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Case Report

Microscopic Colitis and Rheumatoid Arthritis: What does this Duet Tell Us? Literature Review and Clinical Case

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Abstract

RA is a chronic, autoimmune, systemic disease of unknown etiology that can cause joint deformities. In its treatment, non-steroidal anti-inflammatory drugs (NSAIDs), steroids, non-biological DMARDs and biological DMARDs are used in various combinations according to the degree and progression of the disease. NSAIDs are often used for a long time in combination with proton pump inhibitors (PPIs) because they act quickly and provide symptomatic relief. Microscopic colitis; It is a chronic bowel disease characterized by watery diarrhea. It is thought that the use of NSAII and PPI alone or together increases the risk of microscopic colitis. The primary disease itself and/or infection may also be triggers.

Keywords: Rheumatoid Arthritis; NSAID; PPI; Microscopic Colitis

Introduction

Microscopic colitis (MC) is a chronic inflammatory disease of the large intestine, consistent with two histological subtypes, lymphocytic colitis (LC) and collagenous colitis(CC). The most common presentation of MC is chronic watery diarrhea associated with abdominal pain, fecal urgency, and incontinence [1,2]. Microscopic colitis was considered a disease of old age, but now the incidence is rising in the younger population. The updated incidence and prevalence of MC are 25.8 cases/per 100,000 and 246.2/per 100,000, as reported by Tome., *et al*. in an epidemiological study performed in Olmsted County, MN, USA [3,4]. The possible explanation for the increasing incidence of MC is better awareness and understanding of the disease and better and readily available diagnostic modalities such as endoscopy and biopsy [5].

The inflammation of the colon in response to luminal antigen exposure is suggested to underlie the mechanism of MC, but the exact pathogenesis is still unclear [6]. Endoscopic examination in MC usually reveals normal mucosa. Diagnosis is often established with a microscopic examination, which shows increased intraepithelial lymphocytes, inflamed lamina propria, and damage to the epithelial surface in both LC and CC [7,8]. The histological presence of collagenous bands allows for the differentiation between the two subtypes of MC and is only seen in CC [1,9]. Female sex and increasing age are the established risk factors associated with MC [3]. Rheumatoid arthritis (RA) is a chronic autoimmune systemic inflammatory disease of unknown cause [31]. Medication-based theories comprise several classes of agents, including nonstreoidal anti-inflammatory drugs (NSAIDs), nonbiologic and biologic disease-modifying antirheumatic drugs (DMARDs), immunosuppressants, and corticosteroids [32].

We will try to prove it on our own case in order to find an answer to the question of whether the coexistence of RA and MC is autoimmune. Here we present to you a rare case a 75-year-old case with RA, who has been using steroids, NSAIDs, leflunomide and PPIs for a long time, and who presented with chronic watery diarrhea, was diagnosed with microscopic colitis.

Case Report

A 75-year-old woman with a 25 year history of rheumatoid arthritis presented with nausea, abdominal pain and worsening diarrhea of 3 month's duration. She had been successfully treated 5 months prior for *Clostridium difficile* associated diarrhea which had required hospitalization. She had been initially maintained on prednisolon (5-10 mg od), leflunamide (10 mg od) and salazopyrin (500 mg bid), both medications were discontinued due to the persistent diarrhea. However, she gave a history of frequent use of NSAIDs, particularly diclofenac for her joint complaints which also required her to take lansoprazol for dyspepsia.

She complained of having to empty her bowels 8-10 times a day. Her diarrhea and abdominal cramps seemed to increase with meals which led her to avoid regular meals and eventually losing 6 kg of weight. She described her stool as being profuse watery, but recently noticed the presence of occasional blood stool. On examination, the patient was unwell and dehydrated with low blood pressure (80/50 mmHg) and tachycardia (120/ minute) and was subsequently admitted for further evaluation. Laboratory findings revealed the presence of anemia consistent with iron deficiency, hypoalbubinemia (2.2 gr/dL) and markedly elevated CRP (48 mg/dL) and erythrocyte sedimentation rate (67 mm/hour). Besides slightly elevated serum creatinine and urea levels, serum biochemistry was otherwise normal. Anti-tissue transglutaminase antibody levels were negative. Microscopic examination of stool revealed the presence of erythrocytes and leukocytes. With the detection of *Clostridium difficile* toxin A-B in a stool sample, the patient was started on rifaximine (400 mg tid) and metronidazole (500 mg tid). By the fifth day of treatment, slight improvement in diarrhea symptoms was observed, and despite the absence of blood she still complained of large-volume watery diarrhea. Subsequent colonoscopic evaluation showed generally intact colonic mucosa and minor and non-specific abnormalities such as erythema, edema, and abnormal vascular changes may be seen on colonoscopy. Colonic tears, defined as "cat scratch colon", were observed in colonoscopy (Figure 1,2). However, mucosal fragility and the easy development of mucosal tears during the procedure were noted. Biopsies obtained revealed the presence of increase in intraepithelial lymphocytes within the crypts, as well as a marked increase in the thickness of subepithelial collagen, reching a thickness of > 10 micrometers at its thickest (Figure 3,4).

Figure 1: Generally intact colonic mucosa and minor and non-specific abnormalities such as erythema, edema.

Figure 2: Colonic tears, defined as "cat scratch colon.

Figure 3: Mixed type inflammatory cell infiltration in the lamina propria, lymphoid aggregate and increase in collagen thickness in the subepithelial area (Hematoxylin-eosin 100x magnification).

Figure 4: Increase in collagen thickness in the subepithelial area (200x magnification with Masson Trichrome Dye). (Intraepithelial lymphocyte count and collagen thickness in the subepithelial area were increased in the crypts. There was mixed type inflammatory cell infiltration and lymphoid aggregate in the lamina propria).

Clinical and histopathology findings were considered to be consistent with collagenous colitis, and after an initial subdued response to bismuth subcitrate, complete resolution of gastrointestinal symptoms was achieved after 4 weeks of oral budesonide (3 mg tid).

Discussion

Microscopic colitis (MC) (comprising lymphocytic and collagenous colitis, albeit an incomplete variant is gaining recognition as well) is a chronic, immune-mediated inflammatory state of the lower gastrointestinal tract (colon). The diagnosis requires diagnostic colonoskopy with characteristic histopathological findings. They have a propensity to present in senior populations (above 60 years of age), particularly women – who are approximately 2,5-3 times more likely to develop microscopic colitis. Preexisting other immune-inflammatory diseases are also shown to predispose patients for the development of MC, for example, RA, Sjogren's Syndrome, Hashimoto and Celiac disease. The classic presentation is profuse watery diarrhea, often during the night or early morning hours. Fecal incontinence and abdominal pain are frequent as well. Although there is a lack of unified recommendation for treatment, most clinicals prefer the use of budesonide, and most published guidelines regard this locally acting glucocorticoid as the therapy of choice [36].

Microscopic colitis, of which two major histological subtypes (collagenous colitis and lymphocytic colitis) exist, is a common cause of chronic or recurrent, non bloody, watery diarrhea. Since the symptoms of microscopic colitis are nonspecific and the diagnosis requires histology, the disease risks being overlooked [14]. It is affiliated to the umbrella diagnosis of inflammatory bowel disease (IBD) [15] and is described by a clinicopathological triad characterized by a history of chronic or intermittent watery diarrhea, normal or almost normal endoscopic examination of the colon (e.g., with slight edema, erythema, and/or loss of vascular pattern, although rarely more significant macroscopic changes are reported, including pseudo membranes and 'cat scratch changes') [16], as well as a distinct histological pattern when examined under a microscope – hence the name of this disorder.

Although most patients receive their diagnosis at an age of 60 or above, approximately 25% of patients get diagnosed before the age of 45 [19].

Zahid Ijaz Tarar., *et al*. in theirs meta-analysis studies [20], they reported the effect of medication use on the development of microscopic colitis. They demonstrated that certain medications such as proton pump inhibitors, SSRIs, NSAIDs, and statins are associated with an increased risk of MC, but H2Reseptor antagonist use was not associated with an increased risk of MC when compared to random control groups. This is the first meta-analysis on this topic to the best of our knowledge, and the results of our analysis are significant. And their results showed that using PPIs is associated with significantly higher odds of MC, in accordance with the results of the previous studies [12,22-24]. It is postulated that changes in gut flora, electrolyte imbalance due to acid suppression, and intestinal dysbiosis caused by PPIs are the possible underlying mechanism of MC development [25-27]. The noteworthy result in our analysis is that when MC cases were compared with diarrhea controls, the use of PPI was associated with decreased pooled odds of MC, while in studies in which random controls were selected, the risk of MC in PPI users was high. These results raise a question about the association of MC with PPI use because patients who suffer from gastrointestinal symptoms are more likely to get a PPI prescription compared to the healthy control group, and a similar observation has been made by Law., *et al*. [28]. On subgroup

analysis, it was found that the use of PPI was not associated with a greater likelihood of CC or LC. Lower odds of MC compared to diarrhea control and higher odds with random control warrant further prospective trials to establish or negate the association of MC with PPIs.

The NSAIDs inhibit prostaglandin synthesis, which results in increased gut permeability and impairs the integrity of the mucosal barrier resulting in an influx of bacteria and toxins into the intestinal lumen. The reaction to these luminal antigens is considered an underlying pathogenetic factor for the development of MC in NSAID users [21,29]. We reported significantly higher odds of MC in patients taking NSAIDs, and these results reinforce the results of previously conducted studies [9,12,13,21,23,24,30]. We also found that the odds of developing CC are higher in NSAID users, though no significantly higher risk of LC was seen in patients taking NSAIDs. Again, based on the results of the meta-analysis study by Zahid Ijaz Tarar., *et al*. we see that in the subgroup analysis based on the control group, there was no difference in the risk of MC when MC cases using NSAIDs were compared with the diarrhea control group, when MC cases were compared with a healthy random control group, there was no significant difference. Long-term use of leflunomide may have triggered microscopic colitis as a cause of diarrhea and weight loss. Not only NSAIDs, PPIs and steroids, we also have another agent that causes watery diarrhea and weight loss in our patient, leflunomide, which belongs to the DMARD group and is frequently used in the treatment of RA. In our case, this drug triggered MC by causing watery diarrhea and weight loss in addition to the factors affecting others due to long-term use of this drug, revealing the association between MC pathogenesis and drugs [17]. We have shown that there are significantly higher rates. MC noted. The inconsistency in results based on the control group in this PPI and NSAID group warrants our caution in interpreting these results [20].

There is growing evidence that MC is related to other autoimmune diseases such as celiac disease, thyroid disorders, and rheumatic diseases, and the use of certain medications such as proton pump inhibitors (PPIs), Selective serotonin reuptake inhibitors (SSRIs),NSAIDs, and statins [2,10-13].

There are indirect relationships between MC and several factors suggestive of autoimmunity. CC is more common in the colon, which is a common feature of many autoimmune diseases. About 40% of MC cases are accompanied by other autoimmune diseases such as thyroiditis, type 1 diabetes mellitus, celiac disease, and RA, systemic sclerosis or CREST syndrome [31,32,37,40]. Although some studies show an increase in serum IgM, ANA, p-ANCA concentrations, there is no clinically useful marker for the diagnosis of MC yet [38,39]. Although Taylan Kav states in his scientific article on Microscopic Colitis that there is no diagnostic marker to support autoimmune etiology, lymphocytic MC is generally associated with autoimmune diseases. For example connective tissue diseases, endocrine diseases and diseases of gastrointestinal origin [18]. At the same time, some studies show that some autoimmune diseases are associated with diarrhea and constipation. For example, Barta Z., *et al*. in his clinical studies, Sjogren's disease was only associated with CC and constipation, proving that SLE (2 patients with CC and 1 patient with LC) and UCTD (2 patients with MC/CC) were associated only with diarrhea [41]. And also Istvan Fedor., *et al*. MC: autoimmune comorbidities also showed the frequency of autoimmune diseases in microscopic colitis in his original article on clinical symptoms and controversies. For example, RA 17.5%, Sjogren's syndrome -17.5%, SLE - 10.0, Mixed connective tissue disease - 2.5%, Ankylosing spondylitis -2.5% and these autoimmune diseases are seen especially in MC/CC subtype [42]. As stated above, RA occurs with a frequency of 17.5% as an autoimmune comorbidity of MC, and we think that this proves the result we obtained in our case and that there is any association between the two diseases. Rheumatoid arthritis (RA) is a chronic disease characterised by inflammation of the synnovial tissue in joints, which can lead to joint destruction. An external trigger (eg, cigarette smoking, dental caries, infection, or trauma) that triggers an autoimmune reaction, leading to synovial hypertrothy and chronic joint inflammation, reduce joint damage and disability, and maintain or improve physical function and quality of life. Worldwide, the annual incidence of RA is approximately 3 cases per 10,000 population, and the prevalence rate is approximately 1%, increasing with age and peaking between the ages of 35 and 50 years.

Thus, in the case we are going to present, we prove that the PPI, NSAID, leflunomide, steroid drugs used for a long time in our case with known RA and receiving the necessary treatment trigger MC and increase the clinical symptoms. The same similar case

was previously reported in ACG Case REp J 2019 by Michelle D. Lundholm, MD and et.al. was also presented by them [35].

Coming to our case, she presented with diarrhea that was watery, bloodless, 8-10 times a day for the last 3-4 months, and was diagnosed with MC by colonoscopic biopsy. Because of RA, our patient had been taking steroids, lenflunomide and frequently NSAII (diclofenac) and PPI for a long time. She had a disease duration of 25 years. It was thought that the history of frequent watery diarrhea that developed in the last 3-4 months may have been related to the existing chronic rheumatic disease and the drugs used for the treatment of this disease, and may also have been triggered by the intervening *C. difficile* infection.

Our patient, whose primary diagnosis is RA, is taking steroids and Budenofalk was started for MC treatment. Interestingly, in this patient, MC may have been caused by multiple factors. On the one hand, she has a chronic, systemic, autoimmune disease, on the other hand, the long-term use of our treatment agents and also the intervening *C. difficile* infection has initiated and may have initiated MC.

Conclusion

Thus, using our clinical case, we tried to outline the essence of the relationship between microscopic colitis and autoimmune diseases, in our case with rheumatoid arthritis. Many clinical works, articles also show that Microscopic colitis is associated with many autoimmune diseases, especially of gastrointestinal origin. The results indicate an autoimmune predisposition to microscopic colitis.

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