

Case Report

## Alternative to Rituximab Therapy for a Patient with Ankylosing Spondylitis Who Was Unable to Continue Anti-TNF Therapy

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We herein present a case of a 38-year-old man who had bamboo spine and severe sacroiliitis and who was diagnosed with ankylosing spondylitis (AS). Infliximab (IFX) markedly improved the axial symptom but was discontinued due to the side effect of peripheral neuropathy. Switching from IFX to etanercept worsened the side effect. Rituximab (RTX) administration elicited a good response without side effects. RTX might be a suitable option for AS therapy when TNF inhibitors are difficult to use.

**Key words:** ankylosing spondylitis, rituximab, treatment

Ankylosing spondylitis (AS) is a chronic rheumatic disease that mainly affects the sacroiliac joint and spine. For axial manifestation of patients with AS, there are no evidenced-disease-modifying anti-rheumatic drugs, but the emergence of tumor necrosis factor alpha inhibitors (TNFi) has markedly improved the clinical symptoms of AS patients. Rituximab (RTX), a monoclonal antibody for CD20 that depletes B-cells, is already known to be effective for various rheumatic diseases, such as rheumatoid arthritis and systemic vasculitis.

Recently, RTX has been reported to show some response in TNFi-naive AS patients [1]. We herein report a case of AS in which the patient was unable to continue infliximab (IFX) due to adverse effects and was instead treated successfully with RTX. This case report was approved by the ethics committee of Okayama

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### Case Report

A 38-year-old man visited our hospital complaining of severe back pain and difficulty in neck movement in February 2010. He had been aware of lower back pain, which improved with exercise since 2002, and had been suffering from repetitive uveitis since 2009. On the first radiographic examination at our hospital in February 2010, he was already exhibiting a progressed “bamboo” spine (Fig. 1A, B) and disappearance of the sacroiliac joint space (Fig. 1C). Therefore, a diagnosis of AS was made promptly according to the modified New York criteria [2].

His symptoms were mainly axial involvements without peripheral arthritis or other extra-articular lesions,

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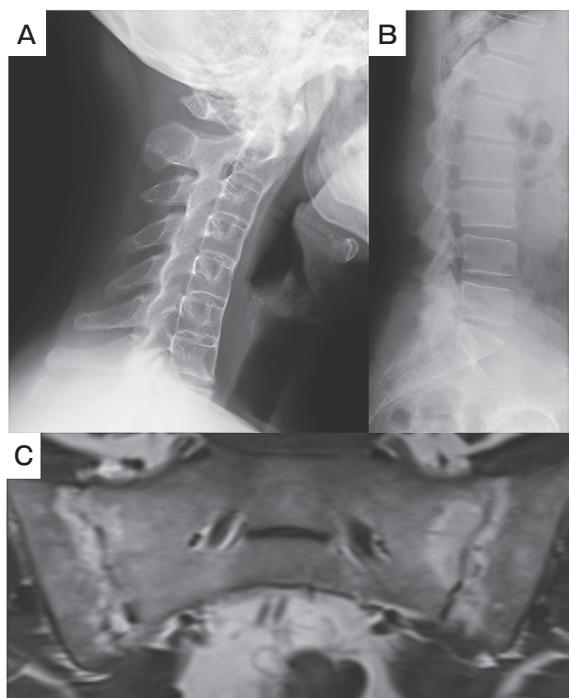
although he had a history of relapsing uveitis. He had difficulties with neck and back flexion. He did not have a history of psoriasis, inflammatory bowel disease, or relapsing aphtha. He had never had urethritis. His Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score was 6.06, and his Bath Ankylosing Spondylitis Functional Index (BASFI) score was 5.14. HLA-A24, HLA-B7, and HLA-B51 were positive and HLA-B27 was negative. Although NSAIDs, 8 mg of methotrexate (MTX) weekly, 5 mg of prednisolone (PSL) daily, and 180 mg of loxoprofen daily were started in March 2010, his axial symptoms did not improve. Therefore, in June 2010, 5 mg/kg of IFX, a TNFi, was added to his regimen. The first administration of IFX led to rapid and significant improvement, and the patient's BASDAI decreased from 7.74 to 5.10 in 2 weeks. However, a few days after the first administration of IFX, he felt numbness and pain in the upper and lower limbs with "glove and stocking" distribution. A neurological examination showed mild hypopalles-thesia of the lower limbs and a decreased Achilles tendon reflex. However, nerve conduction studies and magnetic resonance imaging (MRI) of the spine showed

no abnormalities. Although the numbness and pain in his extremities gradually improved as the days passed after the first IFX administration, his numbness became exacerbated after the second administration, 2 weeks after the first. In June 2011, even after IFX was replaced with 50 mg of etanercept (ETN), another TNFi, the numbness and pain in his extremities relapsed. ETN was then discontinued, and the numbness improved.

Two months after ETN was discontinued, the patient's BASDAI score remained high (5.40) with active axial symptoms. Therefore, after informed consent was obtained, 375 mg/m<sup>2</sup> of RTX was administered intravenously twice at biweekly intervals in October 2011. Two weeks after the first RTX administration, the patient's peripheral blood B-cells were completely depleted (from 323 to 0 cells/ $\mu$ l). His BASDAI score decreased from 6.39 to 3.56, and his serum C-reactive protein (CRP) levels also decreased, from 2.2 to 0.49 mg/dl. His back pain had kept improved for 10 months since the first RTX administration, even after the daily dosage of oral glucocorticoid was tapered from 4 to 2 mg and methotrexate was discontinued. In December 2012, the patient suffered from gradually exacerbating neck and back pain, which was correlated with the recovery of B-cells in the peripheral blood. His BASDAI and serum CRP levels were increased to 7.03 and 1.72 mg/dl, respectively. He was administered a second course of RTX therapy, after which his BASDAI decreased promptly to 2.56 (Fig. 2).

## Discussion

For predominant axial disease in patients with AS, NSAIDs and TNFi are recommended by ASAS/EULAR [3]. A previous meta-analysis indicated that a TNFi, such as adalimumab, ETN, or IFX, exhibited similar efficacy [4, 5]. However, 20-40% of all patients with AS treated with a TNFi changed their treatment due to inefficacy [6], and some patients had difficulty continuing with TNFi because of adverse effects. The present patient complained of numbness in his hands and feet after TNFi therapy, which was suspected to be TNF-related demyelinating disease. Our patient reported this numbness a few days after the initiation of TNFi therapy, so we surmised this symptom to indicate TNF-related neuropathy, though we found no abnormal findings with MRI and a nerve conduction study. Numerous case reports have reported demyelinating



**Fig. 1** A radiograph of the spine shows **A**) cervical spondylosis and **B**) linearization of the lumbar spine. Magnetic resonance imaging shows **C**) inflammation and narrowing of the sacroiliac joint.

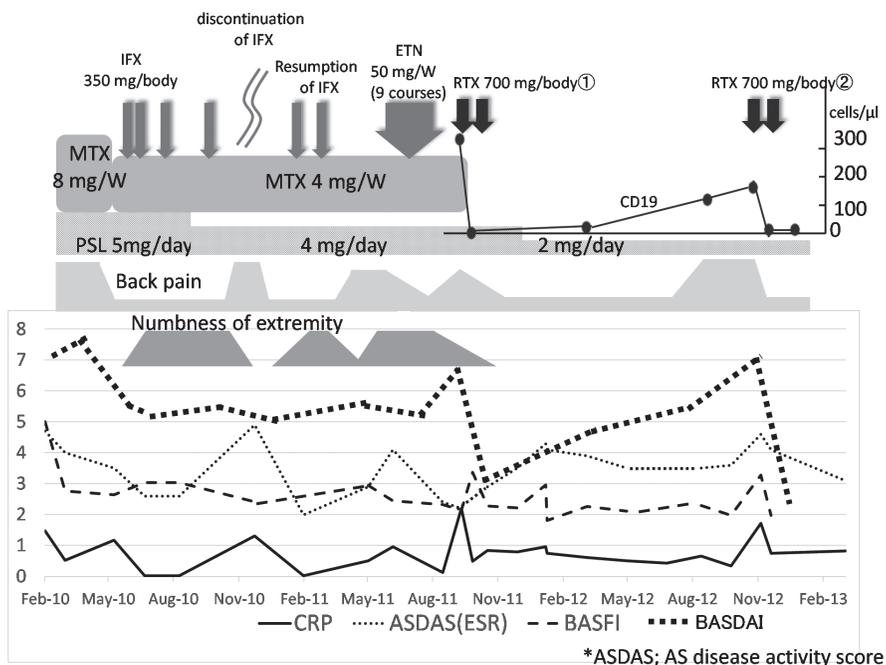


Fig. 2 Clinical course.

adverse effects in patients taking a TNFi, and there is a report, similar to our case, in which a patient treated with IFX developed a small-fiber sensory symmetrical polyneuropathy with normal electrophysiological studies [7]. The timing of the onset of TNFi-related neuropathy varied considerably, and there is even a case of extremely early onset of neuropathy, in which neuropathy started to worsen 8 h after the first infusion [8]. In our case, neuropathy occurred relatively early as an adverse effect of IFX.

In addition to TNFi, various biologic agents, such as secukinumab, ustekinumab, anakinra, sarilumab, tocilizumab, and abatacept, have been evaluated as alternative treatments for patients with AS [9-15]. However, they do not appear able to exceed the efficacy of TNFi at present.

RTX elicited a good response in the present case, though complete remission was not achieved. The efficacy of RTX in AS patients was reported in several cases [16-18]. Radiographic improvement with RTX has been demonstrated, resulting in a marked improvement of the high signal intensity on sacroiliac joint inflammation in clinical symptoms as well as MRI findings in active AS patients with axial disease and left knee arthritis without TNFi [19]. Although RTX did not show a therapeutic effect in any of the 10 patients with

TNF failure studied, some response was noted in 10 TNF-naïve patients in an open study [1]. Another open study demonstrated that RTX had greater efficacy in TNF-naïve than TNF-failure patients [20]. Therefore, we considered that RTX is indicated in patients with AS who, despite responding well to TNFi treatment, had difficulty continuing TNFi due to adverse effects.

Pathologically, several reports have demonstrated an association between B-cells and AS. Some reports showed that T-cells and macrophages were histologically dominant in active sacroiliitis of AS and spondyloarthritis [21,22], whereas CD20<sup>+</sup>B-cells were also detected immunohistochemically in the spine of AS patients. Heiner A *et al.* reported a significant difference in the number of CD20<sup>+</sup>B-cells between AS patients with persistently inflamed joints and AS patients without active joint inflammation [23]. It has been reported that the percentage of CD19<sup>+</sup>B-cells in AS patients was positively correlated with BASDAI scores [24]. In addition to the presence of B-cells in inflammatory regions, it has been revealed that immunoglobulin variable heavy chain (IgVH) 2 was overexpressed in the peripheral blood of AS patients, indicating that different rearrangements in IgVH genes might cause abnormal molecular events in B-cells [25]. In the present case, the axial symptom flared as the peripheral B-cell num-

ber increased. These reports suggested that B-cell activation is partially related to the pathology of AS. Therefore, B-cell depletion could be a potential targeted treatment for AS.

In conclusion, we experienced a patient with AS who was forced to discontinue TNFi treatment but ultimately had an acceptable response to RTX. Because B-cells may play an important role in the pathogenesis of AS, RTX may be an alternative treatment option.

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