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Are collagenous and lymphocytic colitis different aspects of the same disease?

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Short title: Conversion in microscopic colitis

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Abstract

Objective. Collagenous colitis (CC) and lymphocytic colitis (LC) are two subtypes of microscopic colitis (MC). Even though they most often are described as different entities they share many clinical and histological features. The aim of this study was to investigate the occurrence of conversion between CC and LC in a larger cohort of patients. **Materials and methods.** All 664 patients in our Pathology register with a diagnosis of CC and LC were scrutinized and those where additional endoscopies had been carried out were included, and their biopsies were re-examined. **Results.** Sixty five patients (55 women, 10 men, median age 58 years; range 29-86) fulfilled our criteria for inclusion. The primary diagnosis was CC in 47 patients (39 women, 8 men, median age 58 years; range 29-86) and LC in 18 patients (16 women, 2 men, median age 58 years; range 33-74). Conversion occurred in nine of the 65 patients (14%, all women, median age 59 years; range 41-72), three from CC to LC and six from LC to CC. **Conclusion.** This study has found that patients can show histological features consistent with both CC and LC over time. These patients could represent a subgroup with a true conversion between two separate entities. Alternatively, MC could be a spectral disease where the varying histological features are manifestations of the natural fluctuation. A third possibility could be that the histological changes reflect different manifestations during the disease course and consequently, the diagnostic criteria could be too vague.

Key words: *Bile acid diarrhoea, coeliac disease, collagenous colitis, conversion, follow-up, lymphocytic colitis, microscopic colitis*

Introduction

Microscopic colitis (MC) affects predominantly middle-aged women and results in chronic non bloody, watery diarrhoea. Other common symptoms include nocturnal diarrhoea, diffuse abdominal pain and weight loss [1]. Lymphocytic (LC) and collagenous (CC) colitis are two main subtypes of MC. They share many features, such as the clinical symptoms, association to autoimmune diseases and response to treatment [2, 3]. Although they share some histological features they can be separated by histopathology [1].

Conversion between classical inflammatory bowel disease (IBD) and MC has been observed [4-8]. In addition, conversions from LC to CC and from CC to LC have been described as case reports [9-14]. This may indicate that the two types of MC are more closely related to each other than previously anticipated.

Due to symptomatic CC a 58-year old woman visited our out-patient clinic at the Department of Gastroenterology in Malmö, Sweden, in 2009. Her medical history showed that she had gone through several colonoscopies which had revealed both LC and CC. In 1992 CC was diagnosed. In 1995 the disease had changed to LC but in 1998 and 2001 the disease had changed back to CC again. This unexpected case history led to discussions and resulted in this study where the aim was to investigate the occurrence of conversion between CC and LC in a larger cohort of patients.

Patients and methods

Patients

In Malmö patients with CC have been registered in files at the Department of Pathology since Clas Lindström described the first patient with the disease back in 1976 [15]. LC has been registered since 1989, when the disease was first described [16]. In 2009 the catchment area for the Department of Pathology in Malmö covered Malmö, but also Trelleborg, Svedala and Vellinge, a mixed urban and rural population comprising 388 587 inhabitants (31st December 2009). In 2009 we retrospectively identified 664 patients with a diagnosis of CC or LC at the Department of Pathology in Malmö. Those who had undergone at least two endoscopies with

at least three months interval were identified. If the diagnosis could be verified after histopathological re-evaluation the patient fulfilled our criteria for inclusion.

Patients with a transformation from MC to IBD or vice versa were not included.

Histopathology

The histopathological criteria used for CC were:

- A chronic inflammatory infiltrate in the lamina propria
- A thickened subepithelial collagen layer ≥ 10 micrometers (μm)
- Epithelial damage such as flattening and detachment

The histopathological criteria used for LC were:

- A chronic inflammatory infiltrate in the lamina propria
- Intraepithelial lymphocytes (IEL) ≥ 20 per 100 surface epithelial cells
- Epithelial damage such as flattening and detachment
- A subepithelial collagen layer $< 10 \mu\text{m}$

All cases were reassessed by a gastrointestinal pathologist with a special interest in and knowledge of MC (M Olesen). The original colonic mucosal biopsy specimen sections were used at the re-evaluation. If the quality was insufficient for reassessment new sections were made from the original paraffin wax embedded biopsy blocks. New sections were also made if special stains or immunohistochemistry were missing but considered needed for reassessment.

The subepithelial collagen layer was measured with an ocular micrometer in a well orientated part of a mucosal section. Measurement of the collagen layer was made in haematoxylin-eosin, but whenever considered necessary special stainings for collagen fibres (Masson's trichrome or van Gieson) or reticulin fibres (Sirius red) were carried out. Counting of IEL was performed in haematoxylin-eosin. Whenever needed sections were immunohistochemically stained with antibodies against T-lymphocytes (CD3). Counting was avoided in areas where the surface epithelium was overlying lymph follicles in the lamina propria.

Bile acid diarrhoea was diagnosed with the $^{75}\text{SeHCAT}$ test at the Department of Clinical Physiology in Malmö according to the procedure previously described by Thaysen et al [17]. A retention value $< 12\%$ was considered as abnormal, while values 12-18% were considered as borderline. The cut-off values were calibrated at the Department of Clinical Physiology through analysis of a group of 25 patients, mean age 35 ± 8 years (18 females, 7 males).

Results

In all, 65 patients (55 women, 10 men, median age 58 years, range 29-86) fulfilled our criteria for inclusion. See Table I.

In 47 patients the initial diagnosis was CC (39 females, 8 males; median age 58 years (range 29-86). Of these 47, 17 had normalised their histology at follow-up, while 27 persisted. The remaining three patients changed from CC during the disease course; two changed to LC and one changed to LC and then back to CC again.

LC was initially diagnosed in 18 patients (16 females, 2 males; median age 58 years (range 33-74). Of these 18, eight normalised their histology at follow-up and four persisted. The remaining six patients changed; all changed to CC and two of them later normalised their histological appearance. One of the patients diagnosed with LC at disease onset later developed paucicellular colitis, also known as LC incomplete. This disease is characterised by less increased number of IEL, 10-20 per 100 IEL, but fulfills the other criteria for LC [18]. Later this patient converted to CC.

The group of nine patients that changed from one subtype of MC to another (i.e. the three patients that changed from CC and the six patients that changed from LC) had a median age of 59 years (range 41-72, all females). They had a median follow-up period of 9.0 years (range 2-14) and a median number of 4.0 endoscopies (range 2-5). The indications for colonoscopy in the nine patients with transformational states are denoted in Table I. A substantial number of these patients did smoke (seven out of nine) and four had definitive bile acid diarrhoea, but none of the patients had coeliac disease. See Table I.

In the group of 56 patients that did not change between subtypes the median age was 58 years (range 29-86) and the interval between the first and last endoscopy was 5.0 years (median) (range 1-18 years). In this group 2-6 endoscopies per patient were performed, median 2.0.

Discussion

It has previously been reported that histology in patients with classical IBD could mimic MC early in the disease course but also during follow up [6]. Furthermore, conversion between classical IBD and MC has been observed [4-8]. Some studies have reported occasional patients with CC that changed into UC [5-7]. In another study they observed a child developing Crohn's disease from CC [8]. In a study comprising 163 patients with CC, three patients with Crohn's disease later developed CC and one patient had ulcerative proctitis before CC [4]. As many patients with IBD are followed on a regular basis with repeated endoscopies, changes in histological appearance in these patients may rather easily be detected.

Since the reported risk for colorectal cancer or adenomas in patients with MC is not increased [19, 20] and the treatment is fairly much the same in both CC and LC, it is not common with repeated endoscopies, for example after a relapse. As a consequence information is lacking on any putative changes in histology during the disease course. Despite this limitation some authors have identified occasional cases with conversion from CC to LC and vice versa. Transformation from LC to CC has been described in one patient after a follow-up of seven years [13], two (out of 23) patients after a median follow-up of four years [14], two patients after a follow-up of two years [10], and five out of 25 patients after a median follow-up of two years [12]. Conversion from CC to LC has been reported in one patient that underwent colectomy [9]. In ten patients with CC, one patient converted to LC during a follow-up period of two years [10]. In contrast Mulhaupt carried out a second colonoscopy in 27 patients with LC that had been followed for 38 months and found none that had transformed into CC [21].

In 23 patients with bile acid diarrhoea (BAD) and MC, Ung and co workers wanted to confirm the earlier histological findings. Two of 23 LC patients had transformed into CC during the time of the study. The authors suggested that CC and LC could represent two variants of the same disease [14]. Olesen et al studied 199 patients with LC with respect to

clinical features, associated disease and outcome of treatment. In 25 of these a follow-up colonoscopy was performed. Nine of 25 had normalised their histology, eleven had remaining LC. Five patients had changed into CC [12]. Thus both these studies report conversion from LC to CC in a substantial number of patients after a fairly short follow-up period (four and two years, respectively). Thus even if several cases with conversion between CC and LC have been noted as mentioned above the primary aim in these studies have not been to study this phenomenon.

Of the 65 patients followed in the present study, nine patients converted from one subtype of MC to another over a period of median nine years. In order to minimise the risk of diagnostic errors [22, 23] all colonic biopsy specimen sections were prepared and re-examined by a gastrointestinal pathologist with a special interest in gastrointestinal pathology. It is well-known that the thickened collagen layer in CC may be patchy and that the collagen layer thickness may be normal in the distal colon and rectum. If too few biopsy specimens are taken during endoscopy of a patient with CC this could result in an incorrect diagnosis of LC (due to sampling error). However, since our routine to take several biopsy specimens (two biopsies specimens each from six to eight segments) as part of the endoscopic investigation and follow-up of patients with loose stools, we consider the probability of an incorrect diagnosis of LC due to sampling error to be low. To avoid misinterpreting LC cases as CC cases, due to tangential sectioning of the subepithelial collagen layer, the subepithelial collagen layer thickness was measured in a well orientated section of the mucosa. Finally, counting of IEL was avoided in areas where the surface epithelium was overlying lymph follicles, since counting in these areas could result in a focally increased number of IEL and an incorrect diagnosis of LC. Unless the histopathological criteria used in the study are inadequate or too vague, a reasonable conclusion is that conversion from one subtype of MC to the other is possible.

Since treatment, for instance corticosteroids [24, 25], could influence the histology as in classical IBD [26], we cannot exclude that at least steroids could have an impact on the disease course and the histological features. Consequently, the patient files were scrutinized for information about treatment. Several of these nine patients had suffered longstanding diarrhea and had tried varied treatments. In Table II, the different treatment regimes in the nine patients are listed. Oddly enough, many of the patients had had the same medication for years independently of whether this medicine had any significant effect or not. This can to

some extent be due to the fact that many of the patients suffered from their disease during the early 90-ies before any clear cut criteria for treatment were established and consequently three of them recovered after introduction of Budesonide as the primary drug of choice. A majority of the other patients recovered spontaneously. However, as can be seen in Table II, no significant changes in medication were done before any conversion took place. In other words, we found no obvious explanation to the transformations as a consequence of the medication.

Earlier reports have shown a strong association with coeliac disease in both CC and LC [27-29]. In a review reporting data from ten articles, where the association between CC and coeliac disease was studied, the occurrence of coeliac disease varied from 0 % (out of 66 patients) to 20 % (out of 30 patients). The weighted mean was 5 % (95% CI 4-6) [28]. Consequently, we could expect to find at least one or maybe two patients with coeliac disease in our group of nine patients that changed between CC and LC. However, no one of these nine patients had serological findings of this and in five of the nine patients additional duodenal biopsies were also collected with negative results. The lack of patients with coeliac disease in this small subgroup of nine MC patients could be interesting. Could it be that MC patients without coeliac disease represent a subgroup with MC that is more prone to transform between different MC subtypes? Nevertheless, the number of patients that transformed in the present study is too small to be able to draw any conclusion.

Microscopic colitis is known to be associated with BAD, especially in CC [14, 30]. Hypothetically, bile acids could injure the epithelium, something that might progress to an inflammatory state such as CC or LC. Another possibility is that both MC and BAD could share some common pathogenetic mechanisms although any evidence supporting this has not yet been reported. Eight of our nine patients were investigated for BAD and only two had a normal result. Consequently, in this small group, the occurrence of BAD was rather high and the previously reported association between MC and BAD could be confirmed. The question remains whether this group with BAD in combination with MC is more prone to transformational states. BAD in CC in general is reported to be about 40% [28]. A majority of the nine patients (seven of nine) were also smokers (Table I). This is in line with previous observations indicating that both CC and LC patients tend to be smokers [31, 32].

Transformation or a mixed presentation between different diseases within an organ system is not restricted to the large bowel. In the liver overlap syndromes are described, where autoimmune hepatitis (AIH) may co-exist with either primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC), while simultaneous co-existence of PBC and PSC is described only rarely. A review article has recently discussed the controversies within this field [33]. In accordance with the unsolved issue of possible conversion in MC several explanations for these overlap syndromes are postulated. Two disorders may be sequentially presented, they may occur both at the same time, there could be a continuum of pathological changes without strict boundaries, overlap syndromes may be distinct entities of their own or a primary disorder could present with characteristics of another. A majority of investigators have been in favour for the last suggestion in overlap syndrome.

If the true incidence of putative transformational cases should be looked for it would be necessary to carry out a prospective study with repeated endoscopies regularly in a defined number of patients with MC according to a well defined schedule. Since both preparations and colonoscopy are unpleasant it may be difficult to include a sufficient number of patients to be able to calculate the true incidence. Nevertheless, a prospective histological evaluation would enable us to better understand the pathogenesis and the disease course in MC.

Several differences have been observed between the two subtypes of MC; the female: male-ratio has previously been higher in CC although the difference seems to decrease in recent studies [34]. CC is also regarded as a more inflammatory active disease with longer disease duration [21, 35, 36], even though a recent review indicates that the difference in disease activity might not be as pronounced as previously anticipated [28]. Differences in HLA between CC and LC have been observed [37]. Despite these facts our nine patients have histological features that fulfill criteria for both CC and LC but over time. Our observations indicate that conversions do exist, something that should be taken into consideration when the nature of MC is discussed. Even though transformations are found, the reason for this is not possible to find with a retrospective study. A retrospective study does not have a design that can provide complete information on the natural history of the disease. CC could be a more active disease form than LC that could be a manifestation of early CC or CC in remission, i.e. when the collagen layer is developing or on its way to decline. Even if a conversion between CC and LC has been confirmed the reason for this process remains to be determined. We suggest three possibilities. These patients could represent a subgroup with a true conversion

between two separate entities, CC and LC. Alternatively, MC could be a spectral disease where the varying histological features are manifestations of a natural fluctuation, especially during early and late periods of the disease course. A third possibility may be that the histological criteria are too vague, thus leading to a risk of misinterpretation of the observed histological changes. Studies with prospective histological follow-up are needed in order to be able to discriminate between these suggested possibilities.

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Table I Characteristics of the nine patients at the time for transformation between different forms of microscopic colitis

Pat id	Diagnoses at colonoscopy	Age at first diagnosis	Smoking ¹	Follow-up ² (years)	Coeliac disease	BAD (%)	Indication for biopsy
1	CC-LC-CC-CC	41	Yes	9	No #	No (22)	Persisting diarrhoea
2	CC-LC	61	Yes	3	No *	No (48)	Persisting diarrhoea
3	CC-LC	72	No	2	No *	Borderline (12)	Research study
4	LC-LC-CC-CC	44	Yes	14	No *	Yes (5)	Persisting diarrhoea
5	LC-CC-CC	58	No	6	No #	Yes (5)	Relapse
6	LC-CC-CC-CC	59	Yes	9	No #	Not done	Persisting diarrhoea
7	LC-CC	62	Yes	4	No *	Borderline (13)	Persisting diarrhoea, research study GI bleeding (gastric ulceration)
8	LC-LC-PC-CC-N	52	Yes	9	No #	Yes (5)	Relapse
9	LC-LC-CC-N	72	Yes	12	No #	Yes (3)	Persisting diarrhoea

Patient number 1 is the index case described in the introduction.

CC = collagenous colitis, LC = lymphocytic colitis, PC = paucicellular colitis/LC borderline.

1 Smoking was defined as daily smoking.

2 Follow-up is the time from first to last endoscopy.

SeHCAT reference value < 12 definitive bile acid diarrhoea (BAD), 12-18 borderline, >18 negative.

Coeliac disease was excluded with analysis of endomysial antibodies (*) and / or biopsy (#).

Table II Treatment given to the nine patients during follow-up

Pat id	Treatment tried but with side effects or without effect	Treatment during the follow-up period	Changes in treatment before conversion (that could influence the disease course)	Other medication
1	Loperamide, Mesalazine, corticosteroids	Colestipol 15 g daily		
2		Budesonide 3 mg daily	More active disease due to reduced dosis	Isradipine 5 mg daily, Pindolol 50 mg daily, Bendroflumetiazol 5 mg daily
3		Cholestyramine 4 g daily		
4	Cholestyramine	No treatment (intolerances)		
5	Cholestyramine, Mesalazine, corticosteroids	Loperamide and sterculia whenever needed		
6		No treatment		Fluvastatin 20 mg daily
7		Codeine whenever needed		
8		Mesalazine 400 mg BID, Cholestyramine 4 g daily		Paroxetin 20 mg daily ASA 75 mg daily, Folic acid 5 mg daily, Paracetamol whenever needed, Calcium/D-vitamin
9	Mesalazine, Metronidazole	Corticosteroids 5-10 mg daily, Loperamide whenever needed	Azathioprine 100 mg daily due to active disease	

Patients number 4, 5 and 8 later received Budesonide. Patient number 6 recovered after increased dosis Fluvastatin. The other patients either recovered spontaneously or during treatment with their previous medication.