Two Cases of Rheumatoid Arthritis that Exhibited Bilateral Hip Joint Destruction since Early Stage of Onset

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Abstract
Here, we report two cases of rheumatoid arthritis (RA) that exhibited bilateral hip joint destruction since early stage of onset. Both patients were postmenopausal women. Arthritis developed at the right shoulder joint while the patient was on non-steroidal anti-inflammatory drugs and pain in the right shoulder joint was relieved. However, she subsequently developed bilateral destruction of the hip joints with acetabular dysplasia, which progressed rapidly during the next 6-12 months, for which she had to undergo bilateral total hip arthroplasty. Our second case featured bilateral hip joint destruction. Despite the single administration of methotrexate and the subsequent use of biological products, the efficacy of this treatment gradually weakened. However, the biological product used as the fifth agent was effective, and the progression of joint destruction was suppressed for 3 years until the final examination. RA rarely occurs in the hip joints in the early stage of the disease, but when it does, the process of joint destruction may progress rapidly in patients with a morphological abnormality such as acetabular dysplasia. Therefore, when hip arthralgia appears, it is necessary to perform morphological evaluation by X-ray photography and follow-up in parallel with active treatment using disease-modifying anti-rheumatic drugs.

Keywords: Rheumatoid arthritis; Hip joint; Rapidly progressive destruction; Diagnosis of early RA; Acetabular dysplasia

Introduction
Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology which may occur in any joint in the body. Small joints such as those of the hands and feet are the first to be affected, followed by major joints such as those of the hip and knee [1,2]. Although rheumatoid arthritis develops in the hip joint in 5% to 15% of cases, the progression of joint destruction is gradual in most cases [3].

Here, we report on two cases of early stage RA wherein the patients developed bilateral hip joint destruction since early stage of onset but underwent different clinical courses. The patient provided written informed consent for the publication of their data and accompanying images.

Case Presentation
Case 1
The patient was a 64-year-old unemployed woman who had no history of smoking. Her height and weight were 155 cm and 55 kg, respectively. Her elder sister had been diagnosed with polymyalgia rheumatica. The patient had undergone valvuloplasty for mitral regurgitation 11 years earlier, but did not notice any pain in any joint including the hip joint. Approximately 1 year prior to presentation, she visited a nearby clinic for pain in the right shoulder joint. Blood biochemistry showed rheumatoid factor (RF) of 15I U/mL and C-reactive protein (CRP) of 0.07 mg/dL.

Figure 1: MRI axial image taken one month after onset of pain in the right shoulder joint showing bone erosion and fluid accumulation at the proximal extremity of the humerus.

Though magnetic resonance imaging (MRI) revealed fluid accumulation accompanied by bone erosion in the proximal extremity of the humerus (Figure 1), she had a diagnosis of undifferentiated arthritis without aspiration of joint fluid, and pain in the right shoulder...
joint was relieved with the administration of non-steroidal anti-inflammatory drugs. However, 4 months before presentation, the patient had an MRI for pain in both hip joints which revealed bilateral bone erosion, fluid accumulation in the joints and acetabular dysplasia (Figure 2).

**Figure 2:** MRI coronal image taken 2 months after onset of pain in both hips showing localized giant cystic bone destruction (geode type) at the right ilium, bilateral fluid accumulation in the hip joints, and acetabular dysplasia.

Blood biochemistry at the time showed CRP of 0.10 mg/dL and anti-galactose-deficient immunoglobulin G antibody (CA-RF) of 47.9 AU/mL. The patient was referred to our hospital because of gradually increasing joint pain, radiographic findings of joint destruction, and worsening of claudication. Initial radiography revealed bilateral narrowing of the hip joints and flattening of the right femoral head (Figure 3A). On examination, the right and left Sharp angles were 45.1° and 43.7°, the right and left C-E angles were 16.3° and 19.8°, and the right and left acetabular head indexes were 58.8% and 70.1%, respectively. RF was 32 IU/mL, anti-cyclic citrullinated peptide (anti-CCP) antibody was <0.5 U/mL, matrix metalloproteinase-3 (MMP-3) was 340.0 ng/mL, QuantiFeron® was negative, CRP was 1.24 mg/dL, and erythrocyte sedimentation rate (ESR) was 67 mm/h. Due to the absence of pain anywhere other than the hip joint, the patient scored only 5 points in the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for RA 4) and her condition could not be classified as RA. Because the view that we doubted did not accept other causes of inflammatory arthropathy, we believed the condition to be atypical early RA and decided to start methotrexate (MTX) therapy at a dose increasing gradually from 6 mg/week and re-evaluate the diagnosis at a later date. Total hip arthroplasty (THA) was postponed for personal reasons, during which time the inflammatory reaction abated (CRP, 0.06 mg/dL; ESR, 35 mm/h) with MTX 8 mg/week, but joint destruction worsened on the right side (Figure 3B).

**Figure 3:** Frontal radiogram taken 4 months after onset of pain in both hip joints showing bilateral narrowing of hip joints and acetabular dysplasia; (A) Narrowing of the joint space was worse on the right side, with almost no joint space at all; (B) Two months later (6 months after onset), the right femoral head was depressed and flattened around the plane of loading and also deviated toward the anterolateral side; (C) The left joint space also disappeared 1 year after disease onset; (D) Patient had to undergo bilateral THA.

In December 2015, 2 months after MTX therapy started, we performed right THA and observed a light yellow effusion and synovial proliferation in the joint. The synovial fluid collected wasn't muddy. By the next day, the patient could sit on the bed and was discharged 1 month after surgery, walking with the help of a T-cane. Examination 2 months after surgery showed CRP of 0.1 mg/dL, ESR of 33 mm/h, and MMP-3 of 44.8 ng/mL. The patient continued to take oral MTX 8 mg/week and maintained a low disease activity score (DAS28ESR level=3.121) at 4 months immediately after right THA. However, because of the gradual progression of joint destruction on the left side and worsening of the joint pain (Figure 3C), left THA was performed 6 months after the first surgery (Figure 3D). The patient was discharged 1 month later. As at 10 months after the left THA, the patient remained in remission (DAS28ESR level=2.48), with no pain in the hip joints or any other joints. For two years since initial evaluation, hand X rays were normal and no subtle change was seen.

Histopathological examination of synovial tissue collected in the first THA showed proliferation of capillaries, and formation of lymphoid follicles on a background of villous proliferation of the synovium with inflammatory infiltrate including lymphocytes. A final diagnosis of RA was made based on these findings (Figure 4).
Figure 4: Histopathological examination showed proliferation of capillaries and formation of lymphoid follicles on a background of villous proliferation of the synovium with inflammatory infiltrate including lymphocytes. There were a few fibrin depositions. Lymphoid follicles were clear but rather small. Hematoxylin and eosin stain. Original magnification X4.0.

Figure 5: Frontal radiogram taken 10 months after onset of RA in left hand showing narrowing of the space in the left-hand joint and bone erosion in some carpal bones.

Figure 6: Frontal view of the bilateral hip joints XP immediately after the occurrence of left hip joint pain; (A) No narrowing of the hip joint or bone erosion was observed; (B) Before switching to Abatacept, the bilateral hip joint space narrowed and the femoral head was somewhat flattened; (C) Three years before the final examination, osteophyte formation-like osteoarthritis was observed under the femoral head, but little change was observed in the hip joints.
Case 2

The patient was a 59-year-old unemployed woman who had no history of smoking. Her height and weight were 152 cm and 59 kg, respectively. There was nothing of note in terms of the family history or medical history. Ten months ago, she had experienced pain in her left-hand joint and visited a nearby clinic. Since her anti-CCP antibody level was 15.4 U/ml, she was diagnosed with RA. The dose of MTX was gradually increased to 8 mg/week but was determined to have an inadequate effect, and she was referred to our hospital. At our initial examination, her CRP was 3.85 mg/dL and RF was 69 IU/mL. In addition to pain in the left hand joint, she complained of pain in the left hip and knee joints. X-ray identified joint destruction in the left-hand joint (Figure 5).

However, joint destruction was not observed in the hip joint. Her sharp angle measured 41.7° (right) and 43.0° (left), CE angle measured 34.1° (right) and 31.4° (left), and acetabular head index measured 92.9% (right) and 91.8% (left) (Figure 6A). Owing to elevated liver enzymes, the MTX dose was limited to 12 mg/week. Eleven months after onset, CRP was 4.85 mg/dl and DAS28ESR level was 4.409. Subsequently, a combination therapy of biological products was commenced. The medications used for treatment are shown below (in order of use). Adalimumab was discontinued because erythema was observed after the first administration. Due to secondary failure, golimumab, certolizumab pegol, and etanercept were discontinued at 8, 4, and 4 months, respectively. During this time period, destruction was observed in the bilateral hip joints (Figure 6B). After switching to abatacept, the disease activity decreased. Over the 3 years starting from 6 months after medication switching until the final examination (DAS28ESR level=3.144), disease activity was maintained at a low level. In the hip joint, there was a slight change in the osteoarthritis level and very little progression in joint destruction (Figure 6C).

Discussion

The 2010 ACR/EULAR classification criteria for RA are useful for classifying early RA patients [4-6]. However, in cases in which only the major joints are affected, such as in Case 1, scores are low and the expression of RF or anti-CCP antibody at the onset of RA is limited to approximately 50% [7], making early diagnosis difficult. MRI [8,9] and ultrasound [10-12] have attracted attention as techniques that can improve the diagnostic performance of the 2010 ACR/EULAR classification criteria in patients who are negative for CCP antibodies. However, because there is insufficient evidence, extensive clinical research on patients who are negative for CCP antibodies is necessary. CA-RF, one of the RA serum markers, has a slightly higher positive rate in healthy individuals and a high positive rate in those with RA despite lower specificity, as in those with RF [13]. Unlike anti-CCP and RF, CA·RF has a higher positive rate among patients who developed RA less than 1.5 years previously, accounting for approximately 70% of these patients. The positive rate is also as high as 50% in RF-negative sero-negative RA patients and 15-40% in patients with non-RA connective tissue disease. Case 1 exhibited bone erosion and synovial fluid accumulation in painful joints upon MRI diagnosis, and CA-RF was positive at the onset of hip joint pain in this case. However, it was presumed that RA was not diagnosed and treatment with DMARDs was not initiated.

Large-scale surveys in Europe and the United States have shown that commonly RA first develops in the hands, fingers, legs, and toes [1,2]. Similarly, there have been many Japanese reports regarding the initial development of RAs in the peripheral small joints. However, there have also been reports stating that the frequency of cases in which RA first develops in major joints, especially knee joints, is similar to that in which RA first develops in peripheral small joints [14]. Shoulder joints were the second most common sites of RA onset, following knee joints, whereas hip joints were the least common among the major joints included in the ACR/EULAR classification criteria. Although RA develops in the hip joint in 5 to 15% of cases, most instances occur during the late phase, and the progress of joint destruction is moderate [3]. Previous reports of rapid hip joint destruction associated with RA have all involved patients with established RA who were taking long-term steroids and who had high disease activity with DMARDs resistance, as observed in Case 2 [12,15,16]. We were unable to find previous reports involving early RA patients who did not take DMARDs or steroids, as observed in Case 1. Rapidly destructive coxarthrosis, which was extensively discussed by Postel and Kerbour [17] also followed a similar process. Despite the difficulty in diagnosing Case 1, the condition was eventually diagnosed as RA by pathological examination.

Generally, there are more male patients showing aged onset RA compared with juvenile onset RA, and reports highlight development in major joints, such as the shoulder joint [18]. However, a previous report, albeit limited to patients with RA developed less than 1 year ago, noted no sex difference with respect to the development of RA in the primary joints [2].

In two cases, the hip joint was not the first joint in which RA developed. However, these were both rare cases that developed RA in the bilateral hip joints since early stage of onset. We confirmed the importance of early diagnosis and early treatment in Case 1 and a treat-to-target strategy in Case 2. If RA develops in a hip joint with morphological abnormality, such as acetabulum dysplasia, joint destruction may progress [19]. However, if there is no morphological abnormality, it may be possible to suppress the progression of rapid hip joint destruction with appropriate treatment. If RA is suspected, we recommend the prescription of DMARDs centered on MTX from an early stage. When persistent and significant pain appears in the hip joint without any trigger, we recommend that physicians evaluate morphology by radiography and continuously check the progress of joint destruction.

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References


