Microscopic colitis: Overview

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Abstract

Microscopic colitis (MC) is an inflammatory disease of the large intestine that causes persistent watery diarrhea especially in older patients. Microscopic colitis encompasses 2 different subtypes: lymphocytic colitis and collagenous colitis. MC is characterized by a nearly normal-appearing colonic mucosa. Diagnosis is based on histology. Risk factors for MC include increasing age, female sex, presence of other autoimmune diseases and possibly use of certain drugs, including proton pump inhibitors, nonsteroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, and statins. In the last decade, emerging evidence regarding disease pathogenesis has provided advances in the management strategies for this disease. This is a comprehensive review on disease etiopathogenesis, diagnosis and therapeutic management.

Key words: *Microscopic colitis; diarrhea; collagenous colitis; lymphocytic colitis*

INTRODUCTION

Microscopic colitis (MC) is characterized by the presence of non-bloody diarrhea with normal colonoscopy and microscopic evidence of mucosal inflammatory changes of the colonic tissue [1]. Microscopic colitis encompasses two different disorders: lymphocytic (LC) and collagenous colitis (CC) [1]. Microscopic colitis may occur in patients of any age but typically emerges in late middle age and the elderly and is more prevalent in women. The gender difference is more significant for collagenous colitis. Non-bloody diarrhea is the predominant symptom, although abdominal discomfort and weight loss may also occur. Both diseases run a benign course and there is no risk of malignancy. Sometimes patients present a relapsing course with a need for immunosuppressive therapy and rarely for surgery [1, 2].

Because both lymphocytic and collagenous colitis, manifest with histologic evidence of chronic mucosal inflammation, in the absence of endoscopic or radiologic abnormalities of the colon, diagnosis is only possible through histological analysis. Patients with lymphocytic colitis have an increased number of intraepithelial lymphocytes in the colonic epithelial layer and increased number of sub-epithelial chronic inflammatory cells compared with healthy individuals. Patients with collagenous colitis have a thickened subepithelial collagen layer that can vary between 7 to 100 μm. Similar changes in inflammatory cell populations such as increased number of intraepithelial lymphocytes also occurs in collagenous colitis [1,2].

Microscopic colitis' etiology and pathogenesis remain unknown. No genetic factors have been identified, although some familial cases have been described [3,4]. Several hypotheses have been advanced, including autoimmune dysfunction or an abnormal immune or inflammatory response to an unknown luminal antigen or luminal factor. This later hypothesis is supported by the regression of inflammation following diversion of the fecal stream and recurrence of inflammation following restoration of intestinal continuity in some patients [5]. However, the identity of the inciting antigenic factors is uncertain. A variety of luminal factors have been implicated in the pathogenesis of MC, including drugs, bile salts, bacterial products, and toxins. NSAIDs, aspirin, proton pump inhibitors, ticlopidine, SSRI, acarbose and statins, are some of the drugs that have been more frequently associated with the disease.

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Autoimmunity is another condition that has been proposed to have a role in the pathogenesis of microscopic colitis. In epidemiological studies a strong association with other autoimmune diseases has been reported in patients with microscopic colitis, including celiac disease, thyroiditis and rheumatoid arthritis. Budesonide, the only drug that has been tested in multiple randomized controlled trials (RCT), is highly effective and achieves clinical remission in approximately 80% of patients. However, symptoms' relapse occurs in 60% to 80% of patients after treatment withdrawal [6].

EPIDEMIOLOGY

Previously considered to be a rare diagnosis, microscopic colitis accounts nowadays for 4 to 13% of patients investigated for chronic diarrhea [7, 8]. The incidence of microscopic colitis seems to be increasing. In the United States, the overall prevalence of microscopic colitis is around 103 per 100,000 persons. The reason might be a more accurate diagnosis with biopsies, or possibly increased incidence of immune-mediated disorders. MC is nearly as common as classic Inflammatory Bowel Diseases (IBD) [7,8].

A strong female and elderly predominant have been identified. However, 25% of MC patients are younger than 45 [1].

CLINICAL PRESENTATION

The key clinical feature is chronic non-bloody diarrhea, which is typically watery, leading to urgency in 70% of patients and, ultimately, fecal incontinence in 40% of patients [9, 10]. The two forms of MC have similar symptoms. Relapses occur in 60%–80% of the cases after discontinuation of budesonide treatment, indicating that the course of the disease if often chronic. Abdominal discomfort or cramps may occur in up to 50%. Of note, a differential diagnosis between MC and irritable bowel syndrome may be challenging in these patients. Moreover, weight loss is observed in 50% of patients with active disease [9,10].

ETHIOPATHOGENESIS:

Auto-immunity in microscopic colitis

There is some evidence in the literature pointing to a possible role of autoimmunity in microscopic colitis. In some case series, CC is more frequent in women, as other autoimmune diseases. An overrepresentation of autoimmune diseases is found in microscopic colitis [11]. Epidemiological studies have shown an association with autoimmune diseases that reaches 30-40%. The most common diseases which have been associated with microscopic colitis are celiac disease and several forms of arthritis. Sjögren's syndrome, scleroderma, Raynaud's disease, recurrent iritis, giant cell arteritis, systemic lupus erythematosus, diabetes mellitus, sarcoidosis, psoriasis, myasthenia gravis, Crohn's disease, ulcerative colitis have also been reported to be associated with MC. In patients with collagenous colitis there have been reports of a significant increase in mean serum concentration of immunoglobulin M and a non-significant trend toward increased concentrations of antinuclear antibodies and perinuclear antineutrophil cytoplasmatic antibody in collagenous colitis. TNFα gene polymorphisms were found to be more frequent in patients with MC than in controls; these polymorphisms have been associated with susceptibility to several autoimmune diseases, such as juvenile idiopathic arthritis, systemic lupus, dermatitis herpetiform and celiac disease. Some studies have revealed an association with the HLA genes. Three HLA alleles [HLA-B*08:01, HLA-DRB1*03:01, and HLA-DQB1*02:01], related to the ancestral haplotype 8.1, were significantly associated with increased CC risk [12]. These HLA alleles were not associated with LC. Moreover, lymphocyte infiltration at the site of inflammation can be found and the majority of patients respond to steroid therapy.

Role of bacteria

There is some evidence supporting a role for bacteria or for bacterial dysregulation (dysbiosis) in the pathogenesis of microscopic colitis, although no specific causative agent has been identified. The strongest argument for a luminal agent, which could be a bacterial agent or a bacterial toxin, comes from the fact that the diversion of fecal stream in patients with medically refractory diarrhea results in the resolution of histological inflammation, that recurs upon transit reconstruction [5, 13].

Recent evidence has also suggested the contribution of an infective agent as risk factor for microscopic colitis. Indeed, gastrointestinal infection has been associated with collagenous colitis [14]. In a small case series, patients with collagenous colitis presented Yersinia antibodies more commonly than healthy controls, leading the authors to speculate that in some cases, Yersinia might have been the triggering factor in the development of collagenous colitis [15].

Genetics

Familial occurrence of MC has been reported, but the exact role of genetic factors remains to be defined. Allelic variation of the matrix metalloproteinase-9 gene does appear to be associated with CC [16]. Three HLA alleles (HLA-B*08:01, HLA-DRB1*03:01, and HLA-DQB1*02:01), related to the ancestral haplotype 8.1, were significantly associated with increased CC risk but not LC [12].

Risk factors

Smoking is a risk factor for MC both for men and women and smokers develop the disease earlier than nonsmokers (by a median of 14 years) [17-19]. Drugs such as acarbose, aspirin, cyclo3 fort, lansoprazole, nonsteroidal anti-inflammatory drugs, ranitidine, sertraline, and ticlopidine have been suggested to act as an environmental risk factor in causing or triggering MC [20]. Of note, nonsteroidal anti-inflammatory drugs and proton pump inhibitors were identified as the 2 drugs with the highest likelihood to cause MC [21]. Of note, given the increased incidence of MC in postmenopausal women, sex hormones disturbances have been suggested as risk factors in the development of inflammatory bowel disease and other immune-mediated diseases as well as in MC [22].

THERAPEUTIC INTERVENTIONS

Currently the primary goal of therapeutic interventions in MC is to achieve clinical remission, whereas the role of histological remission is still unknown [23]. Budesonide is the only drug with strong evidence of response rates up to 80%. Moreover, improvement of quality of life under budesonide treatment has been shown by a small number of studies [24, 25]. No evidence-based alternatives to budesonide have been proposed. There are no RCTs for antidiarrheals drugs. Budesonide has been shown to be superior to prednisolone [26]. Indeed, patients treated with budesonide were less likely to experience a recurrence compared to those under prednisolone [26]. Of note, RCTs have shown that MC patients achieve clinical remission within 4 weeks on induction therapy with 9mg budesonide or maintain clinical remission on 6mg or less of budesonide. 10% to 20% of these patients are non-responders and may be candidates for immunosuppressive therapy [24]. No sufficient data are available for bismuth subsalicylate and data have shown that mesalazine should not be used as induction therapy [25]. Although evidence is limited, biologics should be considered when symptoms worsen, and patients are non-responders to budesonide. Moreover, data are limited on long term use of biologics in MC.

An algorithm for the treatment of MC has been proposed by the European Microscopic Colitis Group. Antidiarrheals and/or cholestyramine may be use if there are mild symptoms. In active disease short-term budesonide (6–8 weeks) should be initiated and re-administered in case of relapse. In more severe cases, biologics should be considered and as maintenance treatment, immunomodulators such as AZA or mercaptopurine. In patients refractory to medical therapy, surgical treatment is a therapeutic option.

CONCLUSION

Microscopic colitis is a chronic disease for which several data on genetics, autoimmunity and microbiome influences have been generated in the last decade. Overlaps with inflammatory bowel disease have offered new insights into the etiopathogenesis of MC as well as into treatment options. Emerging studies suggest a role for biologicals and immunosuppressive therapies for the management of budesonide-refractory or budesonide-dependent disease. MC can have a substantial negative effect on patient quality of life and therefore well-designed clinical trials are mandatory to assess novel therapeutic interventions.

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