

[CASE REPORT]

A Rare Case of Ankylosing Spondylitis Coexisting with Relapsing Polychondritis, Antiphospholipid Syndrome, and Myelodysplastic Syndrome

Hanna Park, Jung Gon Kim and Wan-Uk Kim

Abstract:

Ankylosing spondylitis (AS) is rarely accompanied by other autoimmune diseases and/or hematologic disorders. We herein report a 46-year-old man with AS coexisting with relapsing polychondritis (RP), antiphospholipid syndrome (APS) and myelodysplastic syndrome (MDS). While receiving anti-TNF therapy for AS, the patient developed anemia and was diagnosed with MDS. After six months, he developed swelling and redness of the nose and both auricles. RP was diagnosed by an ear biopsy. Afterward, during the evaluation of a repeated fever, APS was diagnosed. This case of AS with multiple autoimmune diseases and hematologic malignancy successfully responded to a Janus kinase inhibitor (baricitinib).

Key words: ankylosing spondylitis, relapsing polychondritis, antiphospholipid syndrome, myelodysplastic syndrome, Janus kinase inhibitor

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Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease affecting the axial skeleton and characterized by inflammatory back pain (1). Relapsing polychondritis (RP) is a rare autoimmune disease manifested by recurring inflammation of cartilaginous tissues throughout the body, including the ears, nose, respiratory tract, joints, and cardiovascular system (2, 3). Myelodysplastic syndrome (MDS) is a clonal disorder characterized by peripheral cytopenia and dysregulated hematopoiesis of the bone marrow (4). Although there are a few case reports of AS coexisting with RP or MDS, cases of AS coexisting with three or more other rheumatologic and/or hematologic disorders have not been reported previously.

We herein report a patient who was diagnosed with AS, RP, MDS, and antiphospholipid syndrome (APS).

Case Report

A 43-year-old Korean man was diagnosed with AS according to the modified New York criteria (5), in February 2018 (bilateral sacroiliitis, grade 3 in February 2018, and grade 4 in March 2021; Fig. 1A). He was positive for the human leukocyte antigen (HLA)-B27 and there was no family history. He was treated with a non-steroidal anti-inflammatory drug (NSAID) and sulfasalazine, but the lower back pain persisted. In October 2018, golimumab, a TNF α inhibitor, was first prescribed to control his pain. The symptoms and systemic inflammatory markers were partly controlled, but anemia developed, and the patient's condition deteriorated gradually. In May 2019, golimumab was withheld, and the patient was referred to another university hospital.

At that time, blood cell values were as follows: hemoglobin, 5.6 g/dL [mean corpuscular volume (MCV) 103.4 fL, mean corpuscular hemoglobin (MCH) 33.5 pg]; white blood cell count, $6.87 \times 10^3/\mu\text{L}$ (differential count: 50% segmented

Division of Rheumatology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, the Catholic University of Korea, Republic of Korea

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Correspondence to Dr. Wan-Uk Kim, wan725@catholic.ac.kr

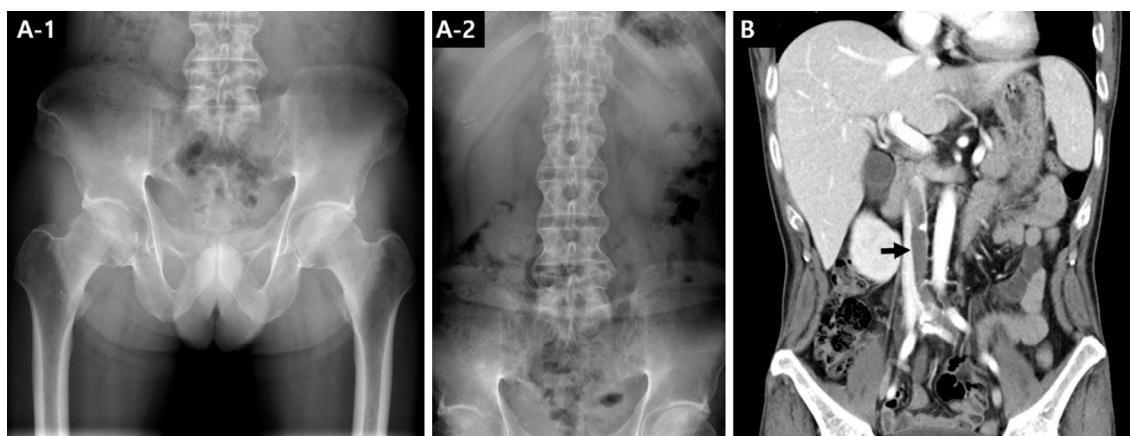


Figure 1. Radiographic findings. (A-1) Bilateral symmetric sacroiliitis; both grade 4. (A-2) Syndesmophytes along the D- and L-spine. (B) Diffuse thrombus from the infrarenal IVC to the left iliac vein (arrow).

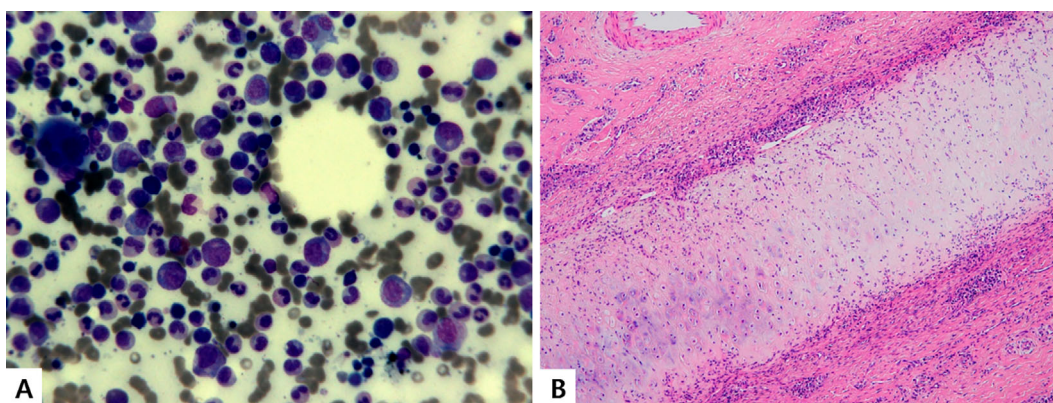


Figure 2. Pathologic findings. (A) Bone marrow aspirate smears show hypercellular marrow with 3-lineage dysplasia (Wright-Giemsa, $\times 200$). (B) Inflammatory cells including mononuclear cells infiltrate into auricular cartilage and adjacent soft tissue (Hematoxylin and Eosin staining, $\times 200$).

neutrophils, 40% lymphocytes, 4% monocytes, and 6% eosinophils); platelet count, $117 \times 10^9/L$. The erythrocyte sedimentation rate (ESR) was 73 mm/h, and the C-reactive protein (CRP) level was 67.4 mg/L. The peripheral blood smear showed macrocytic normochromic anemia, no anisocytosis, and no poikilocytosis. Biochemical tests were all within normal ranges. The serum ferritin level and transferrin saturation were elevated (2,142.9 ng/mL and 51%, respectively). The serum iron level was 113 $\mu\text{g/dL}$. There was no vitamin B12 deficiency or folic acid deficiency. Serologic tests for human immunodeficiency virus (HIV) and hepatitis B and C were all negative. Tests for serum anti-nuclear antibodies and anti-neutrophil cytoplasmic antibodies were negative.

Bone marrow aspiration and a biopsy were thus performed, revealing multilineage dysplasia characterized by dyserythropoiesis, dysgranulopoiesis, and dysmegakaryopoiesis with hypercellularity (Fig. 2A). The myeloid-to-erythroid ratio was 3:1, and about 2% blasts were present. A chromosome study demonstrated a normal karyotype (46, XY). Therefore, the patient was diagnosed with MDS with

multilineage dysplasia in November 2019.

In February 2020, he participated in a clinical trial and received imetelstat, but the transfusion-dependent anemia continued, which led to the development of thrombocytopenia. The patient developed swelling and redness of the nose and both auricles, followed by CRP elevation (up to 112.3 mg/L). An ear biopsy was performed (Fig. 2B), and RP was diagnosed according to Damiani and Levine's criteria (6), in April 2020. The patient began to take NSAIDs and steroids for RP (i.e. naproxen and prednisolone 30 mg), stopped participating in the clinical trial for MDS, and started treatment with 5-azacytidine (Vidaza[®]). Afterward, the frequency of blood transfusions due to anemia and thrombocytopenia was reduced, as were the manifestations of RP.

In November 2020, the patient went to the emergency center with acute mental confusion, seizure, and emotional lability. Blood and urine tests were not suggestive of any medical conditions that might cause an altered mental status. Viral infections were serologically excluded, and blood and urine cultures for bacteria were negative. A lumbar puncture was performed, and cerebrospinal fluid (CSF) showed white

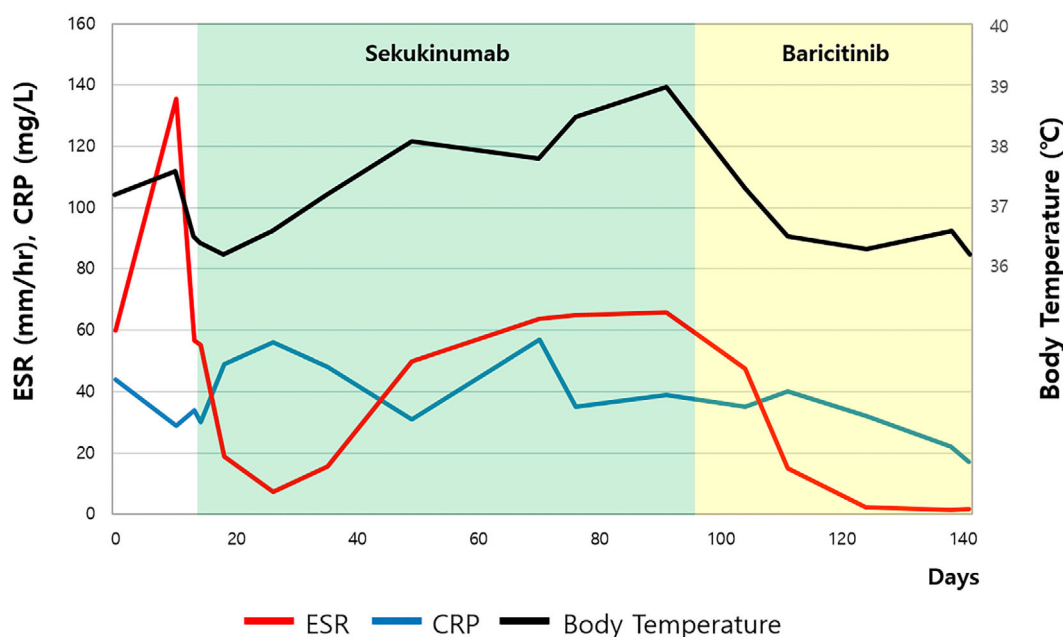


Figure 3. Time courses of laboratory data and body temperature. After starting baricitinib, the inflammatory markers gradually decreased, and the fever subsided (Day 0: first visit to Seoul St. Mary's Hospital).

blood cells at $58/\mu\text{L}$ (63% neutrophils), an elevated protein concentration of 166.1 mg/dL , normal glucose level of 3.0 mmol/L (serum glucose, 8.2 mmol/L), and cytology yielding no malignant cells. In addition, CSF microbiological studies for viruses (including herpes simplex virus (HSV), varicella zoster virus (VZV), cytomegalovirus (CMV)), bacteria, and fungal organisms were negative. Brain MRI revealed sulcal hyperintensity and leptomeningeal enhancement. Broad-spectrum antibiotics for 3 days did not resolve the fever or CRP elevation (up to 112.3 mg/L). Furthermore, there was no improvement in the patient's mental status, and both ears became red and swollen. Therefore, meningoencephalitis with RP was diagnosed, and the patient commenced intravenous methylprednisolone pulse therapy (IV MPD, 1 g/day for 5 days).

The patient showed a dramatic improvement. He was discharged with a prescription of oral prednisolone 25 mg after 1 month from the initial emergency room (ER) visit. The administration of Vidaza for the patient's MDS was withheld after the ER visit.

After hospital discharge, the mild fever and CRP elevation recurred despite the addition of tacrolimus 0.25 mg daily to the prescription, so tapering the steroid dose failed. The patient was referred to Seoul St. Mary's Hospital for a further evaluation, where he was admitted in March 2021. His body temperature was 37.6°C , and he complained of mild lower back pain. The complete blood cell counts showed a hemoglobin count of 8.7 g/dL , white blood cell count of $6.73 \times 10^3/\mu\text{L}$ with 80.3% segment neutrophils and a platelet count of $122 \times 10^9/\text{L}$. The ESR and CRP levels were markedly elevated at 29 mm/h and 135.6 mg/L , respectively. To evaluate the fever, enhanced chest CT and abdominal CT were per-

formed to rule out any lesions that might have been the source of infection. A diffuse thrombus was incidentally identified in the infrarenal inferior vena cava (IVC) leading to the left iliac vein (Fig. 1B). Coagulation screening was performed. Among the antiphospholipid antibodies, lupus anticoagulant (LA) was positive, while all others (i.e., anti-cardiolipin antibody and anti- β_2 -glycoprotein I antibody) were negative. Previous hospital records showed that LA had been positive three months earlier. Therefore, APS was diagnosed according to the Sydney Revised Sapporo Criteria (7). The patient was started on an anticoagulant, and an IVC filter was inserted. During the same period, we increased the steroid and tacrolimus dosage to IV MPD 0.5 mg/kg and 0.5 mg bid , respectively. After 3 days, the CRP level had decreased to 56.6 mg/L . We then started the patient on secukinumab (monoclonal anti-IL-17A antibody) and tapered the steroid to oral prednisolone 25 mg and maintained tacrolimus. On the eighth hospital day, the patient was discharged.

Following the tapering of steroids, the patient's fever persisted, the CRP levels remained elevated, and the back pain became aggravated. The patient was thus kept on prednisolone 25 mg . After three months, he was switched to baricitinib. During treatment with baricitinib, his symptoms were relieved, and the CRP level decreased to 1.7 mg/L . We tapered the steroid to oral prednisolone 17.5 mg and intend to slowly reduce its dosage. The patient is being followed up in the outpatient clinic and has been maintained on baricitinib 4 mg once daily with an uneventful clinical course.

Discussion

To our knowledge, this is the first case of AS accompanied by multiple autoimmune and hematologic diseases.

Several case reports have described AS accompanied by RP (8-12). In some cases, RP developed in patients with AS while receiving anti-TNF therapy (8, 10). We presented a case of simultaneous development of RP and MDS in a patient being treated with golimumab. We paid close attention to the temporal relationship between the golimumab treatment period and progression of the overlapping features. Despite the temporal relationship, the causality between golimumab and the development of RP and MDS was uncertain. However, there are published cases of RP being successfully treated with TNF inhibitors (13, 14).

MDS is known to be associated with autoimmune diseases, the pathogenesis of which remains controversial (15). An association between RP and MDS has been reported. Dion et al. mentioned that 12 (8%) of 142 patients with RP were associated with MDS and concluded that MDS is highly associated with a poor prognosis (16). Besien et al. reported a case of RP associated with MDS where the RP symptoms improved after treatment of the underlying MDS and strongly suggested a paraneoplastic nature of RP (17). In our case, however, neurological involvement of RP developed when the frequency of blood transfusion was reduced after the administration of Vidaza for MDS. Therefore, it is difficult to clarify the precedence relationship between RP and MDS.

Janus kinase (JAK) is a central signal transducer in signaling pathways that mediates cytokine signaling for innate and adaptive immune responses. JAK inhibitors bind to and modulate the intracellular activity of JAKs. With regard to AS, JAKs are involved in the IL-23/IL-17 pathway, and IL-17A production is mainly JAK-2 dependent (18). The benefits of JAK inhibitors (tofacitinib, upadacitinib, and filgotinib) in AS have been shown in clinical trials (19). The JAK2-V617F mutation is found in 5% of MDS patients, and 60% of those have features of both MDS and myeloproliferative neoplasm (MPN). Ruxolitinib, a JAK 1/2 inhibitor has a well-documented effect in MPN patients, and several JAK inhibitors are undergoing various clinical trials for hematologic malignancies (20). Therefore, we suspected that a JAK inhibitor might be effective in this patient, who was successfully treated with the oral and selective JAK 1/2 inhibitor baricitinib.

In September 2021, the U.S. Food and Drug Administration (FDA) concluded that tofacitinib increases the risks of thromboembolism events and malignancy and required the box warning be revised for the three JAK inhibitors tofacitinib, baricitinib, and upadacitinib (21). The FDA concluded that because baricitinib and upadacitinib share mechanisms of action with tofacitinib, they might have similar risks despite the absence of large safety clinical trials (21). In some safety analyses of baricitinib, the incidence of venous

thromboembolic events was similar to the background incidence in real-world studies of rheumatoid arthritis populations (22, 23). In the present patient, we started administering baricitinib before the FDA's notice, and AS and comorbidities were well controlled with baricitinib treatment. After using anticoagulant, the D-dimer level decreased, and no thrombus-related symptoms developed. Therefore, we plan to maintain baricitinib treatment with close monitoring.

Conclusion

We encountered a case of AS coexisting with RP, APS, and MDS that was successfully treated with a JAK inhibitor. In patients with rheumatic diseases, physicians should consider other rheumatic diseases as well as hematologic diseases to provide timely intervention. Based on the outcome of this case, we propose the possibility that JAK inhibitors may be ideal treatments for AS with multiple autoimmune or hematologic diseases.

The authors state that they have no Conflict of Interest (COI).

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