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Falk Workshop
Microscopic Colitis –
Creating Awareness for an
Underestimated Disease
May 3, 2012
Congress Center Basel
Switzerland

Abstracts
Falk Workshop

MICROSCOPIC COLITIS – CREATING AWARENESS FOR AN UNDERESTIMATED DISEASE

Basel (Switzerland)
May 3, 2012

Scientific Organization:
S. Miehlke, Hamburg (Germany)
A. Münch, Linköping (Sweden)
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Introduction

Putting microscopic colitis in perspective

Curt Tysk
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Microscopic colitis (MC), previously regarded as rare and certainly overlooked, now has emerged as a common cause of chronic diarrhoea, especially in elderly females. MC, encompassing collagenous colitis (CC) and lymphocytic colitis (LC), is characterised clinically by chronic watery diarrhoea and a macroscopically normal or almost normal colonic mucosa, where microscopic examination of mucosal biopsies reveals characteristic histopathological changes.

Historical aspects

Collagenous colitis
In 1976, the Swedish pathologist Clas Lindström described a middle-aged female, who presented with chronic watery diarrhoea accompanied by abdominal pain. A rectal biopsy showed a subepithelial collagen band comparable to what was seen in collagenous sprue. In view of this similarity, Lindström called the condition collagenous colitis [1]. In this first report many of the features of CC were present. In the same year, Freeman and colleagues reported in an abstract a similar case with watery diarrhoea and a thickening of the basement membrane in the rectal mucosa [2].

Microscopic colitis
The term microscopic colitis was introduced by Read and colleagues in 1980 to describe patients with chronic watery diarrhoea and normal findings on sigmoidoscopy and barium enema but who had non-specific mucosal inflammation on microscopic examination; hence the term microscopic colitis [3]. The authors believed that the mild mucosal inflammatory reaction was an incidental finding. Subsequent reports by others used the same terminology and also diagnosed their cases as microscopic colitis [4, 5].

Lymphocytic colitis
In 1989, Lazenby and colleagues at Johns Hopkins Hospital, Baltimore described a subset of patients with chronic diarrhoea and a normal colonoscopy, who had characteristic histopathologic findings including a damaged surface epithelium with an infiltration of lymphocytes in the epithelium and increased lamina propria inflammation. They proposed the term lymphocytic colitis for this condition [6].
Relationship between collagenous and lymphocytic colitis

The relation of CC and LC is not clear. As CC and LC have similar clinical expression and similar histopathologic features except for the subepithelial collagen layer in CC, it has been discussed whether LC and CC are the same disease in different stages of development or rather two different but related conditions. Conversion of LC to CC or the opposite has been reported. However, conversion is seen infrequently and this fact together with the observed difference in sex ratio makes it more likely to consider CC and LC as two separate but related entities. Other subtypes of MC have been described, including incomplete microscopic colitis (MCi), microscopic colitis with giant cells, paucicellular lymphocytic colitis, cryptal lymphocytic colitis, pseudomembranous collagenous colitis, microscopic colitis with granulomatous inflammation, and microscopic colitis not otherwise specified. The clinical features of these conditions are similar to classical MC, but histopathologic appearance differs. Further studies are required to address the relationship and clinical significance of these variants of MC.

Progress in understanding of MC

Several publications followed after the first reports, and CC and LC were further characterised clinically and histopathologically during the following decades. The first epidemiological study of CC [7] was published in 1995 and was followed by further epidemiological studies mainly from Europe and North America [8–10]. The first three randomised controlled trials, comparing budesonide with placebo, were published in 2002–2003 and represented a major step forward in the treatment of MC [11–13]. During recent years, some progress has been made in the understanding of the pathophysiology and mucosal inflammation of MC. However, major research remains to achieve a deeper knowledge of the aetiology and pathophysiology of MC and further to define the optimal treatment.

References:


Session I

Epidemiology and clinical spectrum
Epidemiology and clinical findings in microscopic colitis

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Epidemiologic studies show that microscopic colitis (MC) is almost as common as classic IBD. MC may be diagnosed in 10% of patients investigated for chronic non-bloody diarrhoea, and in 20% or more of such patients older than 70 years. MC must also be considered in younger patients, but seems to be a rare phenomenon in childhood. Recent incidence figures of 4.6–6.2 per 100,000 inhabitants have been reported for collagenous colitis (CC), and an annual incidence of 4–5.5 per 100,000 inhabitants for lymphocytic colitis (LC). The highest incidences for MC are found in the northern Europe and northern America and follow apparently a north-south gradient. The average age at diagnosis is 65 years. A female predominance is found in MC, but less pronounced for LC than for CC. Prevalence estimates for MC are around 100 cases per 100,000 persons.

The main symptom of MC is chronic, non-bloody diarrhoea that may be accompanied by nocturnal diarrhoea and faecal incontinence. Abdominal pain is a usual finding in CC and LC, and weight loss of up to 5 kg is common during the initial course of the disease. 25% of patients report 10 or more daily stools, but mucus or blood in the stools is unusual. LC is clinically indistinguishable from CC, though, in general, the symptoms of LC is milder and more likely to disappear than those of CC. In 40% of the patients the onset is sudden. In most cases, the clinical course is chronic relapsing and benign. Spontaneous remission seems to occur more often in LC than in CC. Autoimmune disorders such as rheumatic disease, coeliac disease, thyroid disease, and diabetes are often reported in patients with MC. Serious complications are uncommon, though there have been reports of patients with colonic perforation. Perforation seems to be related to ‘mucosal tears’ that can be seen at colonoscopy. The risk for colorectal cancer in MC is the same as in the general population.
Health-related quality of life in microscopic colitis: How to define disease activity

Henrik Hjortswang, M.D., Ph.D.
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The fact that microscopic colitis (MC) has a normal or almost normal macroscopic colonic mucosa, and that severe disease-related complications are rare, could make the disease appear harmless and there may be a risk of underestimating disease impact on health-related quality of life. Although the number of studies is still limited the results clearly show that the symptoms of MC can be very disabling and seriously affect the quality of life.

In a population based survey on 116 patients with collagenous colitis (CC) the health-related quality of life (HRQL) in patients with active disease was significantly impaired both compared with CC patients in remission and an age- and gender-matched background population (1). Patients in remission on the other hand scored a HRQL similar to that of a background population. Patients with an on going relapse had considerable impairment in daily activities, increased disease-related worry and lower general well-being. The functional impairment was in social and emotional areas and to a much lesser degree in physical function. Patients were mainly worried about having an ostomy appliance, to loose bowel control, the uncertain nature of the disease, effect of medication, and the energy level.

In two longitudinal intervention trials with budesonide as induction (2, 3) and maintenance treatment (3) patients with relapsing CC experienced an improved HRQL after responding to oral budesonide therapy (2,3), and then maintained unchanged during maintenance therapy (3). Thus effective treatment is available to induce and maintain remission and if this is obtained patients HRQL can be restored.

The main objective of treatment in MC is therefore to obtain symptom relief and thereby alleviate the effects on patients’ HRQL. At which level of symptom burden is then clinical remission achieved? A definition of clinical remission has been proposed based on the results of a natural "break-point" between high and low impact of bowel symptoms on HRQL in patients with CC (4). In the above mentioned survey on CC patients the stool frequency and consistency gave a clear cut-off to define clinical remission. CC patients with a mean of < 3 stools per day and a mean of < 1 watery stool/day during a one week symptom registration, were defined as being in remission since they had no or only mild impact on their HRQL. In contrast CC patients with either ≥ 3 stools/day or ≥ 1 watery stool/day had a significant impact on their HRQL and was thus defined as having active disease (table 1). Further validation of this definition of disease activity in CC is needed, preferably in a prospective study where change in stool frequency or consistency over the defined "break-point" should result in a similar significant change in HRQL.
Table 1: Definition of clinical disease activity in collagenous colitis

<table>
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<tr>
<th>Clinical remission</th>
<th>Stools per day†</th>
<th>Loose stools per day†</th>
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<td>Clinical activity</td>
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†mean during a one week symptom registration

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IBS and microscopic colitis: How to differentiate?

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Irritable bowel syndrome (IBS) is one of the commonest gastrointestinal disorders with an incidence/100,000 of the population/year of 580 females and 190 males\(^1\). Around 25% of IBS are of the diarrhoea subtype. By comparison microscopic colitis (MC) is seen in 11 females and 6 males/100,000/year\(^2\) thus most cases of diarrhoea will be diarrhoea-predominant IBS and not MC. Colonoscopy in patients with IBS symptoms yields a diagnosis of MC in just 1.5%\(^3\) so it would be of great value to be able to distinguish the two conditions. Both share a number of features including female predominance, diarrhoea and abdominal discomfort as well as fatigue and both can begin suddenly. The Rome criteria are not much help in the differential since around half meet Rome I criteria. However the age distribution is very different with MC steadily increasing from the age of 40 while IBS peaks in the mid-20s and declines thereafter. Other useful pointers to a diagnosis of MC include nocturnal diarrhoea and weight loss which is seen in nearly half the cases of MC\(^4\) but very few of IBS patients. The association with autoimmune disease in 35% of MC is probably not much help as it is neither sensitive nor specific and IBS patients often have multiple somatic symptoms which often lead to excessive investigation and over diagnosis of mild versions of autoimmunity. A useful clue to IBS is the marked variability in symptoms with bouts of symptoms lasting a few days interspersed with days with normal bowel function, something not seen in MC. Both conditions can begin with an apparent infectious disease, a feature in 25–43% of MC and around 18% of IBS. Serial biopsies after Campylobacter enteritis show a rise and subsequent fall in markers of immune activation with persistence of increased T lymphocytes and enterochromaffin cells in those who develop postinfectious IBS (PI-IBS)\(^5\). The lymphocytosis is of a lesser degree than that diagnostic of MC and the patients do not respond to prednisolone\(^6\). Other series of unselected IBS report overlap in inflammatory changes with those seen in MC though most of the difference from controls is mainly in mast cell hyperplasia\(^7\) which has been reported in many series of IBS patients. Animal studies suggest mast cell hyperplasia can be driven by stress and in IBS patients mast cell numbers do correlate with psychological factors\(^8\). Recently links have been made between IBS symptoms and gut permeability and mediators from IBS mucosal biopsies have been shown to impair epithelial barrier function\(^9\). Many patients with MC report that stress aggravates their diarrhoea and colonic mucosal permeability has been shown to be increased in MC\(^10\). These similarities in underlying pathophysiology argue that physicians treating MC should be aware that treatments aimed at IBS may be helpful in MC.

Reference List:


**Pathology: Histological criteria**

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Microscopic colitis (MC) is recognized to be a common cause of chronic, non-bloody diarrhea with rising incidence in the last decade. The diagnosis can only be made by histology and the specific histological findings define the subtypes of MC, lymphocytic (LC) or collagenous colitis (CC).

In MC, the lamina propria shows increased numbers of plasma cells and lymphocytes with loss of the normal gradient, even eosinophilic and neutrophilic granulocytes may be present. But these histological features do not warrant the diagnosis of MC even though they may be responsible for the clinical symptoms.

The key histological feature of LC is an increased number of surface intraepithelial lymphocytes (IEL). Usually > 20 IELs/100 epithelial cells are requested to warrant the diagnosis of LC. IELs are mostly cytotoxic CD8+ T-lymphocytes.

The key histological criterion for CC is a continuous subepithelial fibrous band underneath the surface epithelium (> 10 µm). Other hallmarks of CC are chronic mucosal inflammation, the collagen band contains entrapped capillaries, red blood cells and inflammatory cells. Damaged epithelial cells appear flattened, mucin depleted and irregularly oriented. Focally, small strips of surface epithelium may lift off from their basement membrane.

The term MC not otherwise specified (MCnos) was suggested for a subgroup of patients with diarrhea and an increase in cellular infiltrate in the colonic lamina propria and either an abnormal collagenous layer and/or intraepithelial lymphocytes coming short of fulfilling the criteria for CC and LC.

The histological features of MC and their differential diagnoses will be discussed in this talk.
MCi – A broader and clinically relevant perspective

L.K. Munck
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Microscopic colitis (MC) is a leading cause of chronic non-bloody diarrhea. The diagnosis MC rests on strict, albeit arbitrary histopathological findings in colonic biopsies taken from normal or oedematous mucosa oral to the rectum. The clinical symptoms associated with MC subgroups, lymphocytic colitis (LC) and collagenous colitis (CC) are indistinguishable.

Recent results indicate that the present diagnostic criteria may not ensure that all patients with MC are identified and offered treatment. Histological findings in the individual patient are inconsistent over time, as findings of MC interchange with chronic inflammation or incomplete signs of MC (MCi) at prior or repeat endoscopy, and the overlap between CC and LC is significant. Even more important, a large group of patients with chronic diarrhea, clinical symptoms and findings indistinguishable from those with CC and LC, but with MCi appear to have an effect of budesonide treatment similar to that of patients with MC. Furthermore, there is no correlation between symptoms and neither the thickness of the subepithelial collagenous layer nor the number of IEL.

The histological interchange between MC subtypes and the incomplete identification of all patients has lead to the introduction of the term MCi as a third MC subgroup. Patients with MCi display a wider variety of gastrointestinal symptoms and a higher incidence of bile acid malabsorption and lactose malabsorption than cases with MC. The diagnosis MCi rests on the finding of an increase in cellular infiltrate in the lamina propria with minimal distortion of crypt architecture and either an abnormally thickened collagenous band < 10 μm, or an abnormal number of intraepithelial lymphocytes < 20 per 100 epithelial cells. This group of patients have previously been denoted MC nos and paucicellular lymphocytic colitis.

Controlled trials of interventions to induce remission in patients with MC are few and largely concerned with budesonide. Progress has been hampered by restricting each trial to one subtype only. Budesonide has proven consistently effective, although a single definition of remission has yet to be agreed on and validated. Nevertheless, uncontrolled data confirm that budesonide is equally effective regardless of coexisting bile acid diarrhea in all three subtypes, including MCi. Prospective therapeutic trials of patients with MCi should be initiated.
Session II

Pathogenesis
What do we know about pathogenesis and pathophysiology in MC?

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The aetiology of microscopic colitis (MC) is unknown but considered to be multifactorial as many potential mechanisms have been proposed to explain the pathogenesis in MC. As in intestinal inflammation in general, it is believed that noxious luminal agents trigger an uncontrolled immunologic response in genetically predisposed individuals. This is best demonstrated by faecal stream diversion via an ileostomy, leading to clinical and histopathological remission. When rearranging the intestinal continuity, clinical symptoms and the classical histological findings reoccur. The current knowledge on the pathophysiology of MC is limited and mainly based on small observational studies. In-vitro experiments on colonic biopsies from patients with collagenous colitis (CC) revealed a significant mucosal barrier dysfunction in clinical remission, which was aggravated in active disease presenting with increased transmucosal uptake of non-pathogenic bacteria. An experimental study described the diarrhoeal mechanism in CC as being a reduced Na\(^+\) and Cl\(^-\) absorption accompanied by a secretory component of active chloride secretion. The clinical observation that fasting can reduce diarrhoea indicates an osmotic component. Bile acid malabsorption can coexist with MC, leading to more frequent bowel movements. Multiple, mainly small experimental studies have focused on diverse mucosal and faecal factors or mediators of intestinal inflammation in MC and it is unclear which factors may be of pathophysiological importance or are just an epiphenomena. CC demonstrates for example a Th1 mucosal cytokine profile with interferon gamma (IFN-\(\gamma\)) as the predominantly upregulated cytokine and increased mucosal mRNA levels of interleukin (IL) 15 and tumour necrosis factor alpha (TNF-\(\alpha\)). Increased expression of iNOS correlates with luminal nitric oxide (NO) concentrations and clinical activity. In patients with CC, anal-rectal function seems normal and no signs of visceral hypersensitivity were shown.
The mucosal immune system in microscopic colitis

Elisabeth Hultgren Hörnquist
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The intestinal immune system protects us from invading pathogens but simultaneously allows the presence of commensal bacteria in the gut and uptake of food antigens. The immune system comprises innate and adaptive immune responses, being markedly intertwined, the latter comprising e.g. B lymphocytes, plasma cells, CD8\(^+\) cytotoxic T lymphocytes (CTL) and a growing number of CD4\(^+\) T helper (TH) cell subsets.

It is currently well established that dysregulation of the intestinal immune system may result in IBD. Microscopic colitis (MC) is a more recently described chronic intestinal inflammation, including collagenous colitis (CC) and lymphocytic colitis (LC), with an incidence roughly the same as for ulcerative colitis. Although MC is clinically well characterized, knowledge about the pathophysiological mechanisms is limited. Both LC and CC have increased densities of lymphocytes in the epithelium (intraepithelial lymphocytes – IELs) and lamina propria (lamina propria lymphocytes – LPLs), but very little is known about the nature of these T cells. A TH1 cytokine profile has previously been reported in both LC and CC, with increased IFN-\(\gamma\), TNF-\(\alpha\) and IL-15.

Our immunologic studies aim at elucidating the role of a dysregulated adaptive immune response in the intestinal mucosa in LC and CC. It is still unknown whether CC and LC are two different diseases with different pathogenesis and pathophysiology, or different variants and/or stages of the same disease. For this purpose we have collected biopsies from CC and LC patients. All immune changes were related to the immune status in colonic biopsies from healthy controls. In addition, UC patients were included in our study, being previously immunologically well characterized, to help to value the changes observed in MC. Immunohistochemistry was performed on paraffin-embedded biopsies, whereas expression of genes involved in T cell differentiation was determined by real time qRT-PCR on frozen biopsies. In addition, freshly isolated LPLs and IELs were characterized by flow cytometry.

Our data demonstrate increased frequencies of CD8\(^+\) T cells in both the epithelium and lamina propria of both LC and CC patients, whereas the frequencies of CD4\(^+\) T cells were decreased. The proportions of active/memory and proliferating T cells were increased in both CC and LC patients, and the vast majority of the LPLs as well as IELs expressed the conventional \(\alpha\beta\)TcR.

The mRNA levels for both IFN-\(\gamma\) and IL-12 were higher in both CC and LC patients compared to UC patients. In contrast, although both IL-6, IL-17 and IL-21 expression was markedly up regulated in CC and LC, it was still lower than in UC. Whereas IL-22 expression was significantly up regulated in all three diseases, the expression was much higher in CC and UC patients. Transcription factors for T cell differentiation was either unaltered or only slightly upregulated, whereas the chemokine CCL20 was markedly increased in UC patients, but not in the MC group. Thus, in the light of the increased frequencies of CD8\(^+\) T cells, the expression profile demonstrates a mixed TH1/TH17/CTL response with differences between LC and CC.
Faecal markers in microscopic colitis

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In microscopic colitis (MC) assessment of disease is relying on clinical presentation and subsequent endoscopy with biopsies for histological evaluation. No serologic surrogate marker of disease/inflammation exists. There have been several attempts to identify a faecal biomarker of inflammation in MC both to explore pathophysiology and to aid in the prediagnostic screening and subsequent monitoring of MC in a non-invasive manner. Faecal markers evaluated in MC include a heterogeneous group of substances/proteins that either leak from or are generated by the inflamed mucosa in the gut. Proteins studied include lactoferrin as indicator of neutrophilic activation, myeloperoxidase (MPO) and calprotectin as indicators of both neutrophilic and macrophage activation and eosinophil cationic protein (ECP) and eosinophil protein X (EPX) as indicators of eosinophilic activity. Likewise, studies of tryptase, occult blood, cytokines including TNF-α, have been performed.

ECP, EPX, MPO and calprotectin have been found to be significantly increased in faecal samples in patients with active MC compared to healthy controls and MC patients in remission. This indicates that activation of both eosinophilic and neutrophilic leucocytes and/or macrophages and the subsequent faecal excretion of ECP, EPX, MPO and calprotectin play an essential role in pathophysiology in patients with MC. Despite of this finding up to 33% of MC patients with active disease have normal samples and excretion of inflammatory markers in faecal samples are not a general characteristic, probably reflecting differences in degree of inflammation. However, either disease activity evaluated by bowel frequency, stool consistency or histopathological grade of mucosal inflammation seems to correlate with the concentrations of the faecal markers excreted. The most promising marker of inflammation is faecal ECP, however the number of patients examined is small and so far, only data from a pilot study exist.

The role of a faecal marker of inflammation both as a guide in the prediagnostic screening of patients with potential MC and as a surrogate marker of disease activity/monitoring in patients with known MC remains to be established.
Smoking in microscopic colitis

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Smoking is a well-known risk factor for many diseases. It has a complex association with classic inflammatory bowel diseases (1). In Crohn’s disease smoking leads to a negative effect with a higher risk of inflammation and a deeper inflammation. In patients with ulcerative colitis smoking has a different roll since it is well known that smoke stop could trigger a relapse.

During many years the impact of smoking in microscopic colitis (MC) has been unknown but occasional case reports have indicated that there are many smokers among the patients (2–4). One study by Chan et al. revealed that although MC patients do not have an increased risk of colorectal cancer instead there was a significantly increased relative risk of lung cancer in women with collagenous colitis (CC) (5). Based on the established relationship between smoking and lung cancer this finding indicates that CC patients might be smokers to a higher extent than the average population.

During the last year tree studies about smoking habits in MC patients have been published. The first one was a multicentre study from Sweden that showed that smoking is a risk factor for CC and that smokers developed the disease earlier than non-smokers (median 14 years earlier, p < 0.003) (6). Later the same year Yen et al could confirm that smoking is a risk factor for CC and also showed that smoking influences the risk for disease onset equally for men and women. Furthermore, smoking also contributed to an increased risk for lymphocytic colitis (LC) (7). In an abstract from Spain presented at UEGW in Stockholm 2011 it was confirmed that smokers tend to develop MC a decade earlier than non-smokers, but they did not observe any differences between clinical presentation and clinical remission between smokers and non-smokers (8).

Conclusion: Smoking is a risk factor for developing MC of both forms (CC as well as LC). Smokers develop their disease more than a decade earlier than non-smokers.

References:


Genetics in MC

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The etiology and pathogenesis of microscopic colitis is unknown. Whether genetic predisposition is of importance, as in many other gastrointestinal diseases, is unclear and the knowledge about the genetic background is sparse. There are case reports of an accumulation of MC in families (Abdo et al.; Jarnerot et al. 2001). A Swedish study identified a familial occurrence of microscopic colitis in five families. In all these families a sister-sister relationship was found. Two sisters with collagenous colitis had been living apart in different Nordic countries for many years before developing the disease. In one pair, the smoking sister had collagenous colitis and the never smoking sister had lymphocytic colitis. These findings clearly indicate that a genetic predisposition may be present in microscopic colitis. The prevalence of autoimmune disorders is increased in patients with microscopic colitis, and continued efforts have been made to associate both types of colitis with various autoimmune HLA haplotypes. Different small studies found an HLA association that could point to a genetic predisposition towards MC. An increased prevalence of HLA-A1 and a decreased prevalence of HLA-A3 in lymphocytic colitis have been reported, but no such an association was found in collagenous colitis (Giardiello et al. 1992). The association of microscopic colitis to HLA-DQ haplotypes similar to those found in celiac sprue have been reported (Fine et al. 2000), but in a Spanish study, the association with HLA-DQ2 genes was observed only in lymphocytic colitis (Fernandez-Banares et al. 2005). Different gene polymorphism in patients with microscopic colitis underlines a possible genetic background. The IL-6-174 gene polymorphism has a possible association with MC, as the IL-6 GG genotype was more frequent in patients with the disease (Koskela et al. 2011). The same group showed both CC and LC associated with the HLA-DR3-DQ2 haplotype and with TNF2 allele carriage (Koskela et al. 2008). A study of our group could show an allelic variation of the matrix metalloproteinase-9 gene associated with collagenous colitis. In contrast to Crohn’s disease, functional polymorphism in the NOD2/CARD15 gene has not been detected.

References:


Session III

Treatment strategies
Drugs and risk of microscopic colitis

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Drug consumption has been suggested to act as an environmental risk factor implicated as causative or triggering agent of MC. Multiple drugs have been mentioned. For some of them causality is considered to be certain, for other only probable or possibly. Criteria to define certainty (high likelihood of causality) is based on a compatible timing of the start of diarrhoea relative to drug exposure, improvement of the symptoms after stopping the medication (dechallenge), and recurrence of the symptoms on repeat exposure (rechallenge). Case-controls studies have shown the association of drug usage with MC, mainly for aspirin, NSAIDS, lansoprazole, omeprazole, and sertraline consumption. However, in these cases, a cause-effect relationship cannot be established.

Drugs and their metabolites may affect the colon directly through their pharmacological actions or through idiosyncratic direct hypersensitivity reactions by the colonic mucosa. Drugs also can act indirectly on the colon by altering colonisation by gastrointestinal organisms. The rarity of an association between a drug and MC favours the existence of an idiosyncratic hypersensitivity reaction, i.e., it does not occur in most patients at any readily achieved dose of the drug and does not involve the known pharmacologic effects of the drug.

Most of the drugs suggested to be associated with MC are also well known to be associated with the development of chronic diarrhoea as an adverse event. Per example, in a study on diarrhoea and drug use in the elderly use of proton pump inhibitors, NSAIDs, and selective serotonin reuptake inhibitors were associated with the risk of developing diarrhoea. In a study on MC, use of some drugs presumptively associated with MC did not show significant differences as compared to a chronic diarrhoea group. Therefore, considering as certain the association of a drug with MC should imply the improving or disappearing of the histological damage after dechallenge, and recurrence after rechallenge, and not only the effect on the diarrhoea symptom. However, rechallenge followed by clinical and histological relapse has been scarcely reported.

Further studies on the impact of medication discontinuation on clinical symptoms and colonic histology will help advance the understanding of which is the true link between the drugs and the disease.
Medical treatment of microscopic colitis (MC) should take into account the severity of symptoms, their impact on the patient’s quality of life, and the availability of outcome data from randomized controlled trials. The primary aim of medical therapy in MC is to achieve and maintain clinical remission and improve the patient’s quality of life. Budesonide is currently the only drug which fulfills evidenced-based criteria for effectiveness in the treatment of collagenous and lymphocytic colitis. Five randomized controlled trials (RCTs) have demonstrated that budesonide 9 mg/day is highly effective as short-term treatment in collagenous and lymphocytic colitis. However, many patients may suffer from symptom relapse after withdrawal of budesonide. Meanwhile, two RCTs have shown that budesonide 6 mg/day is effective in maintaining clinical remission in collagenous colitis for at least 6 months. The effectiveness of budesonide in collagenous and lymphocytic colitis has also been confirmed by several metaanalyses. Other drugs such as loperamide, mesalazine, bismuth subsalicylate or colestyramine have been proposed for the treatment of MC, however, these drugs have never been formally tested in adequate RCTs. Short-term prednisolone, the probiotic AB-Cap-10 and Boswellia serrata extract failed to show a clear benefit over placebo in RCTs.

Based on the currently available evidence, the European Microscopic Colitis Club (EMCC) is proposing a novel treatment algorithm for microscopic colitis. Patients with active MC should be primarily treated with short-term budesonide. Alternatives drugs may be considered in patients with only mild symptoms, however, this recommendation is not evidenced-based. If relapse occurs after budesonide withdrawal, budesonide can be used again either as intermittent or as low-dose continuous therapy. In patients who do not respond to budesonide, alternative drugs such as loperamid, colestyramine, aminosalicylates or bismuth may be considered, even in combination, if symptoms are mild. Non-responders to budesonide with severe symptoms may be candidates for immunosuppressives or biologics.
What comes beyond budesonide?

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Microscopic colitis (MC) can in most cases be treated effectively with budesonide. However, some patients develop side effects, are dependent or have chronic symptoms refractory to budesonide. These patients have often a poor quality of life, are socially handicapped and need extensive medical attention. A novel definition of non-response, dependency and intolerance in MC patients treated with budesonide is proposed which might be helpful when considering immunomodulatory therapy (table 1).

The experience with immunomodulators in MC is mainly anecdotal. Azathioprine (AZA) or 6-mercaptopurine (6-MP) have been tested in a small group of patients (N = 9) with steroid dependent or refractory collagenous colitis (CC). A response rate of 89% and a steroid sparing effect was found. In a retrospective report, beneficial effects of oral low-dose methotrexate (5–25 mg) were observed but most of these patients had not been exposed to budesonide previously. A small study with CC patients intolerant or refractory to budesonide showed no clinical effect to methotrexate (15–25 mg s.c.).

To date, two independent case reports (total N = 7) have demonstrated positive effects of anti-TNF therapy in patients with severe CC. This option may be tested as a third line treatment or “rescue therapy” to avoid surgery in selected patients. Further studies are needed to confirm long-term efficacy and to further examine safety issues.

In extremely rare cases, the final solution is colectomy with ileostomy or pouch.

Table 1: Definition of non-response, dependency and intolerance in MC patients treated with budesonide

<table>
<thead>
<tr>
<th>Budesonide-dependent:</th>
<th>Demand of at least 6 mg maintenance treatment to stay in clinical remission.*</th>
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| Budesonide non-response: | A. Induction therapy: Non-responsiveness to 9 mg budesonide for at least 6 weeks.  
B. Maintenance therapy: Clinical activity* despite 6 mg budesonide. |
| Budesonide-intolerant: | Unacceptable side effects to budesonide irrespective of dose. |

*Hjortswang criteria for clinical activity in MC

Remission: < 3 stools/day and < 1 watery stools/day #
Clinical activity: ≥ 3 stools/day or ≥1 watery stools/day #
# mean during a 1-week symptom registration
Microscopic colitis: The American perspective

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Many important features of microscopic colitis have been covered in other parts of this workshop. For my presentation, I have chosen to focus on issues that are clinically relevant that were not covered in other parts of the workshop, focusing on data from North America.

The first issue to cover is the overlap between microscopic colitis and celiac disease. Up to 1/3 of patients with celiac disease have microscopic colitis-like changes on colon biopsies and in patients with microscopic colitis, 2–9% will have small bowel changes consistent with celiac disease. In patients with microscopic colitis, sprue serologies may be less sensitive than in the general population. In patients with microscopic colitis, celiac disease should be considered in patients with steatorrhea, otherwise unexplained iron deficiency anemia, or non-response to traditional colitis medication. In a study from Mayo, patients with celiac disease and microscopic colitis were older, more likely female, and had lower body weight than patients with celiac disease alone. In addition, they were more likely to have other disorders such as hyperthyroidism, infertility, and osteoporosis. In a study from Columbia University in New York, performed at a tertiary referral center known for the treatment of celiac disease, microscopic colitis was found in 4.3% of patients with celiac disease, which was many fold higher than expected. Similar to the study from Mayo, these patients were older and more likely to be women. This study also demonstrated that patients with overlap had more severe villous atrophy, and substantial proportion (16%) had only right-sided colitis. Therefore, in patients with celiac disease who are being investigated for microscopic colitis, a full colonoscopy with right- and left-sided biopsies should be performed. Of note, 2/3 of the overlap patients from Columbia required steroids and immunomodulator therapy.

The second issue that we will cover is the creation of a Microscopic Colitis Disease Activity Index. Currently, there are not validated instruments to assess disease activity and different reports have different definitions for response or remission. In addition, patients with microscopic colitis often have significant GI symptoms other than diarrhea which are not typically incorporated into definitions of response or remission. Therefore, we sought to identify which clinical features independently predict disease severity and combine them into an index with weighted scores. In this study of 151 patients, the number of unformed bowel movements in a day, abdominal pain, number of nocturnal bowel movements, and fecal incontinence all strongly correlated with the physician global assessment of activity. When combined into a weighted formula, these symptoms can be used to objectively and consistently score disease severity. Future studies will validate the MCDAI on independent samples, define MCDAI thresholds for response and remission, and correlate MCDAI with histologic activity.

We will also briefly review an update in epidemiology. Several studies from Europe have indicated an incidence of collagenous colitis and microscopic colitis of approximately 5 per 100,000 persons. Some of these studies also showed an increase in
incidence over time. A population-based study from Olmsted County, MN showed similar findings. The overall incidence of collagenous colitis was 3.1 per 100,000 and lymphocytic colitis was 5.5 per 100,000, but with a significant increase in the incidence over time, from approximately 1 per 100,000 in the late 1980s to almost 20 per 100,000 by 2000. This information has recently been updated to 2010 showing that the incidence of both lymphocytic and collagenous colitis have stabilized with no further increase over this latter time period.

Finally, we will focus on issues related to treatment that are not covered elsewhere in this workshop. One treatment that is occasionally used in the United States for mild to moderate microscopic colitis is bismuth subsalicylate. This is based on some old data from an open-label study showing a response rate of 92% to a dose of 8 tablets per day for 8 weeks. In this report, the mean time to response was two weeks and 75% of patients were able to maintain remission after stopping medication, some for longer than two years. This study showed improvement in stool weight, frequency, and consistency, as well as histology. This study was followed by a small randomized controlled trial of bismuth 9 tablets per day for eight weeks versus placebo. Unfortunately, this study has only been reported in abstract form with limited data. The response was 100% in patients given bismuth versus 0% with placebo. There were corresponding improvements in stool frequency, stool weight, and histology. Twenty-five percent of patients relapsed after discontinuation of medication and all were successfully retreated. The placebo patients were given open-label bismuth and 5 out of 6 improved.

The data on the efficacy of mesalamine for microscopic colitis is mixed. There was a randomized controlled trial of 64 patients using 2.4 grams per day of mesalamine with or without cholestyramine. This study showed remission in 85% of patients with lymphocytic colitis whether or not they were taking cholestyramine, as well as 73% of patients with collagenous colitis without cholestyramine and 100% with cholestyramine. This study, as well as an open-label study of mesalamine, suggested that this treatment may be a reasonable option for patients with microscopic colitis. However, three large open-label series of patients with microscopic colitis from the US and Europe showed disappointing results with mesalamine-type products. Therefore, the exact role of mesalamine in the treatment of microscopic colitis remains unclear.

The response to budesonide is covered elsewhere in this workshop, but we will review data from Mayo on the natural history of steroid treated microscopic colitis. In this population-based study, 25% of patients with microscopic colitis were treated with either budesonide or prednisone. The overall remission rate to steroids was 76% with an additional 20% showing response and only 4% not responding at all. Unfortunately, the recurrence rate was 70% when steroids were discontinued. Interestingly, the remission rate was better with budesonide than prednisone (83% versus 53%, p = 0.02) as was the risk of relapse (hazard ratio 0.38, 95% CI 0.18–0.85) and the time to relapse (63.5 days versus 21.0 days).

Finally, we will discuss potential treatment options for patients who do not tolerate or do not respond to long-term treatment with budesonide. A older study from Mayo reviewed 9 patients with steroid dependent or steroid refractory microscopic colitis and showed a good response in 8 out of 9 patients. This includes one patient who
was steroid refractory who responded to azathioprine. A study of low-dose oral methotrexate (median dose 7.5–10 mg weekly) showed complete response in 74% of patients and partial response in another 11%.

In summary, my approach to the treatment of microscopic colitis is first to try to rule out any evidence for drug-induced microscopic colitis including NSAIDs. For patients with mild symptoms, perhaps antidiarrheal therapy would be effective. However, patients referred to gastroenterology typically have failed this approach. If a patient has moderate symptoms, I will try bismuth subsalicylate 3 pills t.i.d. for six to eight weeks. If that is unsuccessful or if the patient has severe diarrhea, I will treat with controlled ileal release budesonide, 9 mg per day for six weeks typically tapered down to 6 mg per day for a week, and 3 mg per day for another two weeks before stopping. If patients have prolonged response they are followed for recurrence. If they have a recurrence, I will often put them back on low-dose budesonide (beginning at 6 mg per day and tapering down to 3 mg per day or even 3 mg every other day if possible). For patient who do not respond to budesonide or do not tolerate it, I will consider cholestyramine, aminosalicylates, or immunosuppressive therapy. For severe refractory cases, treatment with anti-TNF biologics or surgery has been described but this is quite rare.
Summary and future aspects

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Epidemiology: Data from the recent 25 years have disclosed an increased numbers of diagnosed cases of microscopic colitis. The overall incidence of MC is now reported to 12–19/100,000 per year. An increased awareness and increased diagnostic activity among clinicians and pathologist are the most likely reasons for the observed rise in the number of diagnosed patients. MC is more frequent diagnosed in women than in men and is mainly diagnosed in the age of the fifties and sixties. The reason for this difference in gender and age is unclear but suggests a hormonal- or immune-mediated disease.

Etiology: The cause of microscopic colitis is unknown. Diversion studies have indicated that a luminal factor plays a key role in the development collagenous colitis. The suspected agents include dietary antigens, drugs, bile salts, and bacterial products and toxins. However, the nature of this noxious stimulus is not settled and the role of these factors has to be clarified. Studies indicate a role of genetic predisposition and risk factors as smoking. An autoimmune mechanism has been proposed, however the usual associations to auto-antibodies are lacking.

Symptoms: Clinically, microscopic colitis is characterised by watery diarrhoea often combined with urgency and sometimes faecal incontinence. Other abdominal symptoms such as weight loss and abdominal pain are often recognised; however these symptoms are mild and transient. Severe general symptoms are not seen and the disease runs a benign course. Based on symptoms it is not possible to distinguish between collagenous colitis and lymphocytic colitis. Follow-up studies have confirmed that the disease runs a chronic course, with relapsing and remitting symptoms for years. Without effective treatment, continuous symptoms and severe reduction in quality of life must be expected.

Diagnosis: Collagenous colitis should be suspected in patients with chronic watery diarrhoea and normal mucosal appearance at endoscopy. Therefore, multiple biopsies are recommended in these cases. The histological changes can be absent in the rectum in about 50% of the patients with collagenous colitis and biopsies proximal to the sigmoid colon are recommended. The characteristic histological finding in microscopic colitis is intraepithelial lymphocytosis, but inflammatory infiltrate in the lamina propria and epithelial degeneration are also recognised as diagnostic findings. Collagenous colitis is also characterized thickened subepithelial layer in the colonic mucosa. The intra- and inter-diagnostic accuracy of the histological diagnosis seems good. Today lymphocytic and collagenous colitis are considered as separate histological entities with some overlap. However, recent data suggest other forms of microscopic colitis and the spectrum of microscopic colitis may be a continuum of overlapping diseases.

Treatment: Previously the treatment of microscopic colitis was based on the experience from other inflammatory bowel diseases and the results of retrospective analyses. Randomised, double-blind placebo-controlled studies have proved the
effect of oral budesonide treatment on the clinical symptoms and histological changes of collagenous colitis. The treatment has also been demonstrated effective in lymphocytic colitis. Budesonide treatment significantly improves quality of life in patients with microscopic colitis. Therefore, oral budesonide can be considered as standard therapy of microscopic colitis. However, the risk of relapse after discontinuing budesonide treatment is well documented. The risk of long-term treatment with budesonide in this group of patients has to be elucidated. Some patients do not respond to standard treatment and some patients are intolerant to budesonide. Future studies have to demonstrate an alternative treatment option for these patients.

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Microscopic Colitis – Creating Awareness for an Underestimated Disease

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Abstracts

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