Collagenous colitis: Recent developments

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SUMMARY
Collagenous colitis and lymphocytic colitis are two chronic inflammatory conditions, involving the large bowel. These two interesting entities are usually referred to under the general term microscopic colitis. Collagenous colitis is characterized by watery diarrhea, abdominal bloating, and mild loss of weight. The true incidence is unknown. However, it has been estimated that it is unlikely to exceed one case per 100000 population. The etiology is unknown, although the use of non-steroidal anti-inflammatory drugs and lansoprazole, as well as infection by Yersinia enterocolitica, have been implicated in the pathogenesis of the disease. The role of activated eosinophils seems to be quite important. Diagnosis requires the histological detection of a thick subepithelial collagen band on large bowel mucosa biopsies. Treatment includes the administration of mesalamine, corticosteroids, budesonide, cholestyramine, as well as methotrexate, pentoxyphylline and octreotide. Surgery is reserved for severe cases. The course of the disease seems to be quite benign. Although most patients relapse after treatment cessation, most are asymptomatic for a long period of time after the establishment of diagnosis. Progression to ulcerative colitis occurs although in only a small percentage of patients. Fortunately no association with intestinal or extraintestinal cancers has been found.

Key words: Collagenous colitis, Inflammatory bowel disease, Microscopic colitis, Lymphocytic colitis

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1. INTRODUCTION
Microscopic colitis is a general term used today to include two inflammatory bowel disorders, namely collagenous colitis and lymphocytic colitis. Both are of unknown etiology, and both are characterized by chronic watery diarrhea, normal endoscopic picture and characteristic inflammatory lesions seen on large bowel histology. Collagenous colitis represents one of these two arms of microscopic colitis. It is characterized by deposition of a subepithelial collagen layer, causing disturbances in large bowel function. The etiology is largely uncertain and, as a consequence, treatment is also empiric. The course seems to be quite benign, although sufficient follow-up data is required to verify this assumption.

In this review, the current position on epidemiology, diagnosis, treatment and prognosis of collagenous colitis are described in the light of the most valid recent data from the relevant international literature.

2. EPIDEMIOLOGY
Although it is 26 years since the initial description of collagenous colitis in 1976, its incidence remains unknown. However, there are scattered reports, based on the year of onset of symptoms, indicating that the mean annual incidence per 100000 inhabitants is 1.1. A peak incidence is found in older women. The mean age at onset of symptoms fluctuates between 45 and 60 years. Females are affected more frequently than men, the rate of involvement being four to one. Familial aggregation...
has been described, suggesting a possible genetic predisposition.  

### 3. ETIOLOGY – PATHOGENESIS

The etiology of collagenous colitis is unknown. Some reports have tried to link the disease with *Yersinia enterocolitica* infection. Makinen et al.\(^3\), in a retrospective analysis of six patients with collagenous colitis, found three cases with *Yersinia enterocolitica* infection preceding the diagnosis of collagenous colitis. They suggest that *Yersinia enterocolitica* infection may be a triggering factor predisposing to the development of collagenous colitis. Bohr et al.\(^5\) showed that *Yersinia* antibodies are more often detected in patients with collagenous colitis than in healthy controls. Various drugs have also been linked with the appearance of collagenous colitis such as lansoprazole\(^6,7\) and regular non-steroidal-antiinflammatory drug consumption.\(^8,9\)

Bile acid malabsorption has been described in a proportion of patients with collagenous colitis, the rate of malabsorption fluctuating between 27 and 44%. The subset of patients with bile acid malabsorption and collagenous colitis is the proportion of patients that can respond to treatment with cholestyramine.\(^10,11\) Moreover, it seems that idiopathic bile acid malabsorption and microscopic colitis, either lymphocytic or collagenous, are often concomitant conditions.

Various pathophysiological data have been described in patients with collagenous colitis, although their significance remains uncertain. Moreover, we do not know if these events are truly primary or secondary events. It has been suggested that a relevant factor in the pathogenesis of collagenous colitis is the locally appearing, impaired fibrinolysis. In other words, an imbalance between fibrinogenesis and fibrinolysis may be the pathogenetic mechanism. There are also indications suggesting that deposition of an immature interstitial matrix that may be susceptible to degradation.\(^12\)

Transforming-Growth Factor-beta1, a growth factor having the capacity to cause accumulation of collagen in tissues has been suggested as being involved in the pathogenesis of collagenous colitis. In an interesting study, Stahle-Backdahl et al.\(^13\) suggested that eosinophils expressing TGF-beta1 may be of pathophysiological importance in the connective tissue remodelling seen in collagenous colitis. They found an increased presence of eosinophils expressing TGF-b1 in the colonic mucosa of patients with collagenous colitis. The role of eosinophils in the pathogenesis of collagenous colitis is further supported by Levy et al.\(^14\) who found an increased eosinophil infiltration and degranulation in the colonic tissue of patients with collagenous colitis compared to healthy controls. They suggest that eosinophils and their cytotoxic granule proteins could be involved in the pathogenesis of collagenous colitis. However, the mechanisms of activation of eosinophils are unknown.

Colonic production of nitric oxide has been studied in a small number of patients with collagenous colitis and found to be increased. Olesen et al.\(^14\) found increased luminal levels of nitric oxide compared to controls. Moreover, luminal nitric oxide was well correlated with disease clinical activity and histopathological status. They suggest that epithelial cells are the most likely source of this luminal nitric oxide.

The pathogenic mechanism of diarrhea in collagenous colitis is probably related to impaired sodium chloride absorption, active electrogenic chloride secretion and increased subepithelial resistance due to subepithelial collagenous band thickness.\(^15\) Epithelial resistance is diminished and occluding and claudin-4 expression is impaired. The down-regulation of tight junction molecules contributes significantly to the development of diarrhea. Diarrhea in collagenous colitis has been considered a secretory one. However, recent data suggest that in some patients an osmotic factor dominates, while in others a combination of both seems to exist.\(^16\)

### 4. PATHOLOGY

The histologic hallmark of cc is a subepithelial linear broad and usually continuous, eosinophilic band of collagen, associated with mucosal colonic inflammation (colitis)\(^17\). The subepithelial collagen band measures 10 to 70 μm in thickness with a mean of 12 to 30 μm\(^17\) and shows an irregular lower border helping to distinguish it from the normal basement membrane (Figure 1). Masson trichrome stains the collagen band green (Figure 2), which is immunohistochemicaly positive for type I collagen.\(^18\)

Mucosal inflammation includes slightly to moderately increased lamina propria infiltration by lymphocytes, plasmacytes, mast cells and variable numbers of neutrophils and eosinophils, associated with increased intraepithelial lymphocytosis and epithelial injury.\(^19,20\) Damaged epithelial cells appear flattened, vacuolated, mucin-depleted and sometimes detached from the basement membrane, forming clefts and rarely (7.5%)
microulcerations. Neutrophilic cryptitis is usually (30%) focally present. Crypt epithelium appears to be normal, showing only mild regeneration. Paneth cell metaplasia can be found in up to 44% and is associated with clinically more severe disease. Architectural abnormalities have occasionally been found (2,5%)  

The histological features of the disease are more marked in the proximal colon. However, the distal bowel may be spared, showing features of microscopic colitis only. On the other hand, the lesion may be discontinuous, particularly early in the course of the disease, and during the resolving phase.  

On the basis of the available data it is suggested, that multiple biopsy specimens, including specimens from the proximal colon, must be obtained in order to definitely rule-out the possibility of the existence of collagenous colitis. Furthermore, for the unequivocal histological diagnosis of collagenous colitis, the abnormal collagen deposition must measure at least 15μm in 30% or more of multiple biopsies and has to be associated with features of microscopic colitis. 

It is of interest that on histology, subclinical small bowel abnormalities can also be found. Intestinal antigliadin antibodies are elevated and intestinal permeability is abnormal in a proportion of patients. Sapp et al described how the terminal ileum might be involved with a similar pathogenic process as the colon. More specifically, they found an increased number of
intraepithelial lymphocytes in the terminal ileum mucosa compared to patients with inflammatory bowel disease and normal controls.

It has recently been reported that the number of mast cells in the upper part of lamina propria of patients with collagenous colitis is higher compared to controls, although the number of macrophages in the lower part of lamina propria is lower compared to patients with inflammatory bowel disease. These findings indicate that collagenous colitis is more of a Th2 type rather than Th1 reaction.

Histological differential diagnosis includes lymphocytic colitis and lesions associated with increased subepithelial collagen deposition. Collagenous colitis shares with lymphocytic colitis the increased intraepithelial lymphocytosis. However, in the later condition lymphocytic infiltration is more intense (more than 20 lymphocytes per 100 epithelial cells) and subepithelial collagen thickening is absent. Unlike collagenous colitis, the histologic features of lymphocytic colitis are usually uniformly found throughout the whole large bowel.

Collagenous colitis must also be histologically distinguished from the artifactually thickened basement membrane due to tangential sectioning of normal colon mucosa and a number of diseases that can be associated with subepithelial collagen thickening. Diseases that can histologically mimic collagenous colitis are ulcerative colitis, ischemic colitis, radiation colitis, amyloidosis, progressive systematic sclerosis, and diverticulosis. Nevertheless the correct diagnosis is based on proper clinical and histological settings.

5. CLINICAL MANIFESTATIONS

The clinical picture is usually characterized by profound watery diarrhea lasting for several months. Other clinical symptoms include abdominal bloating, and weight loss. A proportion of patients describes non-steroidal anti-inflammatory drug consumption for a long period of time. Seronegative, non-destructive arthritis has been described and therefore, collagenous colitis must be included in the list of causes of enteropathic arthritis. Fortunately, there is no increased risk for the development of either intestinal or extraintestinal malignancy in these patients. Emergency situations such as perforation of the colon may appeared in the course of the disease.

6. DIAGNOSIS

The possibility of collagenous colitis must be considered in all patients - especially in women aged between 40 and 60 years - with watery diarrhea, lasting for more than four weeks. The most useful practical recommendations for the correct diagnosis include the following: a) biopsies must be obtained, preferably from the transverse colon, b) inflammatory changes have to parallel the collagen deposition, c) subjective sensitivity in estimation of collagen thickness in hematoxylin-eosin slides is low, and d) collagenous colitis without increase of inflammatory cells and a special type of collagen deposition is doubtful.

7. TREATMENT

Patients who take NSAIDs at the time of diagnosis of collagenous colitis must discontinue their use. Although there is no direct evidence of efficacy, elimination of caffeine or lactose from the diet, should be undertaken. Symptomatic treatment, including antidiarrheal agents, could be tried, but appeared to be ineffective. Mesalamine at a dose of 2-4 g daily, must be the initial treatment. Bile salt-binding agents, especially cholestyramine, appear to be effective for patients unresponsive or intolerant to aminosalicylates. Corticosteroids, in conjunction or not with mesalamine, should be reserved for patients with refractory disease in whom mesalamine or cholestyramine has failed. Other agents that could be tried in patients with collagenous colitis include antibiotics, bismuth subsalicylate, pentoxiphylline, octreotide and methotrexate. Surgical intervention, with either fecal stream diversion or subtotal colectomy, shows promise as an intervention of last resort.

During recent years budesonide has successfully been used in the treatment of collagenous colitis. The usual dose is 9 mg per day for two months. In the later trial, stool frequency and stool weight decreased significantly, as the histological inflammation grade and collagen thickness decreased. However, 80% of patients relapsed after cessation of treatment. The efficacy of this regime was confirmed in a recently published metaanalysis of four randomized trials.

Predictors of response to treatment include both histological and clinical variables. So patients who were taking NSAIDs are more likely to require corticosteroids. The degree of lamina propria inflammation can be used as a histological predictor to guide treatment, and, finally, patients who respond to antidiarrheal agents or
spontaneous remissions are usually older than those requiring corticosteroids or mesalamine.35

8. PROGNOSIS

Collagenous colitis is considered to be a benign disorder, most often associated with a chronic course. In a follow-up study of 24 patients for 2 to 10 years, no association with other gastrointestinal disorders was found.36 Progression to ulcerative colitis has been described.37 This possibility must be considered in any patient with known collagenous colitis whenever bloody diarrhea occurs, or if red and white cells appear on stool examination.

As far as the bile malabsorption is concerned, the abnormality seems to persist over the years in most patients.38 Histopathology can be improved over the years, independently of bile acid malabsorption, although few patients actually resolve. Treatment could result in complete resolution of diarrhea in almost all patients, although spontaneous cessation can occur in nearly 20%.39 After cessation of diarrhea, 30% of patients will relapse. It is well accepted that more than 70% of patients are asymptomatic during the long-term follow-up.

9. REFERENCES