Gastroenterology in Copenhagen

Falk Lunchtime Symposium: Microscopic colitis – an emerging IBD?

on the occasion of the 9th Congress of ECCO (European Crohn’s and Colitis Organisation) 2014

Scientific organizers and speakers

Prof. Dr. J.-F. Colombel, Mount Sinai School of Medicine, New York (USA)

Prof. Dr. C. Tysk, Örebro University Hospital (Sweden)

Dr. M.J. Pierik, Maastricht University Hospital (The Netherlands)

Prof. Dr. S. Miehlke, Center for Digestive & Inflammatory Diseases Internal Medicine Center Eppendorf Hamburg (Germany)
Falk Symposium 199 (Part I)
Highlights from Hepatology 2015: From Chronic Hepatitis to Hepatocellular Carcinoma
October 14 – 15, 2015

Falk Symposium 200 (Part II)
Therapeutic Strategies in Diseases of the Digestive Tract – 2015 and Beyond
October 16 – 17, 2015

VIII Falk Gastro-Conference
Freiburg, Germany
October 14 – 17, 2015

Falk Workshop
Viral Hepatitis – From Bench to Bedside
Munich, Germany
January 29 – 30, 2015

Falk Symposium 196
Critical Evaluation of Current Concepts and Moving to New Horizons in the Management of IBD
Frankfurt, Germany
March 6 – 7, 2015

Falk Symposium 197
Autoimmune Diseases of the Liver
Lisbon, Portugal
May 8 – 9, 2015

Falk Symposium 198
IBD: East Meets West
Shenzhen, P. R. China
September 11 – 12, 2015

Falk Workshop
Workshop on Gastrointestinal GVHD
Regensburg, Germany
November 13 – 14, 2015
Microscopic colitis: The chronic diarrheal disease remains a puzzle

Microscopic colitis, with its principal forms of collagenous and lymphocytic colitis, is an inflammatory bowel disease (IBD) that significantly impairs the quality of life of those affected. Its significance is demonstrated by the finding in recent epidemiological studies that its incidence and prevalence are roughly comparable to those of the IBD Crohn’s disease and ulcerative colitis.

Even so, the importance of microscopic colitis continues to be underestimated in everyday clinical practice, emphasized Prof. Dr. J.-F. Colombel, New York (USA) and Prof. Dr. C. Tysk, Örebro (Sweden), scientific organizers of the Falk Lunchtime Symposium that took place on the occasion of the conference of the European Crohn’s and Colitis Organisation (ECCO) 2014 in Copenhagen. The chairmen went on to say that there are still considerable gaps in our knowledge of the etiology and pathophysiology of this chronic bowel disease. During the symposium, proven experts in this field discussed the current state of scientific knowledge, the therapeutic options available, and unresolved problems.

Collagenous colitis was first described as a disease in its own right in 1976. However, diagnosis remains a challenge to this day, since in most cases the intestinal mucosa is endoscopically normal, Prof. Dr. S. Miehlke, Hamburg (Germany), emphasized. This means that an exact diagnosis is only possible on the basis of biopsies: histological subtyping is used to identify the collagenous, lymphocytic and incomplete forms of microscopic colitis. The latter form, which was only described relatively recently, exhibits similar clinical symptoms to the other two forms, but histologically, shows less pronounced changes.

Since many patients are not investigated appropriately, they may also not be diagnosed and given adequate treatment. Microscopic colitis should always be considered in patients with chronic diarrhea.

Association with drugs and autoimmune disease

A key factor in the genesis of microscopic colitis is the induction of inflammation in the lamina propria, Dr. M.J. Pierik, Maastricht (The Netherlands) explained. However, we still do not know the precise mechanism of origin and progression of this disease. Infections and genetic disposition may be involved.

The association between the intake of various drugs and microscopic colitis is particularly striking. It is also remarkable that over 40% of patients have autoimmune diseases such as celiac disease or thyroiditis and that microscopic colitis is more prevalent in females.

Similarties and differences with other IBD

Microscopic colitis as a chronic diarrhea condition exhibits some features that are similar to the other inflammatory bowel diseases but also some that differ, said Prof. Dr. J.-F. Colombel. For example, microscopic colitis, unlike the other IBD, occurs mostly in older people. Its natural progression is relatively benign and it can be treated effectively. Surgical procedures are seldom necessary and mortality is not increased.

Crohn’s disease and ulcerative colitis, on the other hand, are characterized by a wider spectrum of symptoms and complications that predominantly occur at a younger age and often require surgery. Other differences from microscopic colitis relate to extraintestinal manifestations as well as the increased risk of colon cancer, which is not present in microscopic colitis.

When should microscopic colitis be considered?

- Intermittent or persistent, also nocturnal watery diarrhea for several weeks (stool frequency ≥ 3/day)
- Commonly over 50 years of age
- Predominantly women
- Accompanying abdominal pain
- Fecal incontinence complaints
- Smokers
- Concurrent medication (PPI (lansoprazole), SSRI (sertraline), NSAIDs, acarbose, ranitidine and ticlopidine)
- Concurrent autoimmune diseases (rheumatism, thyroid disease, diabetes, celiac disease)

Further diagnostic investigation with colonoscopy and biopsies in the complete colon for histopathological assessment are required to make a diagnosis or to exclude microscopic colitis.
For a long time, microscopic colitis was thought of as a rare disease. However, epidemiological studies show that there has been a considerable increase in incidence rates around the world. In one population-based Canadian study the incidence of microscopic colitis increased from 16.9 per 100,000 inhabitants in 2004 to 26.2 per 100,000 inhabitants in 2008 (Stewart M, et al., Aliment Pharmacol Ther. 2011). However, there are regional differences which remain unexplained. It is also unclear whether the increase in the incidence rate is also due to improved diagnosis.

Microscopic colitis is characterized by chronic, watery, non-bloody diarrhea, Prof. Dr. S. Miehlke, Hamburg (Germany) explained. The quality of life of those affected is also frequently subject to considerable impairment due to nocturnal diarrhea, overwhelming urgency, fecal incontinence, abdominal pain, weight loss, and fatigue.

The forms of microscopic colitis exhibit lymphoplasma cell infiltration in the lamina propria. In collagenous colitis there is a striking subepithelial thickening of the collagen band > 10 μm. Lymphocytic colitis is diagnosed histologically where the intraepithelial lymphocyte count (IEL) is greater than 20 per 100 epithelial cells and the collagen band presents normally. In incomplete microscopic colitis the collagen band is only slightly thickened (5–10 μm) and/or the IEL count is only slightly elevated (> 5 IEL/100 epithelial cells) (Fig. 2).

As Prof. Miehlke went on to explain, effective short-term and long-term drug therapy is available in the form of oral budesonide, a topical glucocorticoid with high local activity but low systemic effect. So
far, this is the only drug that has been proven to be effective for collagenous colitis in randomized, placebo-controlled trials and which is approved for this indication.

Six to eight weeks of treatment for collagenous colitis with budesonide 9 mg daily (Budenofalk® 9mg gastro-resistant granules) achieved remission rates of over 80% (placebo 12–38%). Short-term treatment of patients with lymphocytic colitis over 6–8 weeks with budesonide 9 mg daily showed similarly high rates of remission. As Prof. Miehlke emphasized, the adverse event profile of short-term treatment with budesonide is at the level of placebo.

**Risk factors for recurrence**

However, recurrence is a problem in the treatment of collagenous colitis, occurring in up to 80% of patients. This suggests that a large number of patients require long-term treatment. Three trials lasting up to 12 months have shown that average daily doses of 4.5 mg/6 mg of budesonide enabled 75% of patients to maintain clinical remission.

Since then risk factors for recurrence following completion of successful treatment with budesonide have been identified, Prof. Miehlke said. In a multivariate post-hoc analysis of 4 controlled trials (Miehlke S, et al., Inflamm Bowel Dis. 2013), stool frequencies of more than 5 per day at baseline and the existence of diarrhea for more than 12 months were independent risk factors for recurrence. Early consideration should be given to maintenance of remission therapy for this patient group.

For patients who are non-responders, or intolerant to budesonide, the EMCG (European Microscopic Colitis Group) recommends biologics (adalimumab, infliximab) and the immunosuppressive drug azathioprine/6-mercaptopurine ([Fig. 3](#)).

However, according to Prof. Miehlke, the currently available data with respect to immunosuppressant drugs is very limited and also controversial, so that general usage cannot be recommended. Although there are only case reports for the biologics, these have shown positive effects in patients refractory to treatment. Ileostomy should only be considered for patients with severe treatment-refractory diarrhea. Prof. Miehlke concluded that effective short-term and long-term treatment for microscopic colitis exists for most patients, but alternatives to budesonide must be evaluated.
The pathophysiology of microscopic colitis has not yet been explained. Potential triggers currently being discussed are regulatory dysfunction in the immune system and intraluminal agents such as bile acid malabsorption and macrobiotics. There is also a strong association with certain drugs, smoking and a potential genetic disposition.

The notion that an autoimmune response may be implicated is supported by the observation that microscopic colitis is more prevalent in females and is associated in over 40% of patients with other autoimmune diseases such as thyroid diseases, rheumatoid arthritis, and celiac disease as co-morbidities (Fig. 4). Moreover, familial occurrence has been identified in 5 pairs of sisters in an epidemiological study, Dr. M.J. Pierik, Maastricht (The Netherlands), stressed.

Fig. 4 Diseases associated with collagenous colitis
Smoking and other risk factors

Various studies indicate that smoking is a risk factor for microscopic colitis. In one Swedish study, the prevalence of microscopic colitis was significantly higher, at 37%, in smokers than in the control population (17%). Microscopic colitis was also diagnosed 14 years earlier in smokers than in non-smokers (Vigren L, et al., Scand J Gastroenterol. 2011).

Numerous case control studies and cohort studies indicate an association between intake of various drugs and microscopic colitis. Non-steroidal anti-inflammatory drugs (NSAIDs) are particularly striking in this regard. As with smoking, the mechanism of action has not yet been explained in the drugs, Dr. Pierik emphasized.

Other cohort and case control studies and case reports found an association between microscopic colitis and the intake of proton pump inhibitors (PPI). This remains unexplained.
Microscopic colitis is normally characterized by chronic, non-bloody diarrhea that also occurs at night, fecal incontinence, mild weight loss, and abdominal pain. Diagnosis is complicated by the fact that these symptoms are initially misinterpreted as irritable bowel syndrome in many patients. Microscopic colitis also exhibits many similarities with the other inflammatory bowel diseases – ulcerative colitis and Crohn’s disease – but there are also certain differences.

In most cases, the onset of “classic” IBD is at an early age, with the same level of risk in males and females. By contrast, the female: male gender distribution in collagenous colitis is 4:1. The gender distribution in lymphocytic colitis is roughly equal, Prof. Dr. J.-F. Colombel, New York (USA) said. In microscopic colitis, disease onset, in contrast to the other IBD, is in most cases not until middle age, between 50 and 60. Severe complications do not normally present and it does not appear to be associated with an increased risk of colon cancer. In lymphocytic colitis, the symptoms are often milder and may be reversed.

Routine laboratory findings and colonoscopy are usually unremarkable diagnostically. There are no known serological

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**Microscopic colitis and IBD – similarities and differences**

<table>
<thead>
<tr>
<th>Microscopic colitis</th>
<th>Inflammatory bowel disease (IBD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In most cases over 50 years</td>
<td>Mostly young patients</td>
</tr>
<tr>
<td>Higher incidence in females</td>
<td>Male and female incidence equal</td>
</tr>
<tr>
<td>Diarrhea watery</td>
<td>Diarrhea broth-like, watery, bloody</td>
</tr>
<tr>
<td>Weight unchanged/reduced</td>
<td>Weight reduced in most cases</td>
</tr>
<tr>
<td>Normal endoscopic findings in most cases</td>
<td>Endoscopic evidence of inflammation</td>
</tr>
</tbody>
</table>

**Fig. 6** Differential diagnosis microscopic colitis – IBD
markers for microscopic colitis. Endoscopic findings for the large intestine are normal in 70% of cases. Thirty percent exhibit mild, patchy abnormalities such as erythema, edema, minor erosions, and, in rare cases, ulcerations, which are potentially associated with intake of NSAIDs. Histological findings from multiple biopsies from various sections of the colon – including unremarkable areas – are decisive for diagnosis. A diagnosis of whether this is lymphocytic, collagenous or incomplete microscopic colitis is then made on the basis of histological findings. In order to guide patients with microscopic colitis towards treatment as quickly as possible, it is important to differentiate diagnostically from irritable bowel syndrome (Fig. 7).

<table>
<thead>
<tr>
<th></th>
<th>Irritable bowel syndrome</th>
<th>Microscopic colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>First occurrence of disease</td>
<td>commonly younger than 50 years of age</td>
<td>commonly older than 50 years of age</td>
</tr>
<tr>
<td>Stool consistency</td>
<td>soft – variable – hard</td>
<td>watery / soft</td>
</tr>
<tr>
<td>Abdominal pain/ discomfort</td>
<td>obligatory</td>
<td>variable</td>
</tr>
<tr>
<td>Nocturnal diarrhea</td>
<td>very rare</td>
<td>possible</td>
</tr>
<tr>
<td>Feeling of incomplete bowel evacuation</td>
<td>common</td>
<td>no</td>
</tr>
<tr>
<td>Weight loss</td>
<td>rare</td>
<td>common</td>
</tr>
<tr>
<td>Fecal incontinence</td>
<td>rare</td>
<td>common</td>
</tr>
<tr>
<td>Feeling of fullness/bloating</td>
<td>common</td>
<td>rare</td>
</tr>
<tr>
<td>Accompanying autoimmune disease</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Influenced by stress</td>
<td>common</td>
<td>possible</td>
</tr>
<tr>
<td>Accompanying psychosomatic disease</td>
<td>common</td>
<td>rare</td>
</tr>
<tr>
<td>Suspected drug-induced diarrhea</td>
<td>no</td>
<td>yes</td>
</tr>
</tbody>
</table>

Fig. 7  Differential diagnosis: irritable bowel syndrome – microscopic colitis
What is known about microscopic colitis today?

Interview with Professor Dr. Jean-Frédéric Colombel, Mount Sinai School of Medicine, New York, USA

Editors:
Professor Colombel, what are the main clinical signs and symptoms suggestive of microscopic colitis?

Professor Colombel:
Chronic watery diarrhea with urgency and, in some patients, fecal incontinence can indicate microscopic colitis. So it’s clear that these symptoms have a considerable impact on quality of life and those affected are often socially isolated.

Editors:
Are there any known factors that trigger microscopic colitis?

Professor Colombel:
The literature often mentions an association between microscopic colitis and the intake of certain drugs. The drugs most commonly mentioned in this context are non-steroidal anti-inflammatory drugs (NSAIDs) and proton pump inhibitors (PPI). It is still unclear, however, why these substances trigger microscopic colitis.

Editors:
What are the therapeutic options for patients with microscopic colitis today?

Professor Colombel:
Most patients respond very well to the topical corticosteroid budesonide in the short term. A number of patients also need long-term treatment with budesonide, a sustained low dose often being sufficient. In general, patients tolerate budesonide very well.

Editors:
How do you treat refractory cases?

Professor Colombel:
Case reports suggest that immunosuppressive drugs, biologics, and ileostomy are possible treatment options. But these cases are fortunately rare.

Editors:
Is the small bowel also affected in microscopic colitis?

Professor Colombel:
Yes, some data from case studies suggest an involvement of the small bowel as well.

Editors:
What is known about microscopic colitis today?

Professor Colombel,

Professor Colombel, thank you for this interview.
Information material on microscopic colitis designed in collaboration with the European Microscopic Colitis Group (EMCG)

Microscopic colitis is a comparatively “new” disease and has yet to filter through into medical training and doctor’s continuing professional development.

Falk Foundation e.V. provides comprehensive information material designed especially for gastroenterologists and pathologists, but also for non-specialist physicians and patients, with 3 separate leaflets on the subject. This leaflet can be ordered free of charge from Falk Foundation e.V. or the local Falk partner.

Further information on microscopic colitis you may receive from EMCG www.emcg-ibd.eu

Publisher
FALK FOUNDATION e.V.
Leinenweberstr. 5
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www.falkfoundation.org

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Data of image: 03/2014

Budenofalk® 3mg capsules; Budenofalk® 9mg gastro-resistant granules, Budenofalk® Rectal Foam. Active ingredient: budesonide.

Composition:
1 gastro-resistant hard capsule of Budenofalk® 3mg (1= hard capsule with gastro-resistant pellets) contains: active ingredient: 3 mg budesonide. One sachet of Budenofalk® 9mg gastro-resistant granules contains: active ingredient: 9 mg budesonide. Other ingredients for the capsules and the granules: povidone K29/32, lactose monohydrate, sucrose, talc, maize starch, methacrylic acid-methyl methacrylate copolymer (1:1), methacrylic acid-methyl methacrylate copolymer (1:2), ammonio methacrylate copolymer (type B), ammonio methacrylate copolymer (type A) (= Eudragit L, S, RS and RL), triethyl citrate. Additionally capsules: titanium dioxide (E171), purified water, gelatin, erythrosine (E127), iron(III) oxide (E172), iron(II) oxide (E172), sodium lauryl sulfate. Additionally granules: lemon flavour, citric acid anhydrous, magnesium stearate, sucralose, sorbitol (E420), xanthan gum. Each actuation of Budenofalk® Rectal Foam contains: active ingredient: 2 mg budesonide. Other ingredients: cetyl alcohol, ceteareth-10, polyethylene 60, purified water, sodium edetate, macrogol, propylene glycol, citric acid monohydrate, propellant gases: butane, 2-methylpropane, propane. Indications: Budenofalk® 3mg capsules: Mild to moderate active Crohn’s disease affecting the ileum and/or the ascending colon. Collagenous colitis. Autoimmune hepatitis. Budenofalk® 9mg gastro-resistant granules: Induction of remission in patients with active collagenous colitis. Mild to moderate active Crohn’s disease affecting the ileum and/or the ascending colon. Budenofalk® Rectal Foam: For the treatment of active ulcerative colitis limited to the rectum and the sigmoid colon. Contraindications: Hypersensitivity to budesonide or any of the other ingredients. Hepatic cirrhosis. Pregnancy. Lactation. Children. Close medical supervision is required in the following diseases: septicemia, tuberculosis, hypertension, diabetes mellitus, osteoporosis, pepsic ulcer (gastric or duodenal), glaucoma, cataract, family history of diabetes or glaucoma. Chickenpox, herpes zoster or measles. Local infections of the intestine (bacteria, fungi, amoebae, viruses). Severe hepatic impairment. Late stage primary biliary cirrhosis (PBC). Additionally capsules and granules: hereditary problems of galactose intolerance, fructose intolerance, (the Lapp) lactase deficiency, sucrose isomaltase insufficiency, glucose-galactose malabsorption. Severe hepatic impairment. Late stage primary biliary cirrhosis (PBC). Additionally capsules and granules: hereditary problems of galactose intolerance, fructose intolerance, (the Lapp) lactase deficiency, sucrose isomaltase insufficiency, glucose-galactose malabsorption.