Microscopic colitis: a missed diagnosis?

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Context Collagenous colitis and lymphocytic colitis, collectively designated microscopic colitis, have until recently been considered as rare gastrointestinal disorders. New data suggest, however, that these disorders are relatively common, and to reach the correct diagnosis both the gastroenterologist and the pathologist must be aware of these diagnoses when evaluating patients with persistent watery non-bloody diarrhoea.

Starting point In an epidemiological study of a well-defined Swedish population, Martin Olesen and colleagues showed that microscopic colitis needs to be considered as a common gastrointestinal disorder (Gut 2004; 53: 346–50). In colonic biopsy specimens from 1018 patients who had a colonoscopy because of non-bloody diarrhoea in 1993–98, 97 patients (9.5%) were found to have microscopic colitis. In about a third of these cases, the diagnosis was missed in the primary histological evaluation. Median age at diagnosis was 64 years for collagenous colitis and 59 years for lymphocytic colitis. The annual incidence of the diseases was higher than previously considered and matched the incidence of Crohn’s disease, and in combination they approached the incidence of ulcerative colitis.

Where next The high regional incidence of microscopic colitis means that both clinicians and pathologists need to be more aware of the diagnosis, especially in the elderly female population with a clinical picture of watery non-bloody diarrhoea. Because of the potentially disabling symptoms, clinicians need to develop and evaluate new therapies.

Microscopic colitis consists of the entities collagenous colitis and lymphocytic colitis. These disorders are characterised clinically by persistent watery non-bloody diarrhoea with normal mucosal appearance during colonoscopy and without radiological abnormalities, but histopathologically the changes are fairly specific. Microscopic colitis has until recently been considered as uncommon.

Collagenous colitis was first described in 1976 in middle-aged women whose clinical examination for chronic diarrhoea was normal and in whom histological examination of colonic biopsy specimens revealed a thickened subepithelial band of collagen and an increased number of intraepithelial lymphocytes. The term microscopic colitis was originally applied in 1980 to a group of patients with chronic diarrhoea and normal colonoscopy with only minor histological changes. Microscopic evaluation of colonic biopsy specimens revealed modestly increased inflammation in the lamina propria without subepithelial collagen deposition or other mucosal changes. As this disease and collagenous colitis were clinically similar, the term lymphocytic colitis was proposed in 1989, and microscopic colitis was used to designate both entities.

Aetiology and pathogenesis The cause of microscopic colitis is unknown. The most widely held hypothesis is that it arises from a poorly regulated epithelial immune response to luminal or epithelial antigens, which is supported by regression of colonic inflammation after diversion of the faecal stream and recurrence after restoration of intestinal continuity. The identity of the inciting factors is uncertain: bile acids, toxins, and infectious agents have been suggested, but proof is lacking. The intake of non-steroidal anti-inflammatory drugs or proton-pump inhibitors has been linked to microscopic colitis as a possible cause. One of the postulated mechanisms is increased colonic permeability, allowing luminal antigens to enter the lamina propria and elicit an inflammatory response. However, because the use of non-steroidal anti-inflammatory drugs is more common than microscopic colitis, other causes must be invoked. The report of accumulation in certain families suggests some degree of genetic susceptibility.

The prevalence of autoimmune disorders, such as arthritis, hyperthyroidism, diabetes mellitus, scleroderma, and coeliac disease, is increased in patients with microscopic colitis, and continued efforts have been made to associate both types of colitis with various autoimmune HLA haplotypes as well as with immunological serum markers. Up to 25% of patients with coeliac disease also have microscopic colitis, and both conditions share some of the HLA-DQ loci linked to the expression of coeliac-disease-associated luminal antigens. However, there are some differences worth highlighting: patients with microscopic colitis do not respond to a gluten-free diet; neither collagenous colitis nor lymphocytic colitis is associated with other HLA types associated with coeliac disease (eg, B8 and DR3); and, by contrast with microscopic colitis, the intraepithelial T lymphocytes in coeliac disease are CD8-negative.

The pathogenesis of the collagen deposition in collagenous colitis is unclear. In the normal colon the epithelial basement membrane consists mainly of type IV collagen, whereas the collagen deposition in collagenous colitis is of type VI. Also, the subepithelial band contains significant amounts of the glycoprotein tenascin, the pathogenic role of which is unknown.
In both collagenous colitis and lymphocytic colitis, the volume of diarrhoea (stool output 500–750 g a day with electrolyte composition of secretory diarrhoea) seems to be related to the intensity of lamina propria inflammation and not to the extent or the thickness of the collagenous band.12

Epidemiology
In two recent regional studies from Örebro, Sweden, and Olmsted County, Minnesota, large increases in the annual incidence of microscopic colitis during the past two decades were reported.9,13 The Swedish study included 1028 patients with non-bloody diarrhoea who had a colonoscopy in 1993–98. Histopathological examination of colonic biopsy specimens revealed that 97 (9.5%) fulfilled the diagnostic criteria of microscopic colitis (51 collagenous colitis and 46 lymphocytic colitis). The patients were mainly elderly people with a median age of 64 (collagenous colitis) and 59 (lymphocytic colitis), and with a predominance of women (female to male ratio 7.5:1 for collagenous colitis and 2.1:1 for lymphocytic colitis). The incidence had increased from 3.7 per 100 000 inhabitants during 1993–95 to 6.1 per 100 000 during 1996–98 for collagenous colitis, and from 3.1 per 100 000 to 5.7 per 100 000 for lymphocytic colitis.9 The US findings were similar: an increased incidence of microscopic colitis from 0.8 in 1985–89 to 2.6 in 1990–93, 10.3 in 1994–97, and 19.1 in 1998–2001 (all per 100 000).11

Diagnostic criteria
The histopathological characteristics of collagenous colitis and lymphocytic colitis are not pathognomonic but can occur in various inflammatory conditions in the colon. However, with the proper clinical findings (ie, a history of persistent non-bloody watery diarrhoea, and a normal or near-normal colonoscopy), the diagnoses can be made with almost certainty (figure).

Both collagenous colitis and lymphocytic colitis show an increased number of intraepithelial CD8+ T lymphocytes, exceeding 20% of the surface cells. This finding is accompanied by a variable inflammatory infiltrate of the lamina propria consisting of CD8+ T lymphocytes, eosinophils, mast cells, and neutrophils. A diffusely distributed thickened collagenous band lying just beneath the surface epithelium is also needed to make the diagnosis of collagenous colitis. Most investigators agree that the thickness of this band in a well-oriented biopsy sample must exceed 10 µm (the normal basement membrane is about 3 µm thick), but a tangentially cut basement membrane section should not be misinterpreted. Secondary changes, such as mucin depletion and mucosal atrophy, might be seen.11 Crypt distortion is not a feature of microscopic colitis.

Several other colitides must be excluded before making a diagnosis of microscopic colitis. Thus, as the most relevant differential diagnoses, ulcerative colitis and Crohn’s disease, colonic infections, diverticular disease, and amyloidosis must be ruled out by proper diagnostic testing and by thorough histopathological investigation.

Therapy
There is a high spontaneous resolution of symptoms, and only a few controlled trials in collagenous colitis have been done (and none in lymphocytic colitis). Therefore the treatment of microscopic colitis is largely empirical. A relevant therapeutic approach might be to eliminate the intake of secretagogues such as caffeine and non-steroidal anti-inflammatory drugs, and mesalazine in standard doses for ulcerative colitis might be administered. However, a recent Cochrane review14 concluded that budesonide (three 3 mg tablets daily) and bismuth subsalicylate (nine 262 mg tablets daily in three divided doses) is effective in the initial
treatment of collagenous colitis (ie, in the first 8 weeks from diagnosis). However, future trials should concentrate on investigating the efficacy of drugs in lymphocytic colitis and in the later course of the diseases, especially as maintenance treatment.

**Prognosis**
The natural history of microscopic colitis is benign, but patients are often severely affected. The course is variable with alternating spontaneous remission and relapse, as in ulcerative colitis and Crohn’s disease. A few cases of microscopic colitis have been reported to develop into Crohn’s disease or ulcerative colitis, but it is debated whether this is a true evolution, initial misdiagnosis, or variations in the histopathology of microscopic colitis. The cancer risk, including colorectal carcinomas, and the mortality is similar to that of the general population.17

**Reaching the diagnosis**
The higher incidence of microscopic colitis than was previously appreciated might in part be due to changed diagnostic criteria and an increased awareness of the diseases. The symptoms of microscopic colitis are often disabling, and the current treatment is far from optimum. Because new treatment protocols are therefore needed, it is important to improve the detection of patients with this disorder. First, clinical awareness of the condition is essential. Second, in the correct clinical settings and without colonoscopic signs of inflammation, it seems even more important to do biopsies for histopathological examination. Third, because both the density of intraepithelial lymphocytes and the thickness of the collagenous band tend to be patchy, it is essential to do multiple biopsies throughout the colon. Involvement of the left colon seems to be less intense than that of the right, and biopsy specimens from the left part miss about 10% of the cases. It is therefore recommended that tissue samples should be obtained from the transverse or ascending colon to definitely rule out collagenous colitis.18

**Conclusions**
The important role of the pathologist is clearly illustrated by the latest Swedish study showing difficulties in diagnosing microscopic colitis, and especially lymphocytic colitis, histopathologically. Terms such as “unspecific chronic inflammation” or “signs of chronic inflammatory bowel disease but not diagnostic” should be avoided to include patients in the proper therapeutic group. By considering the clinical history and symptoms, the pathologist should be able to reach the correct diagnosis in most cases. Good communication between the pathologist and the clinician is therefore essential.

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**References**