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REVIEW

Histology of microscopic colitis—review with a practical approach for pathologists

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Histology of microscopic colitis—review with a practical approach for pathologists

Microscopic colitis has emerged as a major cause of chronic watery non-bloody diarrhoea, particularly in elderly females. The term is used as an umbrella term to categorize a subgroup of colitides with distinct clinicopathological phenotypes and no significant endoscopic abnormalities. Lymphocytic colitis is defined by an increased number of surface intraepithelial lymphocytes, and collagenous colitis by a thickened collagen band underneath the surface epithelium. There is increased inflammation in the lamina propria, but only little or no crypt architectural distortion. Incomplete and variant forms showing less characteristic features have been reported under different names. The differential diagnosis mainly includes resolving infectious colitis and changes related to the intake of drugs such as non-steroidal anti-inflammatory drugs. Substantial clinical and histological overlap between lymphocytic and collagenous colitis has been described, raising the suspicion that the conditions are two histological manifestations of the same entity, possibly representing different manifestations during the disease course or different stages of disease development. In this review, we provide a practical approach for pathologists, with a focus on diagnostic criteria and differential diagnosis, and discuss recent insights into the pathogenesis of disease and the relationship with classic chronic inflammatory bowel disease, i.e. Crohn's disease and ulcerative colitis.

Keywords: collagenous colitis, differential diagnosis, histopathology, incomplete forms, inflammatory bowel disease, lymphocytic colitis, microscopic colitis, pathogenesis, variant forms

Introduction

Biopsies of endoscopically normal large-bowel mucosa are generally believed to yield little information. As has recently been shown in a large retrospective analysis, which involved >600 subjects,[1] a history of

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diarrhoea does not in itself identify patients at higher risk of abnormal histology (14.5% versus 11%; $P = 0.41$). Patients aged >60 years, however, have a markedly increased likelihood of having a specific histological abnormality as compared with younger patients [odds ratio 2.76; 95% confidence interval (CI) 1.30–5.79; $P = 0.0045$], and microscopic colitis is the most common diagnosis.

Microscopic colitis is a common cause of chronic or recurrent watery non-bloody diarrhoea.[2] The term was coined by gastroenterologists in 1980 to describe a series of patients with incidental microscopic findings, and in whom the unifying feature was chronic idiopathic diarrhoea with few or no endoscopic abnormalities.[3] The term microscopic colitis is not encouraged diagnostically. It is used mainly as an umbrella term for two major conditions that are traditionally termed lymphocytic colitis and collagenous colitis.[4]

Lymphocytic and collagenous colitis remain pathological diagnoses, but close correlation with both endoscopy and clinical data (which can also help to identify causative or pathogenetic factors, such as drugs or coeliac disease) is essential for accurate assessment.[2,5,6] Upon endoscopic evaluation, the mucosa is normal in the vast majority of cases, but may occasionally show subtle changes, such as oedema and erythema.[7] Alterations of the vascular pattern and mucosal nodularity have been described for collagenous colitis. Mucosal defects and subsequent cicatriceal lesions have been related to the use of non-steroidal anti-inflammatory drugs.[8]

Recently, the microscopic colitides were included in the European Consensus on the Histology of Inflammatory Bowel Disease, which was published on behalf of the European Society of Pathology (ESP) and the European Crohn's and Colitis Organization (ECCO).[9] The consensus guidelines discussed diagnostic criteria, the differential diagnosis, and practical aspects, such as the number and location of biopsies to be taken. In the present review, we provide a practical approach for pathologists, focusing on diagnostic criteria, variant forms, the relationship with classic inflammatory bowel disease, i.e. Crohn's disease and ulcerative colitis, and features that are useful for differential diagnosis. In addition, we present some recent observations with respect to the pathogenesis of disease. Data for this review were compiled by the use of MEDLINE/PubMed and Thomson Reuters Web of Science®, with assessment of articles published before December 2013. Search terms included microscopic colitis, lymphocytic colitis, and collagenous colitis. Only articles published in English were considered.

Pathogenesis

The pathogenesis of microscopic colitis is still largely unknown, but is likely to be multifactorial, and an abnormal immune response (possibly to a luminal antigen), impaired intestinal barrier function (with increased permeability) and myofibroblast dysfunction (in collagenous colitis) are believed to play a major role. Smoking has been identified as a risk factor in several studies, and smokers may develop their disease >10 years earlier than non-smokers.[10–12] However, the consumption of several types of drug, in particular non-steroidal anti-inflammatory drugs and proton pump inhibitors, has also been associated with the development of disease.[2,6,12,13] It is, however, not always clear whether these drugs are trigger factors for colonic inflammation in predisposed hosts or only worsen self-evolving microscopic colitis.[14] Considering the high number of drug users and the relatively low incidence of microscopic colitis, Keszthelyi *et al.*[15] speculated that drug-induced cases of microscopic colitis result from an idiosyncratic reaction.

The theory of an abnormal immune response to a luminal factor is best supported by observations made in patients with collagenous colitis and ileostomy. In these, faecal stream diversion may cause regression of intestinal inflammation and mucosal barrier dysfunction, whereas reconstruction of bowel continuity may trigger the reappearance of symptoms and histological changes.[16,17] Immunologically, intraepithelial lymphocytes (IELs) have been characterized as CD8+ cytotoxic T cells, bearing the α/β T-cell receptor.[18,19] The status of the lamina propria seems to be more complex: some investigators noted accumulation of CD4+ helper T cells within the lamina propria,[18] whereas others noted a decreased number of CD4+ cells, despite lymphocytic proliferation (Ki67+) and activation (CD45RO+ and Foxp3+).[19]

Is microscopic colitis simply an autoimmune disease? This hypothesis has been supported by the female predominance for both conditions, which is evident from all epidemiological studies, and by the association with well-recognized autoimmune diseases. Thus, 20–60% of patients with lymphocytic colitis and 17–40% of patients with collagenous colitis suffer from autoimmune diseases, such as rheumatoid arthritis, collagen vascular diseases, or thyroid disorders, and there is also a strong association with coeliac disease.[4,9] Genetic predisposition may play a role, as familial occurrence of microscopic colitis has been reported.[20,21] Fine *et al.*[22] reported a high prevalence of coeliac sprue-like HLA-DQ genes in patients with microscopic colitis, but did not observe

differences between patients with lmphocytic and collagenous colitis. In another study, 12 of 25 (48%) patients with lymphocytic colitis ($P = 0.027$ versus controls) and 11 of 34 (32%) with collagenous colitis ($P = 0.38$ versus controls) were *DQ2*-positive; there were no differences in the frequency of *DQ8* positivity.[23]

In collagenous colitis, *in vitro* experiments have shown impaired intestinal barrier function, with increased transmucosal permeability of antigens and bacteria, that is independent of disease activity.[24] Likewise, the immunohistochemical expression of the cell junction proteins E-cadherin and ZO-1 was reduced in active disease.[25] Down-regulation of the expression of tight junction molecules, such as occludin and claudin-4, may be another structural correlate of barrier dysfunction contributing to diarrhoea in affected patients.[26]

The excessive collagen deposition in collagenous colitis has been related to myofibroblast dysfunction, leading to matrix and/or collagen overproduction with matrix remodelling, as shown by consistent expression of the glycoprotein tenascin (a 100-kDa glycoprotein with a widespread distribution in the foetal developing gut) within the subepithelial collagen band.[27] However, there may be a general imbalance between fibrogenesis and fibrolysis, and impaired degradation of extracellular matrix proteins may play a major role.[28]

Lymphocytic colitis

The key histological feature of lymphocytic colitis is intraepithelial lymphocytosis, as shown by an increased number of surface IELs, with little or no crypt architectural distortion (Table 1).[5,7,29] Most investigators refer to a cut-off value of >20 IELs per 100 surface epithelial cells (normal <5 IELs), but some refer to 15 or more IELs (median 30, range 10–66).[30] The cut-off value of 20 IELs has recently been adopted in the European Consensus on the Histopathology of Inflammatory Bowel Disease.[9] The terminal ileum may be affected in lymphocytic colitis: in the study by Sapp *et al.*,[31] 16 of 22 (73%) patients had a mean villous IEL count of >5.

On sections stained with haematoxylin and eosin (H&E), IELs are characterized by usually round, compact nuclei with a dense chromatin pattern and a perinuclear halo. The surface epithelium may show generally mild degenerative and/or regenerative changes, such as vacuolization, flattening, and mucin depletion.[32] Mild thickening of the subepithelial collagen band may be present in some cases. If the thickness of this band exceeds 10 μm, the case should be diagnosed as collagenous colitis (compare below). As compared with healthy individuals, the cellularity in the lamina propria is diffusely increased (with loss of the normally decreasing inflammatory cell density gradient towards the muscularis mucosae). The inflammation mainly consists of lymphocytes and plasma cells, but eosinophils and neutrophils may also be observed, sometimes within the epithelium. Chetty and Govender[5] stressed the histological triad of intraepithelial lymphocytosis, surface epithelial injury and increased lamina propria cellularity as being characteristic and very suggestive of lymphocytic colitis. However, all three features, individually and collectively, are not specific or pathognomonic of the condition, and clinicopathological correlation is recommended (Figure 1A, B). Active crypt inflammation with occasional crypt abscess formation has been reported to occur in 30–38% of patients with microscopic colitis. The acute inflammation should be focal and mild in nature and not predominate within the inflammatory infiltrate.[33]

In most cases, the intraepithelial lymphocytosis is evident without the need for counting.[4] In cases in which the number of IELs is borderline, manual counting is applied, and only IELs in the intercryptal spaces should be considered. The epithelium overlying lymphoid follicles should not be evaluated.[32] H&E-stained slides are sufficient to make the diagnosis, and immunohistochemistry to identify intraepithelial T cells by their positivity for CD3 is not needed routinely (Figure 1C).[5,34]

Collagenous colitis

The key histological feature of collagenous colitis is a thickened collagen band under the surface epithelium (Table 1). The band does not usually extend around the crypts, and is most evident between the crypts immediately beneath the surface epithelial cells (Figure 2A). It has an irregular, jagged appearance at the deeper border, and may contain entrapped capillaries, red blood cells, and inflammatory cells.[5,7,29] As in lymphocytic colitis, the terminal ileum may be affected, but 'collagenous ileitis' has also been described in patients without microscopic colitis as an isolated process: O'Brien *et al.*[35] analysed 13 cases, and noted diarrhoea as a presenting symptom in 11. The subepithelial collagen thickness ranged from 15 μm to 100 μm (mean 32 μm) and involved

Table 1. Key histological features of lymphocytic and collagenous colitis

Lymphocytic colitis
An increased number of surface intraepithelial lymphocytes (>20 per 100 epithelial cells)
Mild surface epithelial injury (vacuolization, flattening, and mucin depletion)
Increased (and homogeneously distributed) mononuclear inflammation in the lamina propria (lymphocytes and plasma cells)
No or little crypt architectural distortion
Thickening (<10 μm) of the subepithelial collagen band may be present
Focal inflammatory bowel disease-like changes (cryptitis and Paneth cell metaplasia) possible
Technical note: H&E-stained slides are generally sufficient to make the diagnosis; CD3 immunostaining may highlight intraepithelial lymphocytes, but is not needed routinely
Collagenous colitis
Thickening (>10 μm) of the subepithelial collagen band (most prominent in the right colon; rectosigmoid may be normal)
Marked surface epithelial injury (flattening, detachment)
Increased (and homogeneously distributed) mononuclear inflammation in the lamina propria (lymphocytes and plasma cells)
No or little crypt architectural distortion
An increased number of surface intraepithelial lymphocytes (<20 per 100 epithelial cells) may be present
Focal inflammatory bowel disease-like changes (cryptitis and Paneth cell metaplasia) possible
Technical note: H&E-stained slides are generally sufficient to make the diagnosis; collagen stains or tenascin immunostaining may highlight the thickened collagen band, but are not needed routinely

H&E, Haematoxylin and eosin.

5–80% of the subepithelial region of the submitted biopsies. Among biopsies taken from other sites, seven of 13 colonic biopsies showed collagenous colitis, four of nine gastric biopsies showed collagenous gastritis, and two of 10 duodenal biopsies were abnormal, with collagenous sprue ($n = 1$) and partial villous atrophy and increased numbers of IELs ($n = 1$) (both coeliac disease-related).

Damage to the surface epithelium is usually pronounced and is more common than in lymphocytic colitis. Detachment of surface epithelial cells from subepithelial collagen is a characteristic finding (Figure 2B). An increased number of IELs is usually seen, but not to the same extent as in lymphocytic colitis, and is not essential for diagnosis. The terminal ileum may also show intraepithelial lymphocytosis: 13 of 23 (57%) patients with collagenous colitis had an increased mean villous IEL count of >5.[31] As in lymphocytic colitis, the cellularity in the lamina propria is diffusely increased by a predominantly mononuclear inflammatory infiltrate, and inflammatory bowel disease-like morphological features, such as active crypt inflammation and occasional crypt abscess formation, may occur, but should not predominate within the inflammatory infiltrate.[33]

According to the European Consensus on the Histopathology of Inflammatory Bowel Disease, the thickness of the collagen band should exceed 10 μm (normal <3 μm) in well-oriented biopsies, i.e. biopsies cut perpendicularly to the mucosal surface.[9] Often, it is much thicker (15–30 μm, up to 70 μm), and diarrhoea is usually observed when the thickness of the collagen band exceeds 15 μm,[30] although a direct relationship between the thickness of the collagen band and the clinical symptoms does not seem to exist. In most cases, the diagnosis can be established without problems on the basis of H&E-stained slides. In borderline cases, additional stains, such as collagen stains (e.g. Masson or chromotrope–aniline blue trichrome,

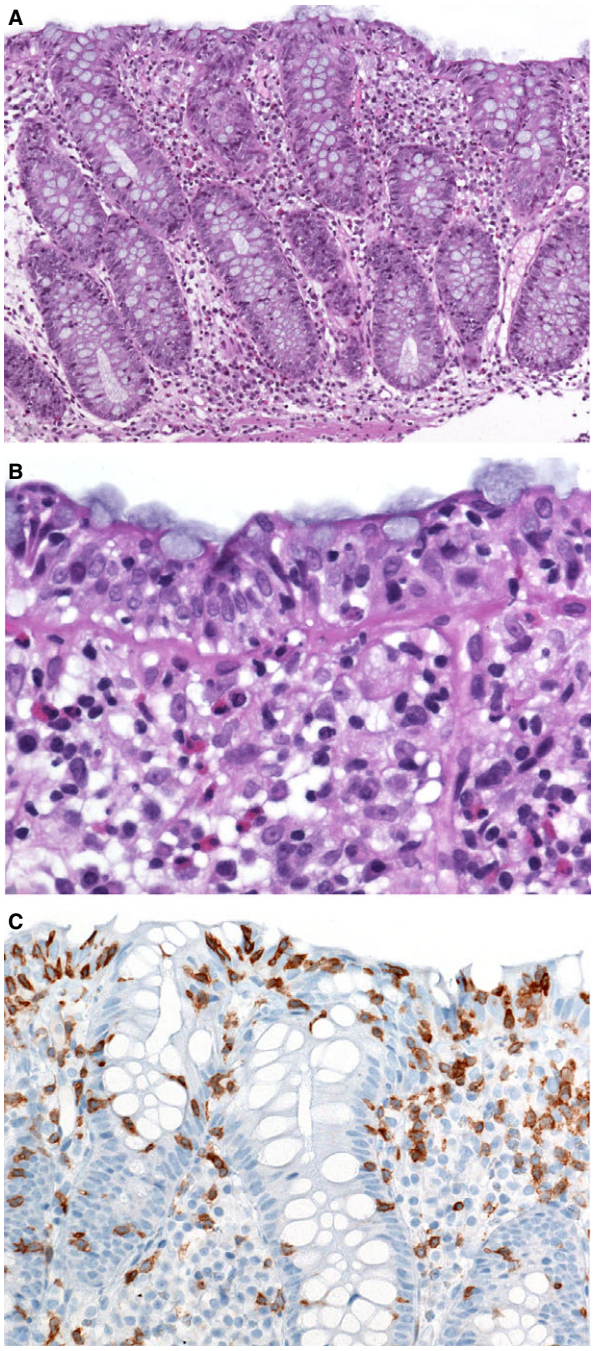

Figure 1. **A**, Lymphocytic colitis with a significantly increased number of surface intraepithelial lymphocytes (IELs) and no crypt architectural distortion. Note increased cellularity within the lamina propria. **B**, Higher magnification showing IELs and degenerative changes of the surface epithelium, such as vacuolization and mucin depletion. **C**, Immunostaining identifies intraepithelial T cells by their positivity for CD3.

Goldner, and Sirius red), or immunohistochemistry with antibodies directed against tenascin may be helpful (Figure 2C–D).[36,37]

In the study by Müller *et al.*,[37] tenascin staining revealed a specific histotopographic distribution pattern. Whereas tenascin deposits within the intercryptal matrix were found in other forms of colitis, selective subepithelial accumulation of tenascin was observed exclusively in collagenous colitis. This difference in the histotopographic distribution of tenascin between collagenous colitis and other forms of colitis, including fibrosis of the lamina propria, e.g. because of radiation therapy, was statistically highly significant. The only condition that showed borderline increased tenascin staining with a subepithelial localization was ischaemic colitis. However, this did not represent a differential diagnostic problem, as concomitant intercryptal positivity for tenascin was always observed in ischaemic lesions.

According to Rubio *et al.*,[38] the diagnosis of collagenous colitis should not be based exclusively on the thickness of the collagen band, but should take into consideration the whole microscopic constellation, which is characterized by a distorted superficial cell arrangement, areas of epithelial denudation, and inflammatory cells in the superficial epithelium and the lamina propria. Special care should be taken to avoid misinterpretation of a tangentially cut basement membrane.[39]

Incomplete and variant forms

Different incomplete and variant forms of microscopic colitis have been reported under separate names (Table 2).[40] These forms have mostly been introduced to denote patients who have clear clinical features of microscopic colitis but fall short of fulfilling the morphological criteria for lymphocytic or collagenous colitis (incomplete forms of microscopic colitis). Histology shows an increased number of IELs, i.e. <20 per 100 epithelial cells (incomplete lymphocytic colitis; Figure 3) or abnormal thickening of the subepithelial collagen band, i.e. <10 μm (incomplete collagenous colitis; Figure 4), in conjunction with an increased inflammatory infiltrate in the lamina propria. The following terms for these conditions can be found in the literature: borderline lymphocytic colitis,[39] minimal collagenous colitis,[41] microscopic colitis incomplete,[6,42] microscopic colitis not otherwise specified,[43,44] and paucicellular lymphocytic colitis.[45,46]

We understand that the term and concept of 'incomplete microscopic colitis' is new and subject to controversy, in particular regarding the minimum criteria required for diagnosis. Lacking available evidence, the authors of this review recommend

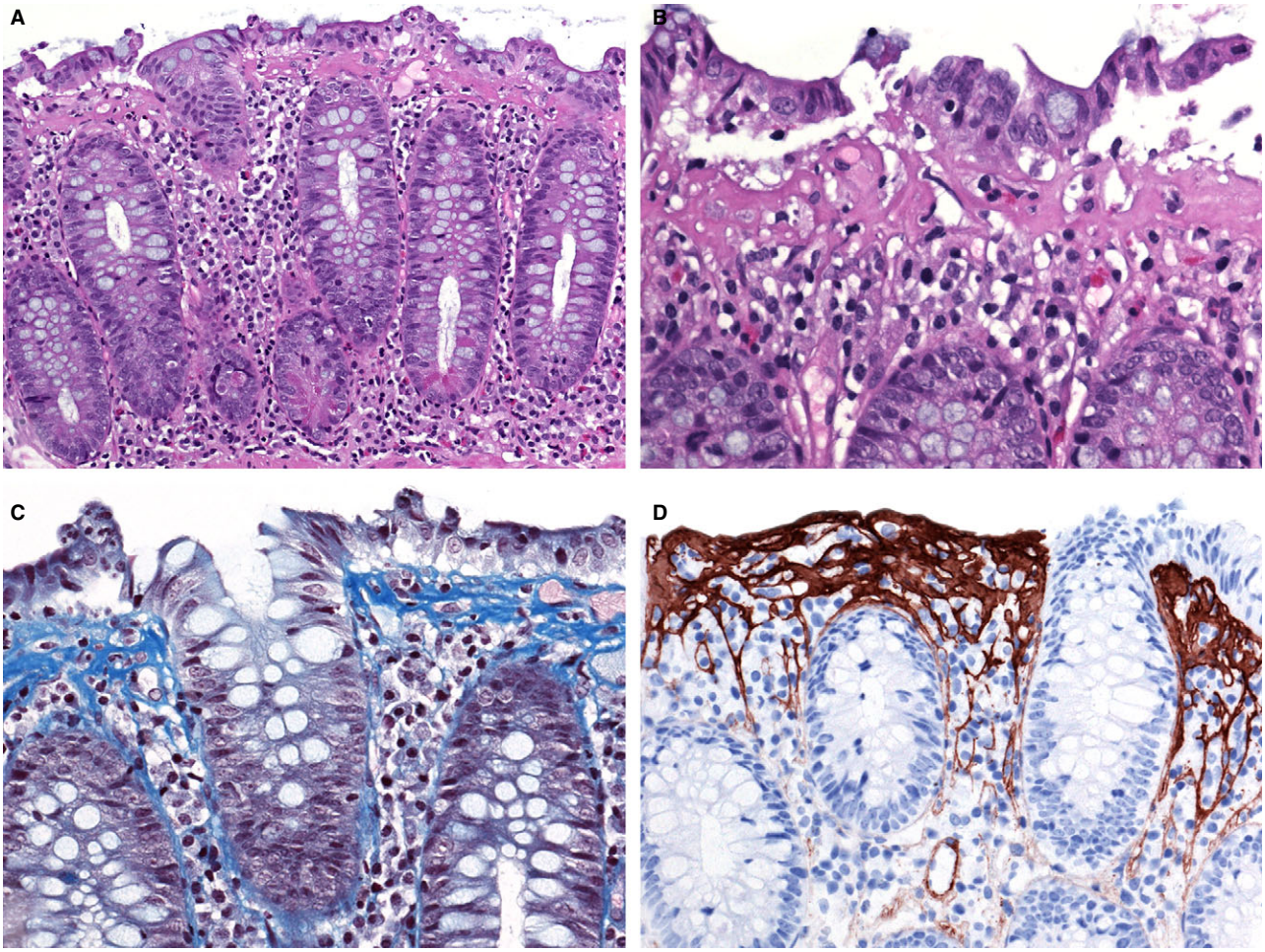

Figure 2. **A**, Collagenous colitis with a significantly thickened collagen band immediately beneath the surface epithelium, and increased cellularity within the lamina propria, but no crypt architectural distortion. **B**, Higher magnification showing entrapped capillaries and inflammatory cells within the collagen matrix, and marked degenerative changes of the surface epithelium with characteristic detachment of surface epithelial cells from subepithelial collagen. **C**, **D**, Masson trichrome (**C**) and tenascin (**D**) immunostaining highlight the collagen band and illustrate the characteristic jagged appearance at the deeper border.

>10 IELs and >5 μm thickness of the collagen band to be used as lower thresholds for the diagnosis of incomplete lymphocytic and incomplete collagenous colitis, respectively (Figure 5). Ongoing studies are evaluating the concept and response to therapy. In the long term, this might lead to new and more stringent histological criteria.

It is of note that IELs can be fairly numerous in the normal proximal colonic mucosa, and the lamina propria at this site can be cellular and may show loss of the plasma cell gradient seen in the remaining colon. In addition, the evaluation of lamina propria hypercellularity can be very subjective. Accordingly, there is a risk of overdiagnosis, in particular if the site of origin of the biopsies is not known. For this reason, clinicopathological correlation is vital, and a definitive diagnosis of incomplete lymphocytic colitis or incomplete collagenous colitis should only be made in the appropriate clinical context, in particular if therapy decisions are based on the evaluation. However, there is also the risk that patients with chronic watery diarrhoea and incomplete forms of lymphocytic and collagenous colitis upon histology will not be recognized and will therefore not be treated.

There are not only incomplete forms but also peculiar variant forms of lymphocytic and collagenous colitis reported in the literature. Rubio and Lindholm[47] described two patients with symptoms similar to those of lymphocytic colitis and an increased number of IELs, but within the crypt epithelium. The mean number of IELs was 39 (range 33–43) or 46 (range 32–55) per 100 crypt epithelial cells, whereas

Table 2. Incomplete and variant forms of lymphocytic and collagenous colitis

Incomplete forms of microscopic colitis
Incomplete lymphocytic colitis (syn. paucicellular lymphocytic colitis, borderline lymphocytic colitis) with an increased number of surface intraepithelial lymphocytes (<20 per 100 epithelial cells) (and increased mononuclear inflammation in the lamina propria)
Incomplete collagenous colitis (syn. minimal collagenous colitis) with thickening (<10 μm) of the subepithelial collagen band (and increased mononuclear inflammation in the lamina propria)
Variant forms of microscopic colitis
Cryptal lymphocytic coloproctitis
Lymphocytic colitis with giant cells
Collagenous colitis with giant cells
Pseudomembranous collagenous colitis

the mean number for the surface was 7 (range 0–13) or 8 (range 1–14) IELs per 100 surface epithelial cells. Immunohistochemistry with CD3 and CD8 antibodies revealed a classic phenotype. The authors suggested the name 'cryptal lymphocytic colitis' (coloproctitis).

Microscopic colitis with giant cells[48–50] is characterized by the presence of multinucleated giant cells in an otherwise classic lymphocytic or collagenous colitis. The subepithelial multinucleated giant cells are positive for CD68 and seem to arise from fusion of subepithelial macrophages. The presence of giant cells does not appear to have any clinical significance, and may merely be a histological curiosity.

Pseudomembranous collagenous colitis[51,52] has been described as another variant form. It is, however, still largely unclear whether the pseudomembranes constitute part of the spectrum of collagenous colitis or are related to superimposed infection. Chang *et al.*[40] speculated that the presence of associated pseudomembranes supports the hypothesis that collagenous colitis may be caused by a toxic and/or ischaemic mechanism. Very recently, Villanacci *et al.*[53] reported another case of pseudomembranous collagenous colitis with superimposed drug damage, as documented by the presence of cholestyramine crystals on the mucosal surface.

It is of note that the reported variant forms are extremely rare disorders, and it is unlikely that they all represent specific entities.[30] Their clinical significance needs to be defined in future studies.

Disease distribution within the large bowel

In microscopic colitis, the morphological findings may be patchy and not continuous. Thus, not all segments of the large bowel may be affected to the same extent, causing significant variation between specimens sampled from different regions of the large bowel or even within a single biopsy specimen.[30] A non-uniform distribution of the subepithelial collagen band is known from collagenous colitis, with less thickness in the distal parts, particularly the rectosigmoid.[54,55] This observation has very recently been confirmed in a large systematic analysis of patients with collagenous colitis from two prospective multicentre trials, in whom biopsies from multiple colonic segments had been obtained during baseline colonoscopy.[56] In this study, a collagen band of thickness >10 μm was more common in the right colon (with the highest levels in the caecum and ascending colon) and less frequent in the sigmoid and rectum, whereas the mononuclear inflammation in the lamina propria was evenly distributed among the different segments of the large bowel.

Lymphocytic colitis usually shows an even distribution of disease throughout the colon, but the findings may be patchy, thereby necessitating multiple biopsy samples to establish a diagnosis with certainty.[57] Thijs *et al.*[58] analysed 12 patients with lymphocytic colitis, and found that only 10 patients had diffuse disease throughout the colon, whereas two patients had disease limited to the right side. In a large investigation of 809 patients evaluated for chronic diarrhoea with no visible abnormalities upon endoscopy, 80 (10%) were found to have microscopic colitis, all of whom had evidence of disease in the left colon.[59] In another study, 95% of patients with collagenous colitis and 98% of patients with lymphocytic colitis had diagnostic histopathology in both the right and the left colon, and normal histology in biopsies obtained from the left colon had a high negative predictive value for the diagnosis of microscopic colitis.[42]

In summary, these observations suggest that normal mucosa, incomplete microscopic colitis and fully established microscopic colitis may coexist at different sites in the colon at the same time point. As rectal biopsies alone appear to be insufficient for exclusion of the diagnosis of microscopic colitis, and sampling within the range of sigmoidoscopy may not be adequate, multiple biopsy samples should be obtained throughout the whole colon and submitted, preferably, in separate containers.[2,5,6,9] This recommendation is well in line with the recommendations put forward by Yantiss and Odze:[57] For 'optimum

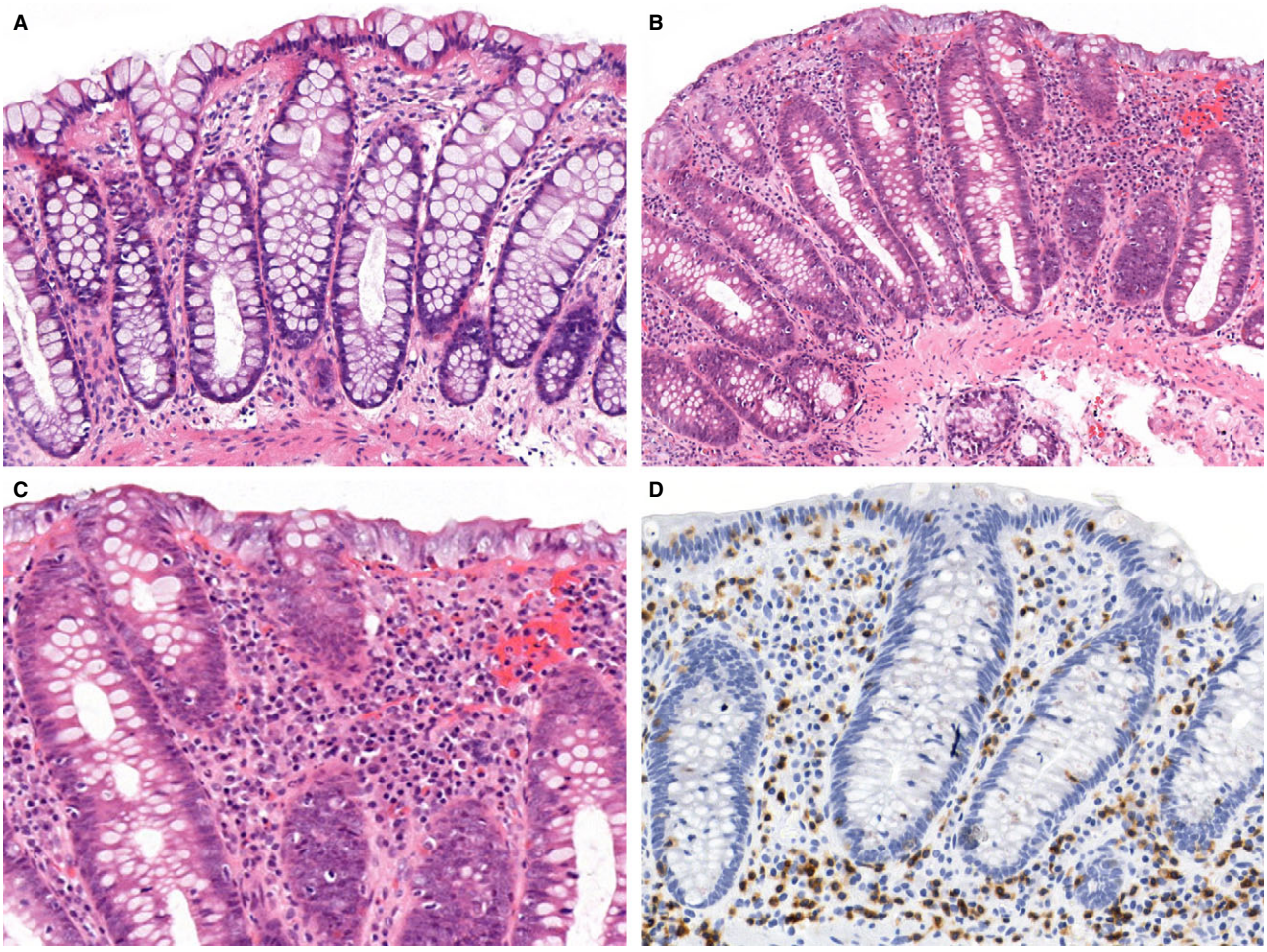

Figure 3. Example of an incomplete variant form of lymphocytic colitis (syn. 'paucicellular lymphocytic colitis'); **A**, normal mucosa is shown for comparison. **B**, **C**, Mild intraepithelial lymphocytosis (10–15 intraepithelial lymphocytes per 100 surface epithelial cells), increased cellularity within the lamina propria, and mild degenerative changes of the surface epithelium: overview (**B**) and higher magnification (**C**). **D**, Immunostaining identifies intraepithelial T cells by their positivity for CD3.

detection', these authors recommend performing full colonoscopy with two or more biopsies each from the right, transverse, descending and sigmoid colon, in addition to sampling of endoscopically visible abnormalities.

Differential diagnosis and relationship with classic chronic inflammatory bowel disease

The differential diagnosis of microscopic colitis mainly includes infectious colitis, particularly resolving acute infectious colitis, post-dysenteric irritable bowel syndrome, and drug-induced changes, particularly those related to the intake of non-steroidal inflammatory drugs, but the classic chronic inflammatory bowel diseases also have to be ruled out (Figure 5). Occasionally, ischaemia, radiation-induced injury and amyloidosis may show histological features reminiscent of collagenous colitis.[9,30]

The relationship with drug intake is complex, as consumption of drugs has been associated with the development of lymphocytic and/or collagenous colitis (compare above). However, in these rare cases, the drug most probably only triggers the disease (or worsens self-evolving microscopic colitis). We believe that these patients should be diagnosed with lymphocytic or collagenous colitis (not with 'drug-related' or 'drug-induced' colitis) to receive the appropriate treatment.

Surface epithelial lymphocytosis has also been observed in patients with Brainerd diarrhoea, but lymphocyte counts are generally low, and degenerative

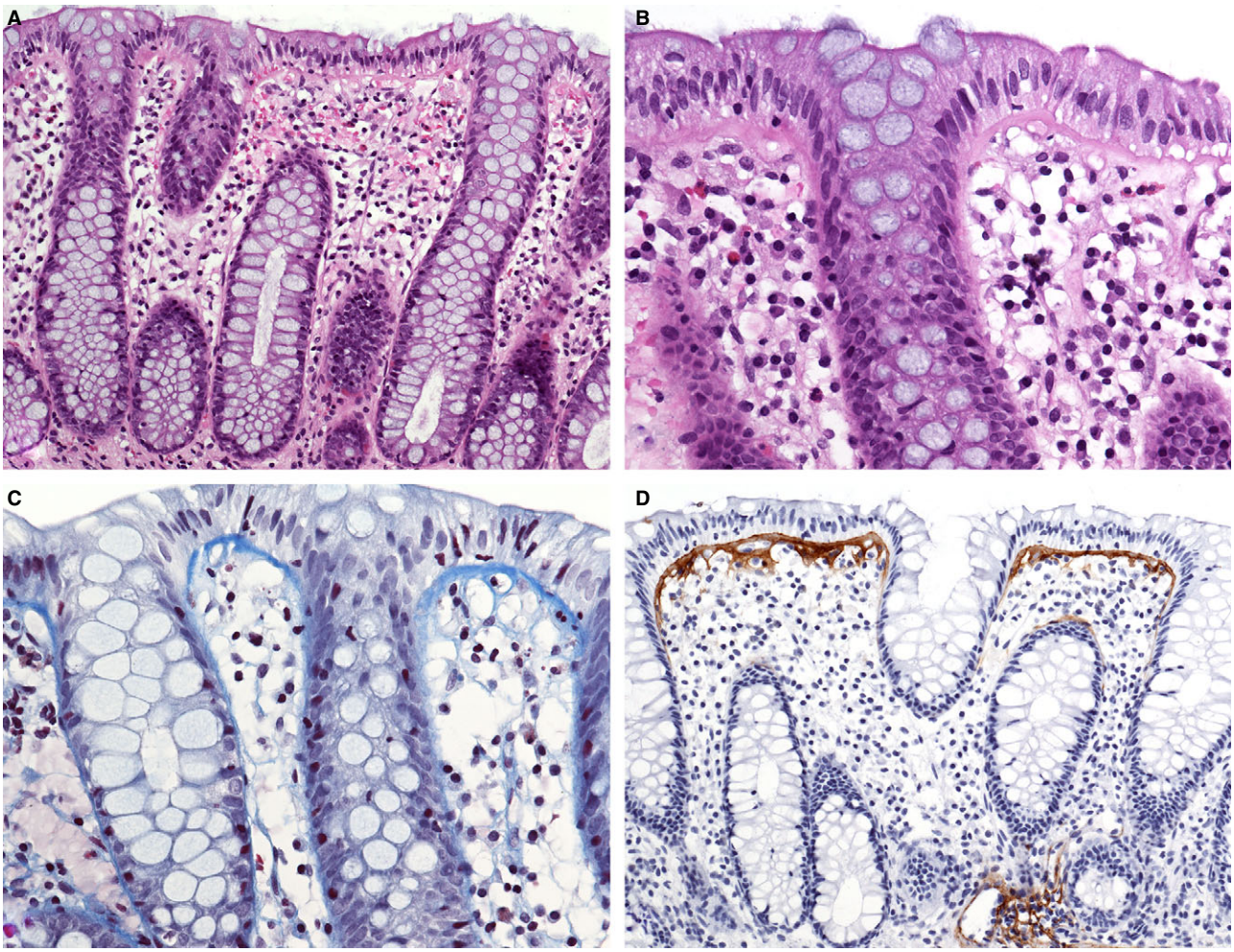

Figure 4. Example of an incomplete variant form of collagenous colitis. **A**, **B**, Mild thickening of the collagen band beneath the surface epithelium (<10 μm), increased cellularity within the lamina propria, and mild degenerative changes of the surface epithelium: overview (**A**) and higher magnification (**B**). **C**, **D**, Additional stains, such as chromotrope–aniline blue trichrome (**C**), and tenascin immunohistochemistry (**D**) highlight the thickened collagen band.

changes of the surface epithelium are not usually observed. A diagnosis of 'Brainerd colitis' can only be made in conjunction with clinical data, such as outbreaks of chronic watery diarrhoea with acute onset and prolonged duration. The cause of the disease is unknown.[60]

The differentiation from chronic inflammatory bowel disease, particularly ulcerative colitis and Crohn's disease, occurs in a different clinical and endoscopic setting, and histological interpretation is usually straightforward in obvious cases of chronic idiopathic inflammatory bowel disease.[5] As noted above, the absence of significant crypt distortion in lymphocytic and collagenous colitis is the major difference between microscopic colitis and chronic inflammatory bowel disease.

However, some inflammatory bowel disease-like features may be observed in microscopic colitis. These include not only active crypt inflammation but also typical signs of chronic disease, such as Paneth cell metaplasia and crypt architectural distortion, albeit only mild and focal in nature. In the study by Ayata *et al.*,[33] Paneth cell metaplasia was frequent in both groups and significantly more common in collagenous colitis than in lymphocytic colitis (44% versus 14%). Crypt architectural irregularity, although rare, was present in six of 79 patients with collagenous colitis (7.6%) and in three of 71 (4.2%) patients with lymphocytic colitis.

In addition, biopsy samples from patients with ulcerative colitis or Crohn's disease may mimic the features of microscopic colitis, both at onset and

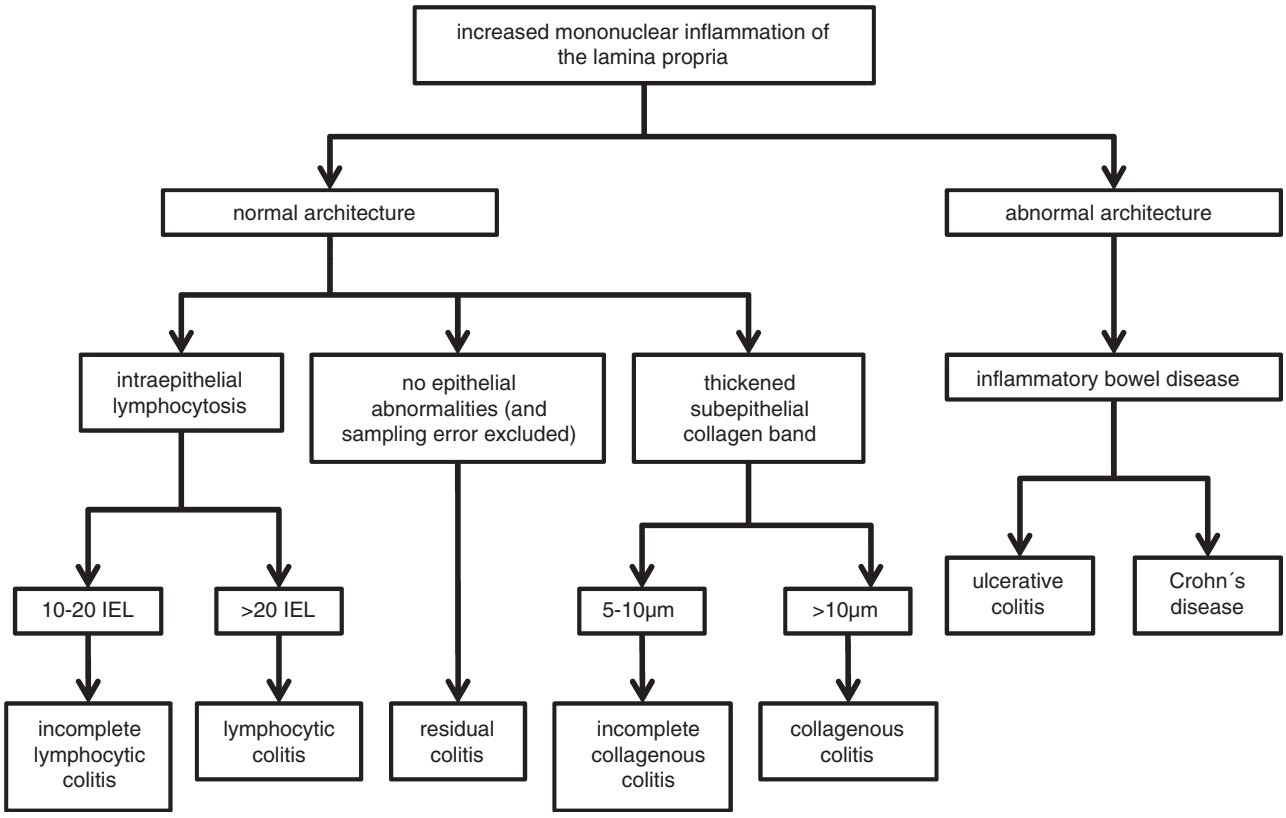

Figure 5. Differential diagnosis of lymphocytic and collagenous colitis against a background of increased mononuclear inflammation of the lamina propria. The term 'residual colitis' was chosen as an umbrella term to designate cases of remaining or enduring colitis characterized by a predominantly chronic inflammatory infiltrate in the absence of architectural distortion, which can predominantly be observed in resolving infections, complicated diverticular disease, and drug-induced colitis, but does not offer a specific aetiological diagnosis.

during follow-up.[30] In this context, it is of note that early inflammatory bowel disease may show lamina propria hypercellularity and loss of the plasma cell gradient, while lacking characteristic crypt changes.[61] In addition, surveillance biopsies from patients with inactive disease may show both collagenous colitis-like or lymphocytic colitis-like patterns.[62] In these cases, however, colonoscopic abnormalities are usually seen, making a diagnosis of microscopic colitis unlikely.[30]

Small series of patients have been identified with a diagnosis of microscopic colitis and classic chronic inflammatory bowel disease at different time points:[30] patients with microscopic colitis evolving into ulcerative colitis[63–65] or Crohn's disease,[66,67] and patients with longstanding ulcerative colitis who were diagnosed with collagenous or lymphocytic colitis during follow-up.[68,69] Studies are needed to determine whether microscopic colitis and classic chronic inflammatory bowel disease, particularly ulcerative colitis, are more related to one another than previously thought, sharing common pathogenetic pathways. Jagadeesan *et al.*[69] speculated that microscopic colitis and ulcerative colitis could represent both ends of the spectrum of the same disorder. The major clinical symptoms and the age of diagnosis are, however, different. Furthermore, the number of cases reported with a diagnosis of both diseases at different time points is small, which does not support a close relationship.

Microscopic colitis: a spectrum of diseases?

At present, lymphocytic colitis and collagenous colitis are mainly considered to be two separate but related entities.[2,6] However, the epidemiological features and clinical symptoms of lymphocytic colitis and collagenous colitis are strikingly similar, and risk factors such as the consumption of non-steroidal inflammatory drugs and the prevalence of concomitant autoimmune diseases, such as coeliac disease, do not differ basically.[70,71] It is of note that approximately one-third of all patients with coeliac disease may show histological features of lymphocytic colitis on

biopsy. Therefore, the European Consensus on the Histology of Inflammatory Bowel Disease recommends excluding coeliac disease, particularly in patients with lymphocytic colitis.[9]

Moreover, there is substantial overlap in histological findings. The most important overlapping histological feature, which can be used to discriminate the microscopic colitides from chronic inflammatory bowel disease, in particular ulcerative colitis and Crohn's disease, is diffusely increased inflammation of the lamina propria in conjunction with an overall absence of crypt architectural distortion. However, there are other overlapping features: mild thickening of the subepithelial collagen band may be observed in otherwise typical lymphocytic colitis, and a mild increase in the number of IELs in otherwise typical collagenous colitis. In the study by Bjørnbak *et al.*,[42] abnormal intraepithelial lymphocytosis (>5 IELs per 100 surface epithelial cells) was present in 48% of patients with collagenous colitis, and a slightly thickened subepithelial collagen band (5–10 μm) was present in 24% of patients with lymphocytic colitis. According to a recent systematic literature review, an abnormal number of IELs can be found in 45% (40–50%) of patients with collagenous colitis, and an abnormal subepithelial collagen band can be found in 16% (13–20%) of patients with lymphocytic colitis.[70]

It is of note that, in the study by Bjørnbak *et al.*,[42] a first diagnosis of microscopic colitis was made in 30% only at repeated endoscopy, whereas another 30% with a diagnosis of microscopic colitis in the first endoscopy did not fulfil the histological criteria at the second procedure. In the study by Shaz *et al.*,[72] 25% of the patients with collagenous colitis and 50% of the patients with lymphocytic colitis with biopsies prior to their definitive diagnosis had pathognomonic histological features on their prior biopsies to some extent, but were not recognized by the pathologists. However, these features were more pronounced in the biopsies from the procedure that established the diagnosis. Nonetheless, 10 of 12 patients with clinical data available had symptoms and were treated at the time of prior biopsies, indicating that symptoms often precede fully developed histological features.

Conversion between lymphocytic and collagenous colitis was noted by Vigren *et al.*[73] in nine of 65 (14%) patients: three from collagenous to lymphocytic colitis, and six from lymphocytic to collagenous colitis. In another report, two patients were diagnosed with lymphocytic colitis at the beginning of the study, but were found to have collagenous colitis on later follow-up biopsies.[74] These data, however, need to be confirmed in further studies, as the overlap of histological features together with the patchy, non-uniform distribution of both diseases along the colon might lead to an erroneous assumption of true conversion if the number of sampled biopsies is small.

The notion of a histological overlap between lymphocytic and collagenous colitis and the rare occurrence of disease conversion caused some authors to conclude that lymphocytic and collagenous colitis are in fact two histological manifestations of the same disease entity, possibly representing different manifestations during the disease course or different stages of disease development.[70,73,74] This hypothesis is, however, still lacking further evidence, in particular experimental evidence, and a definitive conclusion cannot be drawn.

So far, only two studies have assessed the intraobserver and interobserver variation in making the diagnosis of microscopic colitis.[75,76] In the first study,[75] four gastrointestinal pathologists reviewed colonic biopsies from 90 subjects during two independent assessments. Interobserver agreement with final diagnostic categories of microscopic colitis versus non-microscopic colitis was 91% (kappa 0.90, 95% CI 0.82–0.96) and 88% (kappa 0.83, 95% CI 0.73–0.92). The mean intraobserver agreement was 95% (kappa 0.89). The results obtained in the second study, in which three pathologist reviewed 125 cases, were similarly excellent (agreement 93–98%; kappa 0.81–0.89)[76]. However, in this second study, the authors additionally referred to the interobserver agreement on the different subtypes of microscopic colitis, and noted that the ability to discriminate lymphocytic and collagenous colitis from incomplete microscopic colitis was lower, the latter diagnosis being the subgroup with the lowest number of cases agreed on in two assessments (59–67%).

Conclusion

Microscopic colitis has emerged as a major cause of chronic watery (non-bloody) diarrhoea, particularly in the elderly population. An increased number of surface IELs is the predominant histological feature of lymphocytic colitis, and a thickened collagen band underneath the surface epithelium is the predominant feature in collagenous colitis. Incomplete and variant forms have been reported under different names. The differential diagnosis mainly includes resolving infectious colitis and changes related to the intake of non-steroidal anti-inflammatory drugs. Substantial clinical and histological overlap between lymphocytic and

collagenous colitis has been described, raising the suspicion that the conditions are two histological manifestations of the same disease entity, possibly representing different manifestations during the disease course or different stages of disease development.

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Conflict of interests

The authors declare no conflicts of interest.

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