COLLAGENOUS AND LYMPHOCYTIC (MICROSCOPIC) COLITIS

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Introduction

Collagenous and lymphocytic colitis are clinicopathologic syndromes of watery diarrhea with normal colonoscopy and colonic inflammation\(^1\). Both constitute a third type of colitis after inflammatory bowel disease (IBD). Collagenous colitis (CC) shares histological and clinical similarities to lymphocytic colitis (LC), also called microscopic colitis. Thus, both diseases will be discussed here. The terminology remains somewhat controversial. The term 'microscopic colitis', while not recognized by some authorities, generally refers to a group of disorders, but still some consider microscopic colitis as synonymous to lymphocytic colitis. Because of the similarities of these two disorders, they are commonly considered a single category for the purposes of treatment and are referred to as microscopic colitis. It is not known whether LC and CC represent different clinical entities or constitute part of a spectrum of the same disease. Some said that collagenous and LC are similar but not identical\(^2\). Others use the term lymphocytic colitis and microscopic colitis interchangeably and consider that it’s similar to CC, and by all means considered as one of the new colitides\(^1\).

CC was first described by Lindstrom, a Swedish pathologist, in 1976\(^3\). He used this term because of similar histology to the collagenous sprue seen in the jejunal mucosa.

Epidemiology

CC and LC are rare diarrheal diseases of unknown pathophysiology\(^4,5\). They have been described and studied extensively in the past 20 years, but remain poorly understood. They are being recognized more frequently, possibly because gastroenterologists and pathologists are now more aware of these diagnoses. Considered as diseases of middle aged women, they do affect males and children albeit to a lesser extent. Most patients are Caucasians living in industrialized countries such as Northern Europe, Canada, the United States, Australia and New Zealand. The incidence is estimated to be about 16 per 100,000 population\(^6\). The incidence of LC is three times higher than that of CC with patients presenting somewhat earlier and less likely to be active.

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smokers. Both should be considered as a major possibility in the work-up of chronic diarrhea in older people.

Etiology

Etiology and pathogenesis of CC are unknown. However, The diarrhea is secretory. Both diseases are associated with autoimmune diseases including celiac sprue, connective tissue disorders, thyroid disease and myasthenia gravis. CC has been reported in association with other IBD including LC, idiopathic IBD and pseudomembranous colitis. Although some dispute the association with other gastrointestinal diseases, an autoimmune etiology is strongly suspected, but no serological findings have supported such a theory.

Possible causes are: unidentified chronic gastrointestinal infections, immune disturbance including autoimmune diseases, medications (e.g. some non-steroidal anti-inflammatory drugs (NSAIDS), ranitidine and carbemazepine). The finding of fecal leukocytes in 55% of patients with collagenous colitis confirms the inflammatory basis of this disease. There is a possible relation between eosinophil activation and disturbed mucosal permeability in CC with increase in eosinophil infiltration and degranulation in the colonic mucosa. Bile acid malabsorption is common in patients with CC and is probably an important pathophysiological factor. The reduced matrix degradation and not over-activation of matrix synthesis may be the reason for the subepithelial accumulation of matrix proteins in CC. Imbalance between fibrogenesis and fibrolysis may be suspected.

Clinical Features

CC mostly affects women in the middle age over 50 years (90% of patients are women). Often symptoms has been present for several years before an accurate diagnosis is made. Most patients complain of intermittent attacks of diarrhea and crampy abdominal pain, often with multiple loose watery bowel movements per day. Watery diarrhea up to 5 liters per day may occur for a period ranging from 5 up to 20 years, yet sometimes may present in patients with relatively brief duration of diarrhea. In severe cases, this can lead to weakness and dehydration. These episodes may come on suddenly without any obvious explanation. Some patients experience spontaneous remission; in others, the symptoms come and go. Many people suffer from chronic diarrhea for years. Fatigue, and weight loss are also common. A chronic intermittent course occurs in 85%, with a sudden onset in 42%. Chronic watery diarrhea, which is often nocturnal (27%), with abdominal pain (41%) and weight loss (42%) is another presentation. Forty percent of patients have one or more associated diseases. The median age at diagnosis is 55 years (range 16-86), but 25% of the patients are younger than 45 years. Symptoms are milder and more likely to disappear in LC with equal male to female distribution. CC follows a chronic continuous course. Symptoms can be socially disabling, but the disease does not seem to have a malignant potential.

Diagnosis

Routine laboratory data are mostly normal. Fecal leukocytes are found in 55% of patients. The diagnosis can only be made by colonoscopy. The mucosa appears normal, although there may be some very subtle abnormalities. Under the microscope, There are features of colitis which are a mild to moderate with chronic inflammatory cell infiltrate expanding the lamina propria including plasma cells and lymphocytes, but not neutrophiles. There is significant increase in the intraepithelial lymphocytes with thickening of the subepithelial collagenous plate, up to 10
microns or more (normal is 5 microns in thickness). This collagen can be recognized by conventional hematoxylin and eosin stains (HE). Sometimes subepithelial bands may be developed only focally and may be too subtle to allow a definitive diagnosis upon routine HE and Van Gieson's stainings. Immuno histochemical detection of increased amounts of tenascin, selectively in the subepithelial zone, is a specific test for CC with a sensitivity superior to conventional histological and histochemical detection, especially in minimal CC. Of note, tenascin staining also allows the diagnosis of CC in biopsies obtained from the rectum and sigmoid colon, thus avoiding the need for colonoscopic investigations. Tenascin immunostaining is a simple and safe tool to complement conventional histological diagnostics in clinically and histopathologically unclear cases of diarrhea. LC differs only in lacking the thickened subepithelial collagenous plate.

The key differences from chronic IBD are increased intraepithelial lymphocytes with no neutrophils, cryptitis, crypt abscess, erosions or ulcers.

Thickening of the collagen band and CC are not as unusual as usually thought. The biopsies should be taken from several regions of the colon, including the proximal colon (transverse colon and ascending colon). The transverse colon yields the largest percentage of biopsy specimens. Biopsy specimens from both the rectosigmoid and the right colon (ascending and cecum) were significantly less likely to be diagnostic. Only 66% of specimens obtained from the rectosigmoid were diagnostic, and 18% of these were interpreted as normal. Subepithelial collagen deposits proved to be significantly thicker in the transverse (median, 46.8 microm; range, 12 to 212.4) and descending (median, 49.2 microm; range, 6 to 230.4) than in the rectosigmoid (median, 33.6 microm; range, 9.6 to 178.8) and right colon (median, 35.4 microm; range, 6 to 140.4), respectively. Almost all biopsy specimens (97%) had collagen deposits thicker than 10 microm. However, the subjective interpretation "diagnostic of CC" proved to be most consistent with a threshold of 30 microm. So biopsy should include the transverse colon to definitely rule out CC. Furthermore, it is evident that in a given biopsy specimen, markedly abnormal subepithelial collagen deposition has to be present for an unequivocal histological diagnosis of CC. These, in contrary to other recommendations, propose that specimens obtained by flexible sigmoidoscopy are sufficient to establish the diagnosis in most patients, and colonoscopic biopsy of the more proximal area of the colon is usually unnecessary. Celiac sprue infrequently accompanies CC; thus, routine small bowel biopsy is not warranted.

**Differential diagnoses**

Subepithelial amyloid deposits mimicking CC can occur and so it’s of importance for the routine use of histochemical stains for amyloid in all cases of colorectal biopsies showing histologic changes suggestive of CC. Some times limited number of biopsy fragments may be incorrectly interpreted as LC or CC. The temporal relationships suggest that these morphologic patterns precede typical active Crohn's disease.

It is important to differentiate NSAIDS-associated colitis, even if it shows histology of CC, from CC as the two diseases differ in etiology and therapy. CC is frequently misdiagnosed as irritable bowel syndrome (IBS). The key differences are that CC occurs primarily in older women who may have a mildly increased ESR, furthermore, in IBS, constipation and diarrhea may...
alternate while people with CC have diarrhea alone.

**Therapy**

Clinical parameters and response to therapy are similar for collagenous or lymphocytic colitis. They are treatable conditions in most patients. Foods containing caffeine or lactose should be excluded from the diet since they stimulate fluid secretion in the colon. The use of NSAIDS probably should be discontinued, since studies have suggested that they may be associated with CC. If a patient is unable to digest fat, a low-fat diet may be helpful. Although there is no proven treatment, a number of medications are suggested. The response rate for sulphasalazine was 59%, for mesalazine 50% and for olsalazine 40%. Prednisolone was most effective with a response rate of 82%, but the required dose was often high and the effect was not sustained after withdrawal. Antibiotics were efficient in 63% of cases. Cholestyramine and loperamide had response rates of 59% and 71% respectively. Some patients will get better without any treatment. Rarely, patients will require a diverting ileostomy because of intractable diarrhoea.

**Prognosis and Complications**

Although variable in clinical presentation, treatment-free remissions are common. The long-term course and prognosis of the disease are unknown. Though it is a benign disease, patient often run a chronic course. CC and ulcerative colitis may represent extremes in the spectrum of IBD. Furthermore, CC may evolve to ulcerative colitis. Therefore, progression to ulcerative colitis should be considered in any patient with known CC whenever bloody diarrhea occurs, or if red cells, as well as white cells, are noted on stool microscopy.

In CC patients the lifetime relative risk of colorectal cancer and the relative risk after the diagnosis of colitis with a mean observation period of 7 years was not increased. An increase in relative risk of lung cancer in women with CC argue for further investigation of the role of smoking and other factors in this disorder.

Seven percent of patients also develop arthritis, which usually improves when the colitis is treated. Rare complications of peritonitis and perforation of colon were reported.

In Iraq Shubber et al in 2001 described, the disease. Out of 130 patients with chronic colitis, 15(11.5%) were labelled as microscopic colitis, but 6 of them were on NSAIDS. Al-Byatti SM found that microscopic colitis is the cause of chronic diarrhea in 12% of patients (4th leading cause of chronic diarrhea).

**References**