

Microscopic colitis, a forgotten condition: a clinical case and review of the literature

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Abstract. – OBJECTIVE: Microscopic colitis is a not uncommon chronic inflammatory disease of the colon, characterized by watery, non-bloody diarrhea, which is often forgotten and misdiagnosed.

CASE PRESENTATION: In this paper, we present a puzzling case of relapsing chronic diarrhea triggered by non-steroidal anti-inflammatory drug (NSAID) abuse, smoking, inappropriate antibiotic use, and secondary *Clostridium Difficile* infection.

Several tests were performed during hospitalization, all of which were negative apart from fecal calprotectin (> 6,000 mg/kg, normal values < 50 mg/kg) and a positive *Clostridium Difficile* toxin test. Since Vancomycin treatment did not bring about the expected response, colonoscopy was performed, which led to diagnosis, targeted therapy, and clinical resolution. Targeted therapy with budesonide and probiotics was initiated leading to resolution of the diarrhea.

CONCLUSIONS: This case study shows how actual diagnosis may be delayed not only due to having to perform differential diagnosis with chronic inflammatory diseases, but also because certainty can only come from histological evidence, which takes time to obtain, especially when the disease's multifactorial nature is considered (smoking, NSAID abuse, oral proton pump inhibitors, inappropriate antibiotic use, and *Clostridium difficile* infection).

Key Words:

Microscopic colitis, Chronic diarrhea, *Clostridium difficile*, Probiotics.

Introduction

Microscopic colitis is a chronic inflammatory disease of the colon characterized by watery, non-bloody diarrhea. Associated symptoms include fecal urgency (70%), abdominal pain (50%), fecal incontinence (40%) and nocturnal episodes

(50%)¹. It is diagnosed histologically. The two main subtypes are lymphocytic and collagenous colitis². We present a puzzling case of relapsing chronic diarrhea triggered by non-steroidal anti-inflammatory drug (NSAID) abuse, smoking, inappropriate antibiotic use, and secondary *Clostridium Difficile* infection.

Case Presentation

A 74-year-old patient was transferred to our Emergency Department (ED) from a Rehabilitation Unit due to severe dyspnea and chronic *non-Clostridium Difficile* diarrhea. His previous medical history included sequelae of poliomyelitis, multinodular thyroid goiter, cholelithiasis, past chronic diarrhea (three years ago) which resolved with unspecified medical therapy, smoking, and recent abuse of NSAIDs. His current clinical history dated back to the previous month when he was hospitalized for a left hip fracture due to an accidental fall.

During his stay in the rehabilitation ward microbiological tests were performed: a urine culture resulted positive for wild-type *Escherichia coli*, and a fecal screening for *Clostridium difficile* toxins was negative. Diarrhea was, therefore, treated with mesalamine and metronidazole, with scarce benefit. Due to the onset of dyspnea and anasarca, a thoracic-abdominal CT scan was performed, revealing pleural and abdominal effusion associated to pancolitis involving the terminal ileal loop. In the suspect of an activated inflammatory bowel disease (IBD), the patient was thus transferred to our ED and then admitted to our Emergency Medicine Department for appropriate diagnostics and treatment.

Blood tests confirmed hyponchmia (albumin 2.3 g/dl), hypokalemia (2.7 mmol/l), and anemia, compatible with chronic inflammatory disease

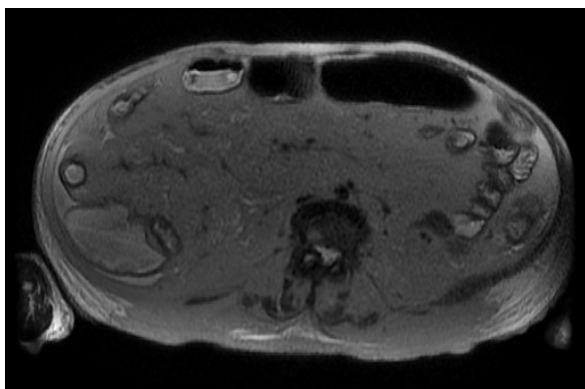


Figure 1. Axial section of the colic mucosal and submucosal inflammation.

(Hb 11.5 g/dl, MCV 98fl), with normal leukocytes and a slight increase in the inflammatory markers (CRP 1.83 mg/dl). The PCR test for SARS-CoV-2 was negative.

The persistent diarrhea (more than three watery stools per day - Bristol type 6) made it hard to preserve a hydroelectrolytic balance, mainly in terms of potassium, with repeated falls in albumin values and recurrent anasarca, treated effectively with albumin and diuretics. Among further tests, thyroid function was found to be normal, celiac disease specific antibodies were not detected, and immunoglobulin levels (IgG, IgE, IgM, and IgA) were in the normal ranges. The physical and chemical stool examination confirmed the absence of fatty acids but revealed the presence of free starch. Procalcitonin levels were in the normal range, and the stool cultures for *Campylobacter jejuni*, *enterotoxigenic* and *Shiga toxin-producing Escherichia coli*, *Salmonella spp*, *Shigella* and *Yersinia* were all negative, as were the parasitological tests for *Cryptosporidium*, *Giardia* and *Entamoeba histolytica*.

Fecal calprotectin was positive with a value greater than 6,000 mg/kg (< 50 mg/kg). In addition, a toxin test for *Clostridium Difficile* was performed once again, resulting, this time, positive, leading to vancomycin treatment that gave little advantage. A colonoscopy was therefore completed, resulting negative for macroscopically evident neoplastic alterations allowing the belated diagnosis of microscopic colitis (lymphocytic subtype) through multiple biopsies which revealed inflammatory lymphoplasmacytic and granulocytic infiltrates of the lamina propria.

Awaiting histological results, of the intestinal biopsies, an abdominal magnetic resonance imaging (MRI) was carried out, confirming the

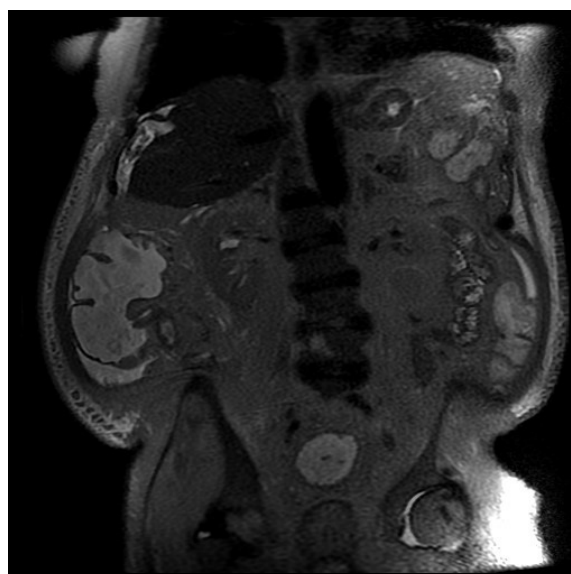


Figure 2. Coronal section of the colic mucosal and submucosal inflammation.

presence of colic inflammation (mucosal-submucosal), excluding post-contrast images of thickening or enhancement of the small intestinal wall, terminal ileal loop, and ileocolic valve making concomitant IBD unlikely (Figure 1 and Figure 2).

The patient was, therefore, treated for microscopic colitis with budesonide and probiotics (*Escherichia coli Nissle 1917*), and oral pantoprazole was discontinued. This brought improvement in clinical symptoms (1-2 stools per day - Bristol 4) and laboratory data (restoration of the hydroelectrolytic balance), subsequently allowing the patient to return to the rehabilitation ward.

Discussion

Microscopic colitis is a chronic inflammatory disease of the colon characterized by watery, non-bloody diarrhea, which occurs in middle-aged patients (approximately 65 years), with female preponderance (52%)¹. The incidence is 2 cases per 100,000 inhabitants per year and is more frequently seen in northern Europe³. It is diagnosed by colonic mucosa biopsy². Microscopic colitis is associated with autoimmune disorders (e.g., autoimmune thyroiditis, type 1 diabetes mellitus, inflammatory bowel disease, and celiac disease)⁴. The HLA-DR3-DQ2 haplotype, which predisposes to celiac disease, is specifically associated with microscopic colitis⁵.

Concerning risk factors, medications certainly play a triggering and causative role: NSAIDs and proton pump inhibitors (PPIs) are implicated, especially when they are used together¹. Smoking also contributes since smokers develop microscopic colitis ten years or more earlier than non-smokers on average⁶. Its pathophysiology is multifactorial, involving mucosal immune responses to luminal factors in genetically predisposed individuals^{7,8}.

Synchronous collagenous and pseudomembranous colitis have also been described in some patients, suggesting a possible etiologic role of *Clostridium difficile*⁹.

The diarrhea is likely caused by mucosal inflammation, and its severity correlates to the inflammatory changes in the lamina propria¹⁰. The secretory component results from the lower absorption of sodium chloride, which is accompanied by a component of active chloride secretion¹¹. An osmotic component can also be observed since fasting also reduces stool volume¹².

Laboratory findings in microscopic colitis are generally non-specific. Mild anemia, a high erythrocyte sedimentation rate and auto-antibodies (i.e., rheumatoid factor, antinuclear, antimitochondrial, antithyroid, and antineutrophil cytoplasmic antibodies) are found in 50% of patients¹³. More uncommonly, subjects may exhibit protein-losing enteropathy associated with hypoalbuminemia, as seen in our patient.

The results of studies to evaluate fecal calprotectin excretion as a marker of active microscopic colitis have been conflicting, thus calling for additional investigations to validate and clarify its possible role in the diagnosis and management of microscopic colitis¹⁴.

Certain diagnosis requires a colonic mucosa biopsy which reveals the characteristic histologic changes. The inflammatory cell response is similar in lymphocytic and collagenous colitis, and consists mainly of mononuclear infiltrates, with a few neutrophils and eosinophils in the lamina propria. However, there are certain key histological features that are used to distinguish the subtypes: collagenous colitis has a colonic subepithelial collagen band ≥ 10 micrometers in diameter, while lymphocytic colitis is characterized by ≥ 20 intraepithelial lymphocytes (IEL) per 100 surface epithelial cells¹⁵. The active disease is defined by ≥ 3 stools/day or ≥ 1 watery stool/day¹⁶.

The primary management goal in patients with microscopic colitis is to achieve clinical remission (< 3 stools per day and no watery stools over a one-week period).

General measures in all patients include avoiding culprit medications, stopping smoking, and glucocorticoids in the case of active disease (e.g., 9 mg of budesonide per day for six to eight weeks with gradual tapering, or prednisone when this is not feasible). If patients exhibit persistent mild diarrhea despite taking glucocorticoids, cholestyramine may be associated (4 g three times a day). In patients with refractory microscopic colitis, treatment with anti-tumor necrosis factor (TNF) (e.g., infliximab or adalimumab) or immunomodulators (e.g. azathioprine) may play a role in avoiding surgery (e.g. ileostomy, sigmoidostomy or colectomy)¹⁷. It has been noted that aminosalicylates, including mesalamine, appear to be ineffective in the treatment of microscopic colitis¹⁷. This emerged from a randomized clinical trial in which 92 patients with active collagenous colitis were treated with oral budesonide (9 mg daily), mesalamine (3 g daily), or placebo for two months: remission rates with mesalamine were comparable to placebo (32% and 38% respectively)¹⁸. Microscopic colitis has a chronic, intermittent course in most patients with frequent relapses (approximately 30-60%). The long-term course of the lymphocytic subtype is more favorable than the collagenous one (84% vs. 74%)¹⁹. Microscopic colitis has not been associated with an increased risk of colorectal cancer²⁰.

Conclusions

Our clinical case underlines how the actual diagnosis of microscopic colitis may be delayed not only because of the struggle in the differential diagnosis with IBD, but also due to the fact that certainty comes solely from histological evidence, which requires practical time. Its tendency of relapsing (same episode three years ago) reflects the multifactorial nature of the disease with dysbiosis representing the fertile ground for its development. Specifically in our patient, triggering factors for persistent inflammation include history of smoking, NSAID abuse, oral PPIs, inappropriate antibiotic use and *Clostridium difficile* infection. The latter, often gets treated without considering that it may hide an underlying disease responsible for refractory diarrhea. Hence, microscopic colitis should always be accounted for when determining the causes of diarrhea, even if another contributing agent has been found (i.e., *Clostridium Difficile*).

Therefore, keeping our microbiota healthy is essential for its protective role on the intestinal

barrier and for its modulating effects on the immune system (such as inducing protective cytokines, like IL-10 and TGF beta)²¹. Consequently, the rationale of using probiotics in gastrointestinal diseases is currently under investigation. Our patient for example benefited from probiotics. Moreover, it was suggested that *Escherichia coli* Nissle 1917 might have a beneficial effect in an open label study on 14 patients with collagenous colitis²². Owing to the poor quality of the data in this study, no probiotic strategies are currently considered as standard. Future large, well designed, multicenter, controlled clinical trials are so needed to clarify their role in specific gastrointestinal disorders.

Conflict of Interest

There are no conflicts of interest.

Informed Consent

The informed consent was obtained from patients before the study.

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