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Case Report

Inflammatory arthritis complicated by inflammatory bowel disease: two case reports

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ABSTRACT

Coexistence of inflammatory arthritis disease and inflammatory bowel disease (IBD) is often considered to be relatively rare, and the underlying mechanisms of the association between them remain unclear. Herein, we report two cases of IBD which occurred during the course of inflammatory arthritis disease. The first case had psoriatic arthritis (PsA) for two and a half years complicated by Crohn's disease and accompanied by inactive carrier state of hepatitis B. The second case had rheumatoid arthritis (RA) complicated by ulcerative colitis four years after the onset of RA. In both cases, colonoscopy was performed, and their clinical presentations improved with a multidisciplinary approach. In the event of complaints related to the gastrointestinal tract in patients with PsA or RA, IBD should be kept in mind, and the clinical evaluation and multidisciplinary interventions should be planned to control the underlying autoimmune process.

Keywords: Hepatitis B; inflammatory bowel disease; psoriatic arthritis; rheumatoid arthritis.

Crohn's disease (CD) and ulcerative colitis (UC), the two main forms of inflammatory bowel disease (IBD), are chronic relapsing inflammatory disorders of the gastrointestinal tract.[1,2] Inflammatory bowel disease affects around 28 million individuals worldwide and its incidence is increasing with future prevalence likely to be considerably higher than the existing rates.[3] Although the underlying etiology and exact pathogenesis of the IBDs are still unknown, the current hypothesis of their pathogenesis involves genetic, environmental, and immunological factors.[4,5] Existing evidences suggest that IBD results from a dysregulated inflammatory response to intestinal microbes in a genetically susceptible host.[6] These data have led to speculation that IBD may share pathogenic pathways with several immune-mediated inflammatory diseases, possibly as a member of the larger autoimmune diseases, particularly rheumatoid arthritis (RA).[7] In addition, IBD is associated with a spectrum of extraintestinal manifestations, including arthritis, uveitis, iritis, pyoderma gangrenosum, erythema nodosum, ankylosing spondylitis, and psoriasis.[5,8] Treatment is usually effective in relieving symptoms, although is not curative. These diseases typically evolve with a relapsing and remitting course. Exacerbations are characterized by diarrhea, abdominal pain, rectal bleeding, anemia, and weight loss.[9]

In this report, we present two cases to draw attention to the association between inflammatory arthritic diseases and IBDs. One of these our cases had psoriatic arthritis (PsA) for two and a half years complicated by CD, and accompanied by inactive carrier state of hepatitis B. The other cases had RA complicated by UC four years after the onset of RA.

CASE REPORT

Case 1- A 49-year-old male diagnosed with psoriasis two and a half years earlier was admitted to our hospital with complaints of tenderness and swelling in the first and second metacarpophalangeal (MCP) joints of the right hand and psoriatic skin lesions on the extensor side of the right forearm (Figure 1).

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His medical history was unremarkable and he never smoked. His family history revealed a brother with IBD. The physical examination on admission revealed a body temperature of 36.4 °C, regular pulse rate of 88/min, and blood pressure of 125/80 mmHg.

Results of the laboratory investigations were as follows: erythrocyte sedimentation rate (ESR): 44 mm/h (normal: <30), C-reactive protein (CRP): 6.5 mg/dL (normal: <3), white blood cells (WBC): 10,200/mm^3 (normal: 7,000-9,000/mm^3), rheumatoid factor (RF): <20 IU/mL (normal: <20), antinuclear antibodies (ANA): <40 (normal: <40), and human leukocyte antigen (HLA) B27 (+); hepatic and renal function tests were all normal. Tests for hepatitis revealed hepatitis B surface antigen (HbsAg) (+), hepatitis B envelope antigen (HBeAg) (-), anti-hepatitis B envelope antibody (anti-HBe) (+), and hepatitis B virus - deoxyribonucleic acid (HBV-DNA): 137 IU/mL; hepatitis C virus, hepatitis D virus, and human immunodeficiency virus (HIV) were all negative. He was confirmed as having an inactive carrier state of hepatitis B. Urinalysis results were also normal.

One month after his application, we began to follow the patient with a PsA diagnosis based on these findings. He was scheduled to start methotrexate (MTX); however, due to the diagnosis of inactive carrier state of hepatitis B, he was referred to the gastroenterology clinic. With three to six-month follow-up of HBV DNA and liver function tests on a regular basis, 7.5 mg/week MTX and 5 mg/week folbiol were prescribed. Topical corticosteroids with an anti-histaminic drug were advised for the skin lesions.

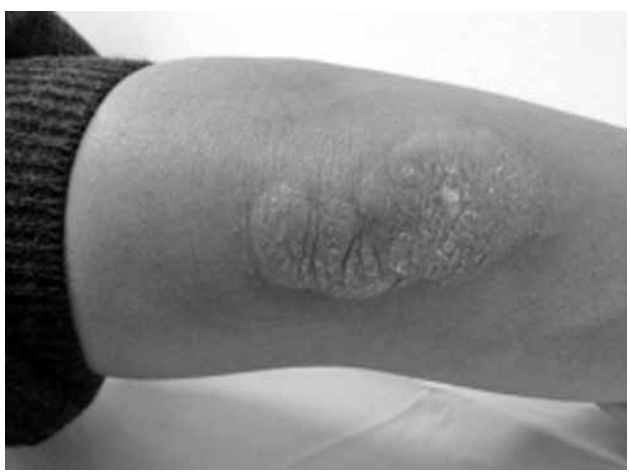

Figure 1. Psoriatic (pruritic and erythematous) skin lesions on the extensor side of the right forearm.

Clinical improvement was achieved one month later with only mild pain remaining in the first and second MCP joints without swelling. Laboratory findings showed ESR: 32 mm/h, CRP: 5.2 mg/dL, and WBC: 8,700/mm^3. Psoriatic skin lesions disappeared completely.

Approximately six months later, he presented with abdominal pain and changes in bowel habits, i.e. diarrheal episodes. No infectious agents were identified in the stool specimens. *Clostridium difficile* toxin was negative in the feces. On suspicion of IBD, colonoscopy was performed, which demonstrated hyperemic eroded areas in the terminal ileum mouth, and edema and multiple exudative ulcers in the ileum, varying in diameter (with the largest being 5-6 mm) (Figure 2). Biopsies of the affected colon showed mucosal inflammation, characterized by focal infiltration of neutrophils, cryptitis and crypt abscess, and non-necrotizing granulomas composed of epithelioid histiocytes. Based on the colonoscopic and histological findings, the patient was diagnosed with localized ileocolonic CD.

As the Crohn's Disease Activity Index (CDAI) was <150, indicating non-active disease, no medical treatment was provided.[10] The patient was kept under a close clinical follow-up and, 10 days later, his abdominal symptoms disappeared and the number of defecations was reduced. There was also no increase in clinical activity of cutaneous, joint, and intestinal symptoms during a follow-up of three months. The patient still remains under follow-up in both our clinic

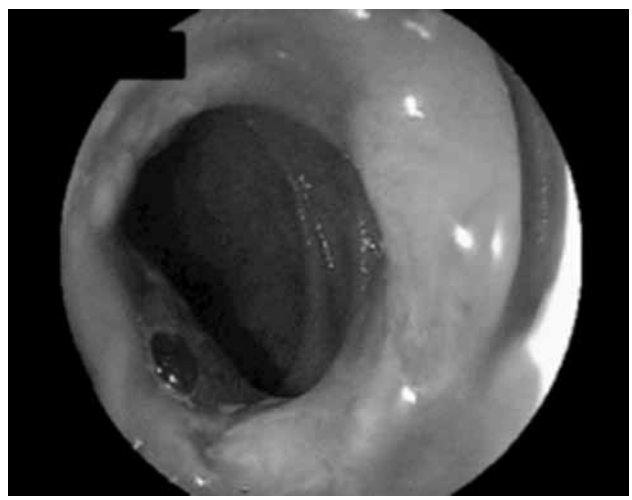

Figure 2. A colonoscopy image showing hyperemic eroded areas in the terminal ileum mouth, and edema and multiple exudative ulcers, of varying diameter (with the largest being 5-6 mm), in the ileum.

and the gastroenterology clinic with the diagnoses of PsA and CD.

Case 2- A 45-year-old male diagnosed with RA four years previously was under follow-up in our outpatient clinic. He was admitted to our hospital with complaints of subfebrile temperature, exacerbated lower abdominal pain, and diarrhea for the past three weeks which was aggravated for three days with bloody diarrhea four to five times/daily. His RA was stable for the last two years under treatment with leflunomide 20 mg/day, salazosulfapyridine (SASP) 1000 mg/day bid, and hydroxychloroquine 200 mg/day bid. He sometimes used diclofenac potassium suppositories, when his arthralgia was severe. He had a history of adverse events, which included elevation in the liver function tests twice. As MTX was suspected as the cause, it was discontinued, and leflunomide was started. Since the withdrawal of MTX, there was no recurrence of elevation in the liver function tests. His medical history was unremarkable. He had smoked one pack of cigarettes per day for >20 years. His family history revealed that his mother also had RA.

On admission, his physical examination revealed A body temperature of 37.4 °C, regular pulse rate of 94/min, and blood pressure of 110/70 mmHg. No signs of arthritis, cutaneous rash, sicca syndrome, photosensitivity, orogenital ulcers or Raynaud's phenomenon were observed. Heart sounds were clear with regular sinus rhythm, and no rales were audible in the lung fields.

Results of laboratory tests were as follows: ESR: 52 mm/h (normal: <30), CRP: 8.4 mg/dL (normal: <3), WBC: 11,500/mm^3 (normal: 7,000-9,000/mm^3), RF: 347 IU/mL, anti-cyclic citrullinated peptide (anti-CCP): 2,000 IU/mL, and ANA: <40. Hepatic and renal function tests were all normal. Urinalysis results were also normal, and the stool culture revealed a normal flora. Also, no infectious agents were identified in the stool specimens including *Entamoeba histolytica* and *Clostridium difficile*.

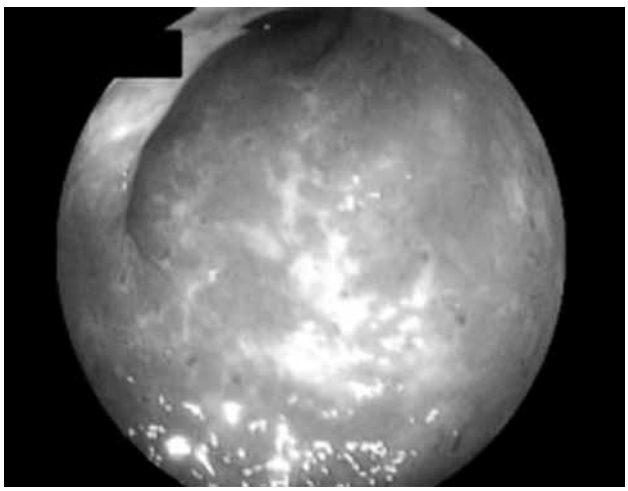

Figure 3. A colonoscopy image showing diffuse mucosal fragility, contact bleeding, loss of vascular appearance, ulceration, and granularity limited to the splenic flexure.

Chest X-ray revealed no abnormalities, such as pneumonia, interstitial pneumonitis, cardiomegaly or pleural effusion. Abdominal X-ray revealed no formation of air-fluid level or free-air. Owing to the probability of IBD, the patient underwent colonoscopy, which demonstrated diffuse mucosal fragility, contact bleeding, loss of vascular appearance, ulceration and granularity limited to the splenic flexure (Figure 3). Biopsies of the affected colon showed distorted crypt architecture, inflammation of crypts, crypt abscesses, and inflammatory cells in the lamina propria. Based on the colonoscopic and histological findings, the patient was diagnosed with moderate, left-sided UC.[11] Mesalamine (5-aminosalicylic acid) enema 1 g/day was added to the existing SASP therapy. Treatment led to dramatic improvement in the clinical symptoms and signs, without any adverse reaction, and to normalization of laboratory tests two weeks later. At the final visit to the outpatient clinic three months later, the patient was still in complete remission with respect to joint and intestinal symptoms. The patient remains under follow-up in both our clinic and the gastroenterology clinic with the diagnoses of RA and UC. A written informed consent was obtained from each patient.

DISCUSSION

Coexistence of RA or PsA with IBDs is rarely observed.[12] Clinical, pharmacological, and epidemiological evidence supports the hypothesis that CD and PsA may share some common genetic control in the pathways of inflammation.[13] In a previous study, an association was revealed between the known CD susceptibility locus, CARD15, and PsA, and it was recognized that patients with CD had an increased risk of PsA development.[14] Recently, a functional haplotype mapping to the organic cation transporter genes was identified as a second CD susceptibility locus.[15] Ho et al.[13] concluded that the OCTN haplotype previously associated with CD was also associated with PsA. Furthermore, they showed that this association was unique to PsA, being independent of both psoriasis

and undifferentiated inflammatory arthritis. In a small study, the prevalence of microscopic inflammation in macroscopically normal colonic mucosa was higher among patients with psoriasis and PsA without bowel symptoms than in patients without psoriasis.[16]

Li et al.[17] observed a particularly high risk of CD among patients with psoriasis with PsA, longer duration of psoriasis, and earlier onset of psoriasis. Such manifestations may reflect greater ongoing inflammation, which could be associated with an increased susceptibility to CD. Although the first case had only a four-year history of psoriasis beginning at the age of 45 years, which does not meet the criterion for earlier onset of psoriasis, the association may be due to sharing a greater number of genetic loci or pathogenic mechanisms with CD and PsA.

Psoriatic arthritis complicated by CD and hepatitis B is a rare clinical association; therefore, a clear consensus regarding treatment has not been established, yet. Crohn's disease and PsA may improve with immunosuppressants; however, hepatitis B can be reactivated, and with cancer chemotherapy, reactivation of hepatitis can occur at a rate of 20 to 50%. Meticulous and close screening of patients with hepatitis B before immunosuppressant treatment and during follow-up is inevitable in an appropriate clinical setting.

Crohn's disease usually involves the ileum and colon; however, it can also affect every part of the gastrointestinal tract. The inflammation is often transmural with episodic progression. Typical manifestations include discontinuous involvement of different segments of the gastrointestinal tract and the development of complications such as intestinal granulomas, strictures and fistulas.[10,18] The first case had the typical localization of CD (terminal ileum) and did not develop any of the aforementioned complications.

Rheumatoid arthritis complicated by UC has been reported rarely (no more than 0.14-0.8%).[12,19] In a prospective cohort conducted among patients with UC, Aoyanagi et al.[20] found no case overlapping with RA; however, they reported cases of RA complicated by IBD. Utsunomiya et al.[21] reported a 0.4% prevalence of RA in 5,833 patients with UC. Sawada et al[22] reported the same prevalence in a smaller study with 1,433 patients. Snook et al.[23] reported only seven cases of RA among 858 patients with UC. For pathogenic mechanisms of the association between RA and UC, it is suggested that changes in gut flora play an important role in the outbreak of IBD.[24] On the other hand, accumulation of HLA data may provide a potential clue on this relationship.[25] Several studies carried out in patients with UC and controls have suggested that HLA-DR4 acts as a protective factor against colitis.[26] This can suggest the rare association, as the antigen of the Class II major histocompatibility complex plays an important role in the pathogenesis of RA.

Ulcerative colitis involves the rectum, and may affect part of the colon or the entire colon (pancolitis) in an uninterrupted pattern. The inflammation is typically non-transmural, confined to the mucosa, with episodic progression. Depending on the part of the colon involved, it can be designated according to the Montreal classification as proctitis (E1), left colitis (sigmoid and descending colon), or extensive colitis (pancolitis).[27] The second case was diagnosed with moderate, left-sided UC based on the colonoscopic and histological findings.

Colitis can complicate the RA course. When colitis appears in RA patients, a differential diagnosis should be made between drug-induced colitis, ischemic colitis due to vasculitis associated with RA, and secondary amyloidosis.[28] Some reports have indicated that therapeutic agents for RA, such as non-steroidal anti-inflammatory drugs (NSAIDs), gold salts, and D-penicillamine are associated with various types of gastrointestinal complications.[29-31] The use of immunosuppressive drugs in the treatment of UC can also play a relevant role in the low frequency of the association with RA. Drugs, such as sulfasalazine and corticosteroids, inhibit the systemic inflammatory response, suggesting the lower incidence of other autoimmune pathologies concomitantly with IBD. In contrast, our case was not treated with gold salts or D-penicillamine. No vasculitic lesion was found in the pathohistological examination, and no other vasculitis symptoms such as scleritis and interstitial pneumonitis were observed. Recent clinical studies have demonstrated that the incidence of amyloidosis confirmed by biopsies in RA patients is about 10%.[32] Kato et al.[33] reported a suggestive case of gastrointestinal amyloidosis secondary to RA manifested as pancolitis resembling UC. The histopathological examination of biopsies taken from colorectal mucosa and rectal mucosa identified no vasculitic lesions or amyloid deposits in our patient. Based on these reasons and endoscopic and pathohistological findings, the colitis was diagnosed as UC.

Psoriasis, PsA, and IBD also share some common environmental risk factors. Smoking has been associated with increased risk of psoriasis, despite

controversial evidences on PsA.[34,35] However, cigarette smoking affects IBDs differently: smokers are at an increased risk for CD and tend to have more severe disease, whereas former smokers and non-smokers are at a higher risk for UC.[6] The first case never smoked, while the second case smoked one pack per day for >20 years, which is not consistent with the literature with respect to IBD. Anti-CCP seems to be directly related to smoking, which amplifies the process of citrullination of autoantigens. High concentrations of anti-CCP are almost exclusively associated with RA, which tends to be consistent with our second case.

The clinical effectiveness of mesalamine suspension enema for the treatment of UC has been established based mainly on direct contact with the damaged colonic mucosa.[36] The second case received SASP 1000 mg/day bid for RA. Although SASP was used as treatment in RA as well as IBD, UC appeared despite administration of SASP. Mesalamine enema (1 g/day) in this case demonstrated a significant and rapid clinical efficacy.

In conclusion, in the event of complaints related to the gastrointestinal tract in patients with RA or PsA, in an effort to prevent diagnostic delay, the rare association of IBD should be considered, and the clinical evaluation and multidisciplinary interventions should be tailored to control the autoimmune process. However, further studies are needed to elucidate the mechanisms underlying the association between RA, PsA, and IBD for treatment approaches which may modulate their occurrence or activity.

Declaration of conflicting interests

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