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CASE REPORT

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An HLA-B27-positive patient diagnosed with ulcerative colitis 15 years after the onset of arthropathy

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Abstract A 28-year-old woman had persistent pain of both hip joints since the age of 13 years. X-ray analysis showed destructive changes in both hip joints and ossification of sacroiliitic joints. The patient had mild diarrhea and slight abdominal pain for 8 years. Blood-stained stool was not noticed. Barium enema showed changes consistent with the diagnosis of ulcerative colitis (UC). Inflammatory bowel syndrome should be considered in patients with persistent coxitis, even in the absence of severe abdominal symptoms.

Key words Coxitis · HLA-B27 · Salazosulfapyridine · Ulcerative colitis (UC)

Introduction

Patients with ulcerative colitis (UC), a chronic inflammatory disorder involving mainly the large intestine, present with abdominal pain, diarrhea, and blood-stained stool. Arthropathy occurs in some patients with UC, although the frequency of this complication varies greatly among published reports, ranging from 4% to 62% of UC patients.[1–5] Both large and small joints may be affected. Arthropathies with inflammatory bowel diseases (IBD) are usually considered as part of a larger entity known as "seronegative spondyloarthropathies," which includes ankylosing spondylitis, Reiter's syndrome, and psoriatic arthritis.

Because typical cases of UC or Crohn's disease are usually not difficult to suspect and to diagnose, it is generally considered that arthropathies with IBD can be easily recognized as well. We report here a patient with UC complicated by arthropathy, whose UC was undiagnosed for 15 years from onset of the initial symptoms. Our experience suggests that it is important to suspect this condition even in the absence of severe abdominal symptoms.

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Case report

A 28-year-old woman was admitted to our hospital in July 2000 because of severe pain in both hip joints. She first experienced pain in the right hip joint in 1985. No abnormality was noted on the X-ray of the hip joints, and nonsteroidal anti-inflammatory drugs (NSAIDS) were prescribed. Thereafter, apart from occasional right or left hip joint pain, which lasted for about 1 week and recurred once or twice a year, the patient was otherwise in good condition. From 1992, she developed occasional diarrhea and mild abdominal pain. No blood-stained stool was noticed, and the patient did not undergo any diagnostic examinations or specific therapies. Episodes of hip joint pain and lumbago gradually increased in frequency and severity. In 1996, she visited the local university hospital. Aseptic necroses of both femoral heads were suspected on plain X-ray and magnetic resonance imaging (MRI). NSAIDS were prescribed, but the patient stopped visiting the local hospital after 1 year. By 1999, bilateral hip joint pain became persistent and worsened on long walks and exercise. In March 2000, she developed severe right hip joint pain, and destructive changes in both hip joints were identified at a local orthopedic clinic. The pain subsided after 1 week of NSAID therapy. In June 2000, bilateral hip joint pain worsened, which was associated with fever of up to 38°C for 4 days. Serum C-reactive protein was elevated to 9.5 mg/dl. In mid-July, body temperature rose to 38.2°C, which was associated with lower abdominal pain and diarrhea. She was admitted to our hospital on July 19, 2000. Back pain was absent throughout.

On admission, body height was 162 cm and body weight was 52 kg. The patient was alert and well nourished. Mild tenderness on the lower abdomen was present, but abdominal guarding, rigidity, and rebound pain were absent. Range of motion restriction and movement pain were present in

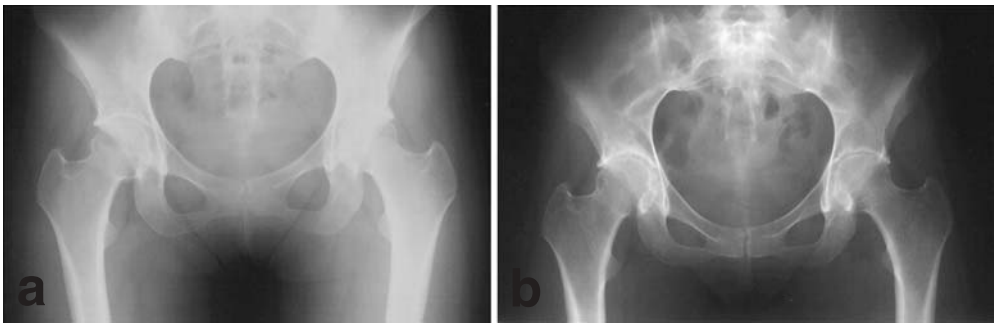

Fig. 1. **a** X-ray of both hip joints taken September 1996. **b** X-ray of both hip joints taken October 2000. Progression of destructive changes in both hip joints is apparent. Ankylosis of sacroiliac joints is also evident

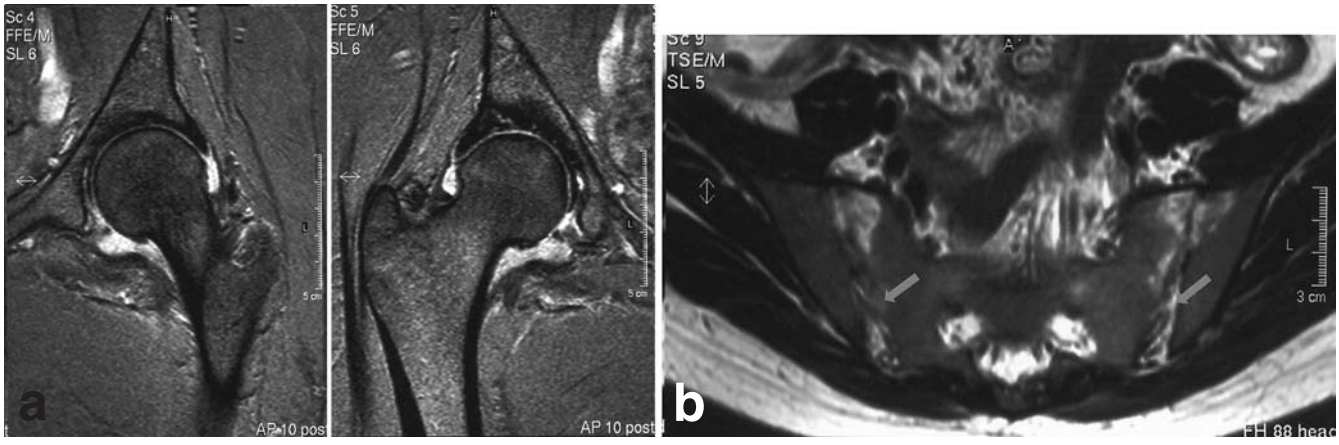

Fig. 2. Magnetic resonance imaging taken July 2000. Protrusio acetabuli and secondary osteoarthritic changes are evident in both hip joints. Ankylosis of sacroiliac joints is also apparent. **a** T2-weighted images of both hip joints. **b** T2-weighted image of the pelvis. Sacroiliac joints are indicated by *arrows*

both hip joints, but other joints showed no tenderness or swelling. No skin lesions were present. Laboratory findings included leukocyte count of 8400/μl, hemoglobin 9.2 g/dl, platelets 40.7 $\times$ 10^4/μl, total protein 7.4 g/dl, albumin 3.6 g/dl, aspartate aminotransferase 9 IU/l, alanine aminotransferase 8 IU/l, lactate dehydrogenase 115 IU/l, blood urea nitrogen 11.9 mg/dl, creatinine 0.5 mg/dl, IgG 1672 mg/dl, C-reactive protein 6.91 mg/dl, erythrocyte sedimentation rate 84 mm/h, ferritin 18 ng/ml, C_3 88 mg/ml, C_4 43 mg/ml, and CH50 44.6 U/ml. Serum complements were within the normal ranges, and autoantibodies, including antinuclear antibody, anti-SS-A antibody, anti-RNP antibody, and rheumatoid factor, were all negative. Urinalysis was normal. Occult blood in the stool was negative. Radiological examination showed protrusio acetabuli and secondary osteoarthritic changes in both hip joints and ankylosis of both sacroiliitic joints (Fig. 1b). MRI findings were consistent with those noted on plain X-ray films (Fig. 2). Comparison with previous films taken in 1996 (Fig. 1a) indicated significant progression of joint abnormalities. The spine was assessed by plain X-ray, MRI, and bone scintigram analysis, and none showed significant findings. Seronegative arthropathy was suspected, and Human leukocyte antigen (HLA) analysis revealed A2, A24, B27, B35, CW1, and CW3 haplotypes.

Barium enema showed lack of haustrations in the large intestine extending from the sigmoid colon to the hepatic flexure, and spiculation-like niches from the rectum to the cecum (Fig. 3a). Pancolonoscopy revealed friability and diffuse granularity in the entire colon, and biopsy specimens (Fig. 3b) showed inflammatory changes compatible with UC (Matts' grade 2). Crohn's disease was excluded, and the presence of UC was established. The condition was diagnosed as seronegative arthropathy associated with UC. Addition of 3000 mg/day of salazosulfapyridine to NSAIDS resulted in a substantial reduction of hip joint pain and abdominal symptoms. Introduction of steroids was postponed because of the significant reduction of symptoms and improvement of laboratory data. During admission, swelling on both elbow and wrist joints occurred but subsided after a few days without any changes in medication. The patient is currently well and is seen regularly in the outpatient department. She is maintained on salazosulfapyridine at 2000 mg/day (Fig. 4).

Discussion

Seronegative spondyloarthropathy is a well-known entity including diseases such as ankylosing spondylitis, Reiter's syndrome, and psoriatic arthritis. Arthropathies could also complicate IBD such as ulcerative colitis and Crohn's disease and are also included in this entity. Gravellese et al.[1]

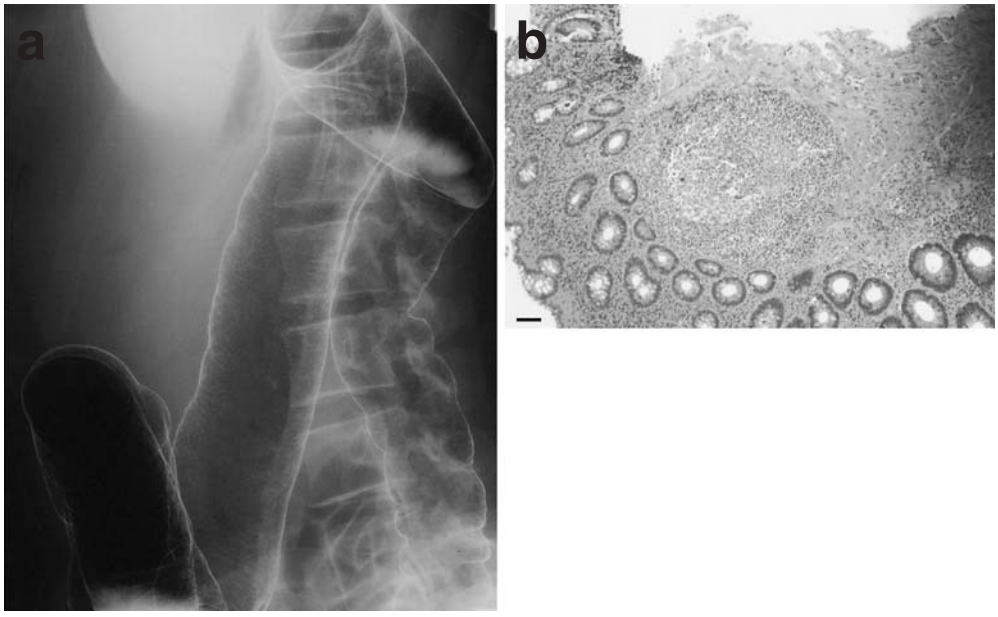

Fig. 3. **a** Barium enema taken October 2000. Note the typical lead-pipe like appearance and spicula formation. **b** Histopathological findings. Note the infiltration of lymphocytes and follicle formation, and ulcerative changes in the mucosa. Hematoxylin-eosin stain. *Bar* 100 μm

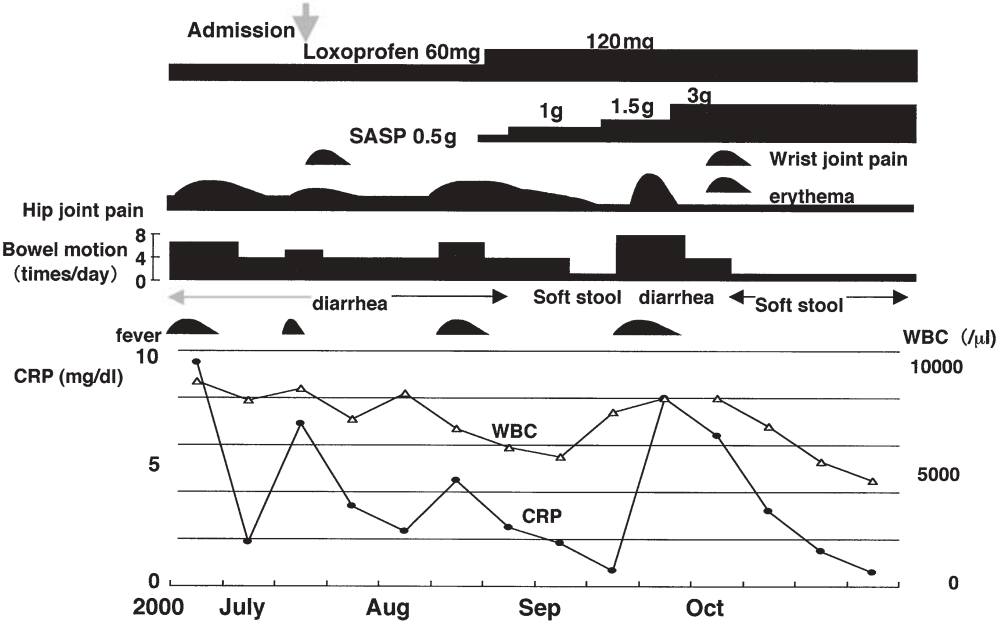

Fig. 4. Clinical course. *SASP*, Salazosulfapyridine; *CRP*, C-reactive protein; *WBC*, white blood cell

reported that arthropathies occur in about 15%–20% of patients with IBD. A recent study by de Vlam et al.[6] showed that 39% of patients with IBD had clinical articular manifestations. In particular, 6 of their 25 UC patients had unilateral or bilateral sacroiliitis. Other groups reported that arthropathies are seen in 4%–62% of patients with UC.[2–5,7,8] Orchard et al.[8] reported that among 976 patients with UC, peripheral arthropathy occurred in 59 (6.1%). Among these patients, arthropathy was present before diagnosis of UC in 6 of them, and at diagnosis of UC in another group of 7 patients.[8] Coxitis occurs in about 7% of patients with peripheral arthropathy complicating UC, and is relatively rare compared with wrist, metacarpophalangeal, knee, or ankle involvement.[8] Hip joint involvement occurs in about 10% of patients.[8] Typically, arthritis in IBD patients occurs concurrent with or after the onset of IBD, although patients in whom arthritis predated the bowel symptoms have been reported.[9] Klausen et al.[10] reported a case of seronegative rheumatoid arthritis, in whom UC developed after 32 years of arthritis history. This patient had bilateral sacroiliitis, Lubinus prothesis of the right hip joint, and was positive for HLA-B27, but without abnormalities in the vertebra. Some of the features of this patient are similar to those of our patient, although the onset of UC in the patient reported by Klausen et al.[10] was sudden, with severe weight loss and 10–20 bowel motions/day of watery and blood-mixed stools. It is also generally considered that the flares of bowel symptoms and arthritis coincide with each other.[9]

HLA analysis in our patient revealed a HLA-B27 haplotype, which is known to be associated with ankylosing spondylitis, psoriatic arthropathy, and Reiter's syndrome. Previous studies reported that HLA-B27 in patients with IBD is associated with ankylosing spondylitis and/or sacroiliitis,[2,11] but not with enteropathic peripheral arthropathy.[11] Mielants et al.[12] performed ileocolonoscopy in 354 patients with spondyloarthropathy. Among their patients, 88 patients had acute inflammatory lesions, and 121 had chronic inflammatory lesions, although the authors did not report the prevalence of UC in their patients. Presence of HLA-B62 was associated with the presence of chronic inflammatory lesions, but the prevalence of HLA-B27 was similar between patients with or without inflammatory lesions. Interestingly, in the aforementioned study, the effect of salazosulfapyridine on inflammatory symptoms of the locomotor system was more favorable in patients with inflammatory bowel lesions than in those without such lesions. Another study by the same group showed that among patients with spondyloarthropathy, HLA-B27-positive patients were mainly men who were likely to have ankylosing spondylitis and a positive family history of spondyloarthropathies.[13] On the other hand, Hyla et al.[14] reported that in their 89 patients with IBD, only 1 of 11 patients with radiographic sacroiliitis had the HLA-B27 antigen, whereas 3 of 4 patients with ankylosing spondylitis were HLA-B27 positive. Thus, the association between sacroiliitis and HLA-B27 in patients with IBD does not seem to be clear at present. Our patient, although positive for HLA-B27, showed no symptoms suggestive of psoriasis, ankylosing spondylitis, or Reiter's syndrome. However, although there were no abnormalities on the spinal X-ray and MRI at this point, it is possible that this patient might develop ankylosing spondylitis in the future. Hip joint involvement occurs in 20%–40% of patients with ankylosing spondylitis, and Will et al.[15] reported that compared with male ankylosing spondylitis patients, female patients tended to have milder spondylitis but more prevalence of peripheral arthropathies. Thus, our case particularly needs a closer follow-up.

An important feature in our patient is that by the time the correct diagnosis was made, significant destruction of both hip joints had already occurred, suggesting that replacement of these joints would be inevitable in the not-so-distant future. Our patient suffered from minor episodes of diarrhea and abdominal pain for 8 years, but because there was no blood-stained stool or severe abdominal pain, IBD was not suspected. Leirisalo-Repo et al.[7] reported that among 85 patients with spondyloarthropathy but without previously diagnosed bowel diseases, 44% had endoscopic lesions as detected by colonoscopy. However, UC was diagnosed in only one patient. In their study, features suggestive of Crohn's disease were more frequently found in patients with chronic spondyloarthropathies. Their findings indicate that the presence of IBD is underestimated with patients with arthropathies, and that the presence of IBD should be ruled out when patients present with a long history of episodic arthritis or joint pain, even when the patient does not complain of gastrointestinal symptoms suggestive of this condition. A timely diagnosis and adequate treatment of IBD would aid in the preservation of joint function in these patients.

NSAIDS and salazosulfapyridine are often used for treatment of arthropathies associated with IBD. These agents were also useful in our patient, and severe joint pain significantly subsided after such therapy. We would have treated our patient with oral steroids, if flares of either articular or bowel symptoms had occurred. Recently, several studies have documented the efficacy of infliximab, an anti-TNFα antibody, currently made available for the treatment of rheumatoid arthritis, in the treatment of UC.[16,17] In addition, Serrano et al.[18] showed that treatment of pediatric IBD patients with infliximab was effective not only with respect to bowel manifestations, but also with respect to their arthropathies. Infliximab therapy should be considered when the disease is refractory to salazosulfapyridine and steroids.

In conclusion, we reported a 28-year-old patient with coxitis and sacroiliitis, whose ulcerative colitis was diagnosed 15 years after the onset of joint pain, and 8 years after the onset of bowel symptoms. Arthropathies associated with IBD seem to be underdiagnosed conditions, and IBD should be considered in patients with arthropathies of unknown etiology.

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