittent in 67% of patients with LC (22,23). Patients with LC have 4.9 bowel movements per day on average; however, 22% of patients have up to 10 bowel movements daily (5,14,21,23). Other symptoms occurring in patients with LC include abdominal pain and weight loss (24-27) (Table I). However, in some patients, constipation is the main symptom of LC (24-27). It is noteworthy that in clinical practice, colonic biopsies are routinely taken during colonoscopy of patients with diarrhea and a macroscopically normal colon, but not in those with constipation. It is therefore, not clear whether LC is exclusively a diarrheal disease.

The reported rate of spontaneous symptomatic remission in LC in follow-up studies has varied between 59 and 93% (23,27). Histopathological normalization reportedly occurs in 82% of patients with LC after approximately 38 months of follow-up (23). A follow-up study over a 6.4-year period also found a high rate of symptomatic remission in patients with LC (28). Moreover, the risk of colon cancer or inflammatory bowel disease is not increased in patients with LC (29).

3. Diagnosis

The results of a physical examination, laboratory tests, small and large bowel radiology and colonoscopy are normal in LC, with the diagnosis instead being based on histological changes in colonic biopsy samples. The typical histological changes include an increase in intraepithelial lymphocytes (≥20/100 enterocytes) and infiltration of inflammatory cells (mainly lymphocytes and plasma cells) in the lamina propria (21,30). Although surface epithelial damage can be observed, the architecture of the mucosa is normal (Fig. 1) (21,30). In clinical practice, the increase in intraepithelial lymphocytes is usually clearly evident with manual counting only required in cases with a borderline number of lymphocytes (21). The surface mucosa overlying lymphoid aggregates always contains higher numbers of intraepithelial lymphocytes; thus, these areas should be avoided when an LC diagnosis is being made (21).

While the histopathological diagnosis of LC is straightforward, it is unclear whether the histopathological changes observed in LC are diffusely distributed throughout the colon or limited to a certain segment(s). Certain studies have found the histopathological changes to be more prominent and easier to detect in the right colon (cecum and the ascending and right transverse colon) (11,31,32), while other authors have maintained that biopsies obtained from the left colon (sigmoid and descending colon) are reliable for the diagnosis of LC (10,33,34). These controversial results question whether colonoscopy with a segmental biopsy is required for the diagnosis of LC, or whether sigmoidoscopy is sufficient. Solving this issue is important for clinical practice, since the risk of complications, the clinicians labor and the economic burden are higher for colonoscopy than for sigmoidoscopy. Since this matter has not yet been resolved, several gastroenterologists perform colonoscopy with a segmental colonic biopsy to ensure an accurate diagnosis.

Table I. Clinical presentation of lymphocytic colitis.

Symptom	Occurrence (%)	Refs.
Diarrhea	88-100	10,22-26
Constipation	2-43	22,23
Abdominal pain	21-94	21-23
Weight loss	33-73	22-26
Fecal urgency	33-92	10,22,23
Gas/bloating	14-69	10,22,25,27,28
Nocturnal stool	25-59	10,21-23,25,26
Fecal incontinence	9-64	10,21-23,25,26
Nausea	16-19	22,25

Chromogranin A is a 68-kDa protein comprising 439 amino acid residues, which was isolated from secretory granules of the adrenal medulla (35). Chromogranin A is co-stored and co-released with monoamines and peptide hormones present in the adrenal medulla, pituitary gland, parathyroid, thyroid C-cells, pancreatic islets, endocrine cells of the gastrointestinal tract and sympathetic nerves (35-37). Chromogranin A is therefore considered to be a general marker for all endocrine cells. Some of the patients in a cohort of irritable bowel syndrome (IBS), showed an extremely high density of colonic chromogranin A-positive cells (Fig. 2), and were subsequently identified as having LC (38). This unexpected observation was confirmed in a larger cohort of patients with LC, and led to the colonic chromogranin A-positive cell density being proposed as a diagnostic marker for LC (Figs. 3 and 4) (39). The use of the chromogranin A-positive cell density as a marker for the diagnosis of LC has a high sensitivity (97 and 100%, in the right and left colon, respectively) and specificity (98 and 94%, in the right and left colon, respectively) (39). The time and cost associated with the use of this marker are the same as those for the detection of lymphocytes. Using the chromogranin A-positive cell density as a marker has several advantages: i) it has a high sensitivity and specificity in the left colon, thus sigmoidoscopy with biopsy can be used in the diagnosis; ii) it is not affected by the artifact caused by lymphoid aggregates and is thus useful in borderline cases where lymphocyte infiltration does not completely fulfill the definition of LC; and iii) it can be used to differentiate patients with LC from those with IBS, refractory celiac disease, lymphocytic enterocolitis, autoimmune enteropathy and lymphoma.

LC and IBS have similar symptoms and normal radiological and endoscopic appearances of the colon (40), which means that patients with LC are at risk of being misdiagnosed as IBS (24,40-43). The task of differentiating between LC and IBS is made even more difficult by the fact that some patients with IBS exhibit an increase in the number of intraepithelial lymphocytes (40,44). The use of colonic chromogranin A-positive cell density as a marker for LC may prove to be beneficial in such cases, since the density of this marker in the colon is low in patients with IBS (45).

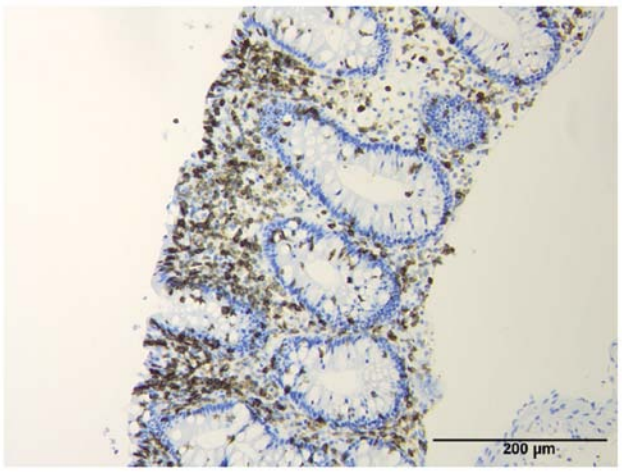

Figure 1. Photomicrograph of the colon of a patient with lymphocytic colitis showing immunostaining with antibodies against CD57, which is a marker for subsets of natural killer cells and $CD8^+$ lymphocytes, and a small percentage of $CD4^+/CD45R0^+$ T lymphocytes.

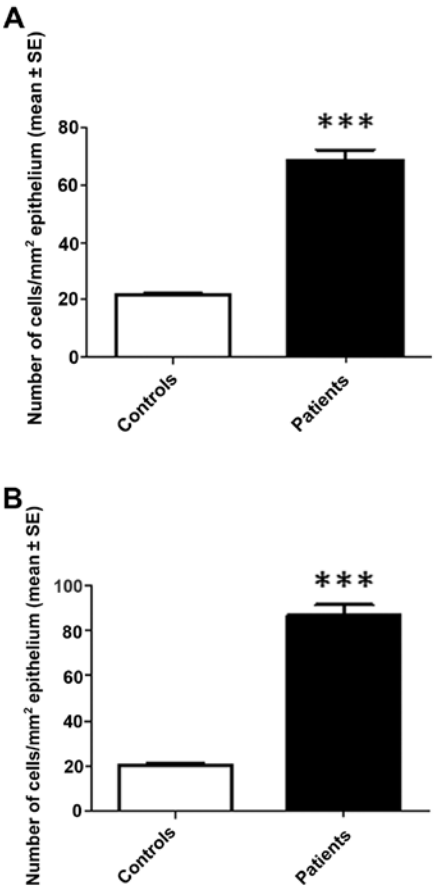

Figure 2. Chromogranin A-positive cell density in (A) the right and (B) the left colon of patients with lymphocytic colitis and healthy controls. ***P>0.001.

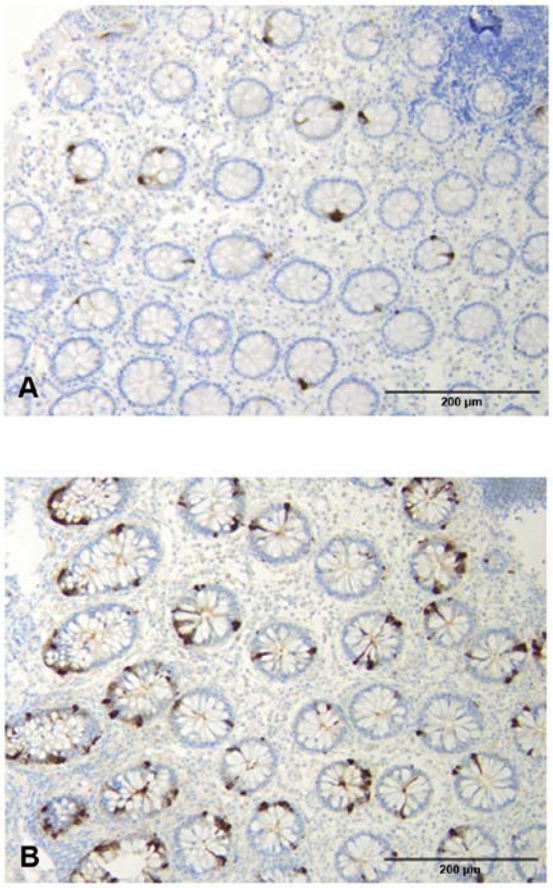

Figure 3. Chromogranin A-immunoreactive cells in the colon of (A) a control subject and (B) a patient with lymphocytic colitis.

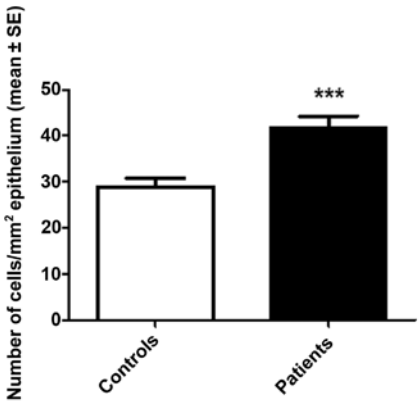

Figure 4. Serotonin-positive cell density in the colon of healthy controls and patients with lymphocytic colitis. ***P>0.001.

Celiac disease has been reported to be associated with LC; between 4.3 and 31% of patients with celiac disease exhibit histopathological changes typical of LC (46-48). Approximately 7% of patients with LC have celiac disease (6,10,23,25,49-51). It has been speculated that colonic lymphocyte infiltration observed in the colon of patients with celiac disease is part of the same autoimmune pathogenesis observed in the small intestine. The coexistence of celiac disease and LC makes it necessary to further examine patients with celiac disease who do not respond to a gluten-free diet. Thus, one of the first tasks in clinical practice is to exclude the possibility of celiac disease in patients exhibiting LC symptomology.

4. Pathogenesis

It is generally accepted that LC is secondary to an abnormal immune reaction in predisposed individuals. Gastrointestinal

infections, drugs and/or autoimmunity possibely trigger this reaction. An abnormality in the colon neuroendocrine system has also been reported and seems to play a role in the pathophysiology of LC.

Gastrointestinal infections. Gastrointestinal infection as an etiological factor of LC is supported by a case report of a 19-year-old patient who developed LC following *Campylobacter* infection (52), and by a significant seasonal pattern in the incidence of LC (53). Associations with *Clostridium difficile*, *Yersinia enterocolitica* and *Campylobacter jejuni* have been observed in collagenous colitis, which is a disease related to LC (54-56). The initial inflammatory response following gastrointestinal infection shows an increase in $CD3^+$ lymphocytes, CD8 intraepithelial lymphocytes and calprotectin-positive macrophages (57). These changes rapidly diminish in most subjects; however, a small number of patients with persistent symptoms fail to show this decline (57). This process can commence irrespective of the type of infectious agents (i.e. virus, bacteria or protozoa). Consequently, a report of no association being found between anti-*Yersinia* antibodies and LC in 19 patients does not exclude an infectious genesis for LC (58). The issue still remains however, of why only a proportion of patients that suffer gastroenteritis develop LC. Genetic factors may be of importance, since variants of the matrix metalloproteinase-9 (MMP-9) gene have been observed in collagenous colitis (59).

A role for gastrointestinal infections in the pathogenesis of LC has been supported by the striking similarity between LC and post-infectious IBS (PI-IBS). These conditions have a similar clinical presentation and both can regress spontaneously (57,60). Both LC and PI-IBS show an intra-epithelial and submucosal infiltration of lymphocytes and mast cells, and exhibit a high density of colonic serotonin and peptide YY (PYY) cells (40,61-64). These similarities have prompted suggestions that LC and PI-IBS are the same disorder (62).

Drugs. A strong association exists between certain drugs and LC (65-67). There are reported cases of both the symptoms and the colonic histopathological changes disappearing following termination of the drug treatment and returning after the re-introduction of the drug treatment (65-67). The implicated drugs include non-steroidal anti-inflammatory drugs (NSAIDs), β-blockers, histamine-2 receptor blockers, proton pump inhibitors, statins, as well as others. NSAIDs are known to induce colonic and small intestinal inflammation and to cause relapse of inflammatory bowel disease (67-69). Patients with LC often have arthralgia, and the association with NSAIDs can thus be confounded (17). It is noteworthy that the age at which the incidence of LC peaks (i.e., 60 years) corresponds to when treatment with β-blockers, statins and low-dose aspirin are common for cardiovascular diseases.

Autoimmunity. Several studies have demonstrated an association between LC and autoimmune diseases, such as celiac disease, diabetes mellitus, arthritis and thyroid diseases (21,70). Moreover, patients with LC exhibit positivity in the antinuclear antibody (ANA) test (21). Associations between microscopic colitis and the TNF2 allele, HLA A1 allele and cytokine gene polymorphism in the IL-6-174 GG genotype have been reported (71-73).

Abnormalities in colonic neuroendocrine system. Colonic nitric oxide (NO) levels are markedly increased in patients with LC, which is due to an increase in NO synthase levels in the colonic epithelium (74-76). The colonic serotonin (Figs. 4 and 5) and PYY cell densities (Figs. 6 and 7) have been reported to be extremely high in patients with LC (62). NO increases intestinal motility and stimulates the intestinal secretion of water and electrolytes (77,78). Serotonin activates the submucosal sensory branch of the enteric nervous system, and controls gastrointestinal motility and chloride secretion via inter-neurons and motor neurons (79,80). PYY stimulates the absorption of water and electrolytes, and is a major regulator of the 'ileal brake' (81). Furthermore, PYY inhibits prostaglandin E2 and vasoactive intestinal polypeptide (VIP) actiation, which stimulate intestinal fluid secretion (82-84). The administration of PYY has been shown to inhibit diarrhea in experimental mouse models by reducing intestinal fluid secretion and delaying colonic transit (85).

Hypothesis. Serotonin secretion by enterochromaffin (EC) cells can be enhanced or attenuated by the secretory products of immune cells, such as $CD4^+$ T cells (86). Furthermore, serotonin modulates the immune response (86). EC cells are in contact with or very close to $CD3^+$ and $CD20^+$ lymphocytes and several serotonergic receptors have been characterized in lymphocytes, monocytes, macrophages and dendritic cells (87-91). It is therefore conceivable that the increase in colonic serotonin cell density in patients with LC results from the interaction between lymphocytes and EC cells. Serotonin stimulates NO secretion, which is partly responsible for its effects on intestinal motility and thus secretion is partly due to the activation of NO (78,88-91). It is reasonable to assume that the increase in colonic NO levels is caused by the increase in serotonin levels observed in patients with LC. The increase in colonic serotonin and NO levels in patients with LC accelerates intestinal motility and water and electrolyte secretion observed in LC diarrhea, which is of secretory character (92). Accelerated intestinal motility and secretion may be the cause of the compensatory secondary increase in PYY levels in the colon of patients with LC. This compensatory mechanism may explain the occurrence of intermittent diarrhea in some patients with LC, as an increase in PYY levels can compensate for the increased secretion and motility for only short periods ot time (Fig. 8).

5. Treatment

The drugs commonly used in the treatment of LC are loperamide, 5-aminosalicylates, budesonide, prednisolone, bismuth subsalicylate, immunosuppression and anti-TNF-α therapies (17,93-95) (Fig. 9). Cholestyramine has also been recommended for the treatment of LC, but its clinical response was possibly due to the fact that the patients treated suffered from bile acid malabsorption (93). Loperamide, which is a symptomatic non-specific anti-diarrheal agent, is often the first-line therapy prescribed. It is administered as a tablet of 2 mg (up to 8 tablets taken daily if necessary). A complete or partial response to loperamide has been observed in 70-73% of patients (11,22). 5-Aminosalicylates, such as sulfasalazine and mesalamine are a common therapy for LC in clinical practice due to positive responses and tolerance in the majority

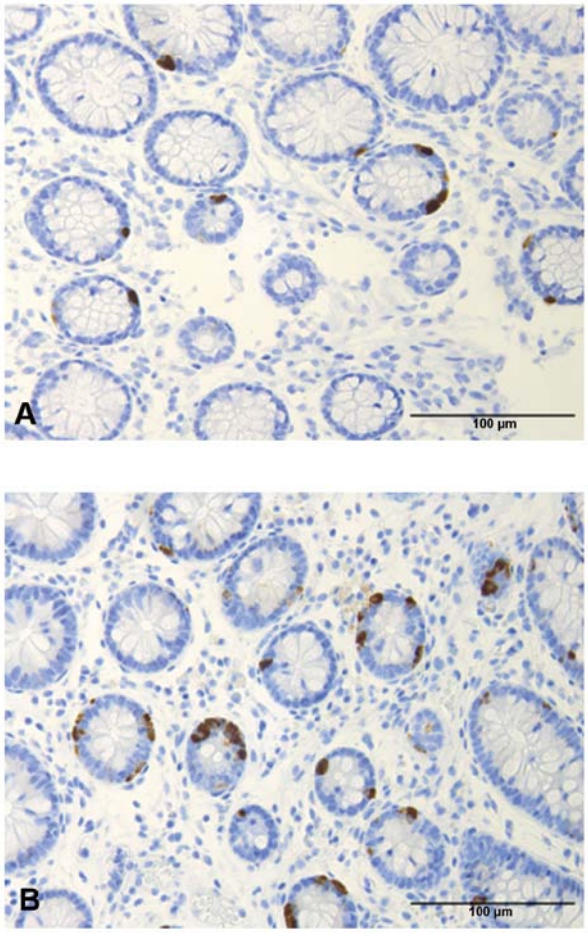

Figure 5. Colonic serotonin-positive cells in (A) healthy controls and (B) patients with lymphocytic colitis.

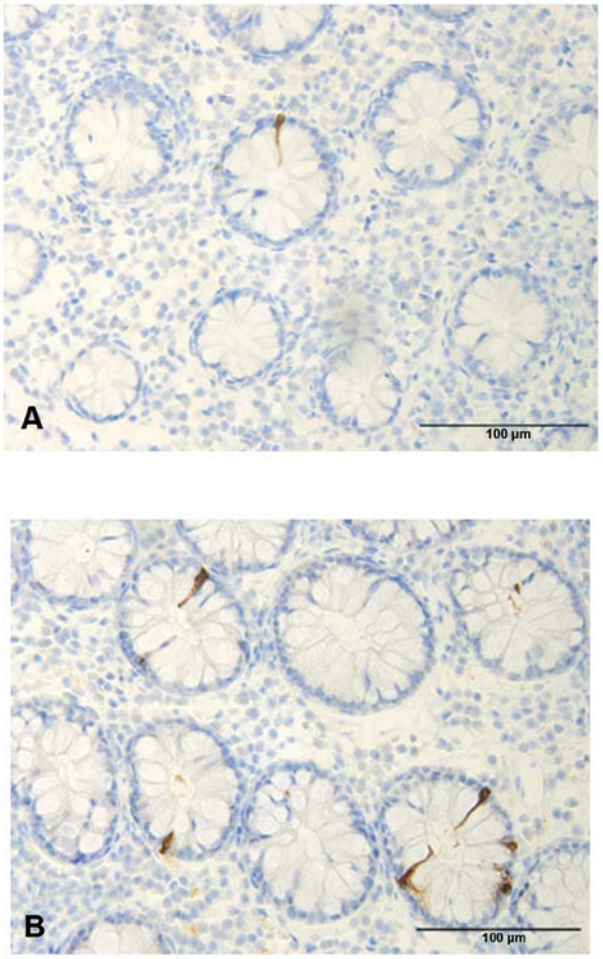

Figure 7. Colonic peptide YY cells in (A) healthy controls and (B) patients with lymphocytic colitis.

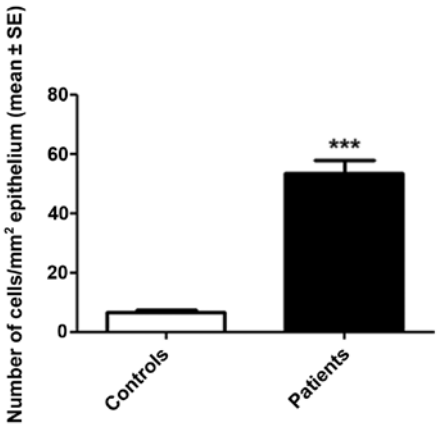

Figure 6. Density of peptide YY cells in the colon of healthy controls and patients with lymphocytic colitis. ***P>0.001.

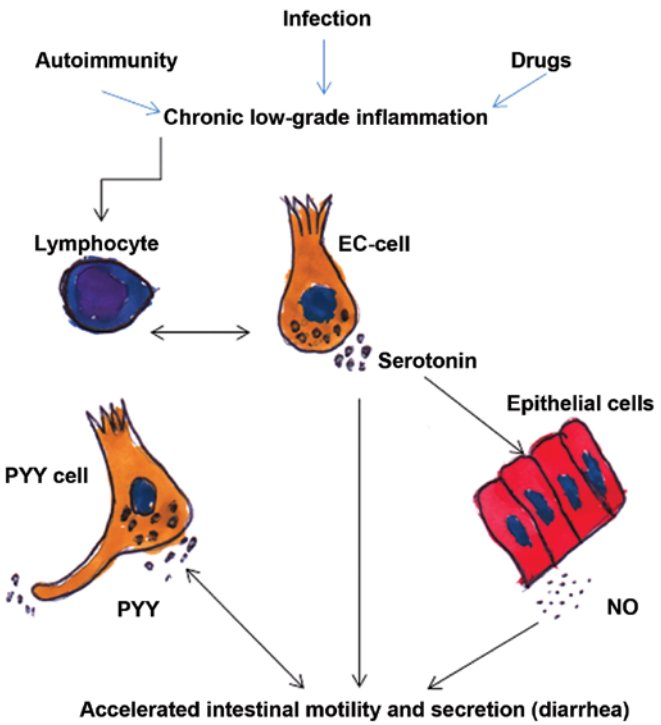

Figure 8. Schematic diagram of the possible pathogenesis of lymphocytic colitis.

of patients (22,96). However, there have been several reports of 5-aminosalicylates inducing remission in <50% of patients (25,97). Budesonide is the most documented drug used in the treatment of LC. It is a glucocorticoid with no significant adverse events that are known to occur in systemic treatments with corticosteroids. This is due to its limited systemic availability caused by the extensive first-pass hepatic metabolism by cytochrome P-450 enzymes. Clinical remission has been

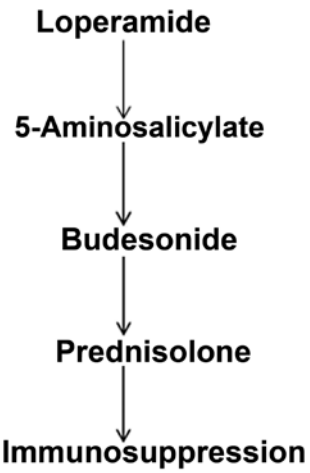

Figure 9. Suggested drug-treatment algorithm for lymphocytic colitis.

reported in 82-86% of patients with LC following 6-weeks of treatment with 9 mg of budesonide daily (11,98). Relapse after cessation of budesonide treatment has been shown to occur in 14-44% of patients after 1-7 months (11,98). The relapsed patients responded to new treatment and remained in clinical remission with a maintenance therapy of a median daily budesonide dose of 3 mg (11,98). Four weeks of treatment with prednisolone at 40 mg daily tapered by 5 mg/week resulted in complete or partial clinical remission in 87-94% of patients with LC (11,99). However, the majority of these patients relapsed after termination of the therapy (11,22). Bismuth subsalicylate at a dose of 2 or 3 tablets (262 mg each) 3 or 4 times daily for 8 weeks induced remission in the majority of patients which was sustained up to 7-23 months (22,100). No toxicity was absorbed despite the high dose of bismuth, which may have been due to the short treatment duration or low bismuth absorption. However, treatment with bismuth is not without any toxic effects and its availability is limited in certain countries. Treatment with azathioprine at 2-2.5 mg/kg/day, with 6-mercaptopurine at 1 mg/kg/day both indefinitely, and anti-TNF-α have produced good results in patients with refractory LC (94,99,101). The indications for surgical therapy are limited (102).

Concomitant drug use should be assessed and drugs that potentially cause drug-induced LC should be discontinued, if possible. Considering the possibility that LC and PI-IBS can be the same disorder, diet, regular exercise and probiotic intake recommendations provided to patients with IBS (103-105) should also be recommended for patients with LC. The benign course and high rate of spontaneous remission of LC denotes that drugs with severe side-effects should be avoided if possible. Furthermore, the drug cost and drug coverage may be limiting factors for some patients. These aspects should be taken into account when selecting treatment. An algorithmic approach to the treatment of LC is recommended (Fig. 9).

6. Conclusion

LC is not a rare disorder as previously thought. Although LC is considered a diarrheal disorder, it can present with other symptoms, such as constipation or abdominal pain. Colonic biopsy samples in patients presenting with symptoms other than diarrhea and with a macroscopically normal colon should be taken more frequently than routinely done at present. The density of colonic chromogranin A-positive cells may be used as a diagnostic tool for LC. The cause of LC may be a low-grade inflammation with an interaction with the colonic neuroendocrine system. There are good reasons to suspect that LC and PI-IBS are one and the same disorder. The benign course and high rate of spontaneous remission, as well as the drug cost and drug coverage should be taken into accout when making decisions regarding treatment. An algorithmic approach to the treatment of LC is preferable.

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