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Case Report

A Case of Essential Thrombocythemia in a Patient with Ankylosing Spondylitis Concomitantly Treated with Adalimumab

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Extreme thrombocytosis in patients with ankylosing spondylitis (AS) is rarely reported. Because the relationship between high disease activity and increased platelet counts is somewhat contradictory, severe thrombocytosis in AS patients can be secondary to infection, iron deficiency anemia, drug administration, and hematologic malignancies. Essential thrombocythemia (ET) is a rare acquired stem cell neoplasm characterized by overproduction of platelets by megakaryocytes in the bone marrow in the absence of other causes of thrombocytosis. There is no report in the literature regarding the association between AS and ET. We report on a case of a 34-year-old Korean man with active AS diagnosed as JAK2V617F mutation negative ET during adalimumab treatment. **(J Rheum Dis 2015;22:51-55)**

Key Words. Ankylosing spondylitis, Essential thrombocythemia, Tumor necrosis factor alpha

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory arthritis that affects the axial skeleton as well as peripheral joints. Extra-articular manifestations are also prominent features of this disease, but hematologic abnormalities including severe thrombocytosis are rarely reported. In addition, although there is some evidence regarding the relationship between increased disease activity and mild thrombocytosis in AS patients [1,2], contradicting data exist [3,4]. Thus, thrombocytosis in patients with AS can be secondary to infection, iron deficiency anemia, drug administration and hematologic malignancy. Essential thrombocythemia (ET) is a rare acquired stem cell neoplasm characterized by the overproduction of platelets (PLTs) by megakaryocytes in the bone marrow (BM) in the absence of other causes of thrombocytosis. While cases of ET in patients with rheumatoid arthritis has been published [5], there is no report regarding to the association between AS and ET. Herein, we describe a case of ET in a patient with AS who was concomitantly treated with adalimumab.

CASE REPORT

A 34-year-old Korean man presented with a six-year history of low back pain, morning stiffness of the back and arthralgia in both shoulder. He had a chronic history of a recurrent episode of uveitis since the age of 20 years. Physical examination revealed tenderness in the shoulder and sacroiliac joints as well as reduced lumbar flexion (positive Schober test). Plain radiography showed bilateral grade-two sacroilitis and squaring of the T12 and L1 vertebral bodies. Based on modified New York criteria, he was diagnosed with AS. On the first day of his visit, laboratory findings were as follows; white blood cell

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(WBC) count 10,700 cells/mm^3, neutrophils 5,990 cells/mm^3, hemoglobin (Hb) 15.1 g/dL, PLT count 475,000 cells/mm^3 (reference, 150,000 to 400,000 cells/mm^3), erythrocyte sedimentation rate (ESR) 8 mm/h (reference, 0 to 15 mm/h), C-reactive protein (CRP) 0.28 mg/dL (reference, 0 to 0.5 mg/dL), serum creatinine 0.8 mg/dL (reference, 0.4 to 1.2 mg/dL), and lactate dehydrogenase (LDH) 334 IU/mL (reference, 135 to 225 IU/mL). Additionally, his laboratory results were positive for human leukocyte antigen (HLA)-B27 and negative for the anti-nuclear antibody, rheumatoid factor and anti-cyclic citrullinated antibody. His Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score was 4.9. We administered non-steroidal anti-inflammatory drugs (NSAIDs) and 2 g of sulfasalazine (SSZ).

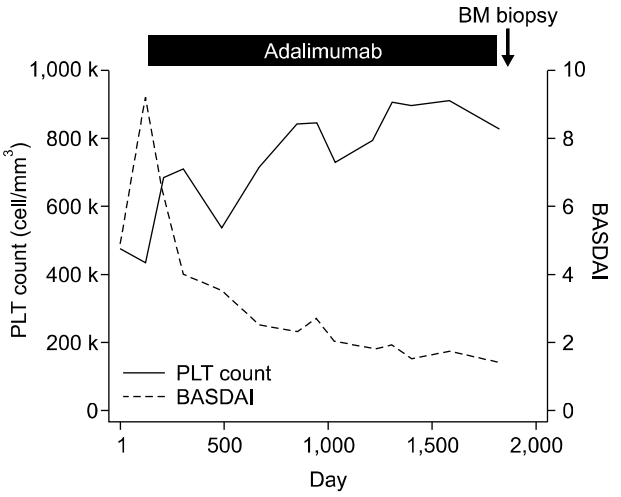

Figure 1. Clinical course of the patient's platelet (PLT) count and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). BM: bone marrow.

After 4 months of treatment, his low back pain and shoulder arthralgia worsened and his BASDAI score increased to 9.25. Acute phase reactants were elevated; ESR was 19 mm/h and CRP was 0.67 mg/dL. Hematologic analysis revealed the following; WBC count 9,800 cells/mm^3 (neutrophils 5,390 cells/mm^3), Hb 16.4 g/dL, PLT count 434,000 cells/mm^3, and LDH, 424 IU/mL. Findings of chest radiography were normal, and the result of the tuberculin skin test was 0 mm. However, he was considered to have an active disease despite conventional treatment so we discussed using therapy with anti-tumor necrosis factor alpha (TNF-α) agents with the patient. Subsequently, the SSZ and NSAIDs were stopped and adalimumab was administered subcutaneously at a dose of 40 mg every other week.

After 3 months of treatment with adalimumab, his back pain and shoulder arthralgia improved and his BASDAI score declined to 6.25. Additionally, his ESR and CRP decreased to 2 mm/h and 0.07 mg/dL, respectively. His WBC count and Hb were within normal limits, but his PLT count increased to 686,000 cells/mm^3 (Figure 1). As the adalimumab treatment was continued, the patient's BASDAI scores continuously dropped. However, his PLT count was persistently elevated. After 28 months from the initial visit, the adalimumab therapy was maintained. His PLT count reached to 844,000 cells/mm^3 and he complained of a headache. A peripheral blood smear

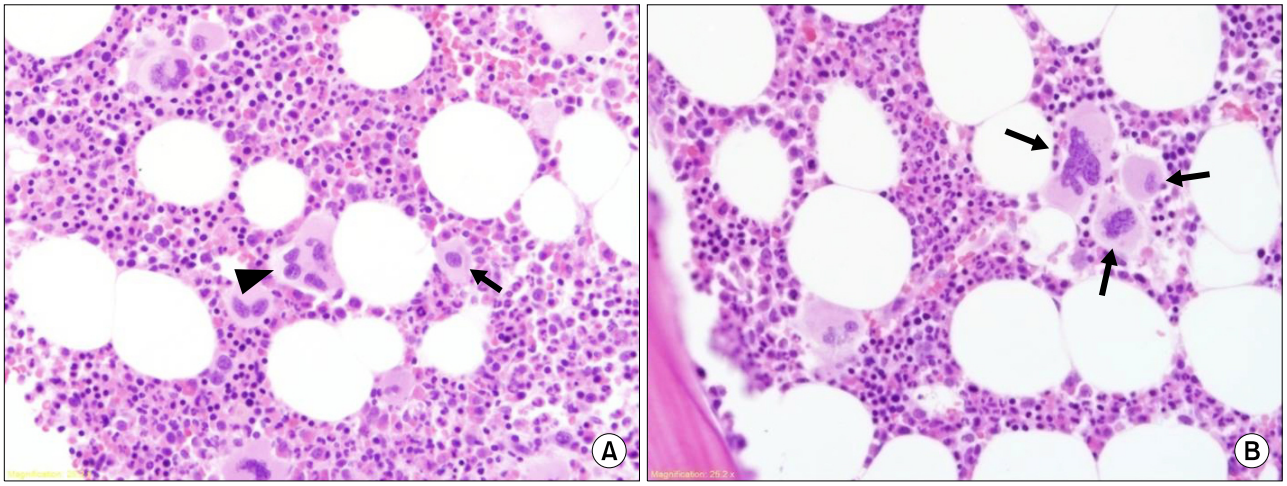

Figure 2. Bone marrow biopsy in the patient shows hypercellular marrow (cellularity: 70%) with increased numbers of megakaryocytes with nuclear atypia such as hypolobulation (arrow in A), multinucleation (arrowhead in A) and grouping (cells <5, arrows in B) (H&E, $\times$400).

was checked but no abnormal finding was reported. The patient had no signs or symptoms of infection. He consulted with a hematologist, and a BM biopsy was recommended. However, the patient refused the biopsy due to personal reasons.

After 60 months from his initial visit, he maintained the subcutaneous adalimumab treatment at a dose of 40 mg every other week. His PLT count was consistently higher than 2 times the upper normal limit (800,000 cells/mm^3) (Figure 1). His mild headache continued, but neither neurological abnormalities nor skin manifestations were apparent. With the consent of the patient, BM biopsy was peformed. The result showed the hypercellular marrow (cellularity: 70%) with increased numbers of megakaryocytes with nuclear atypia (Figure 2). Neither the JAK2V617F mutation nor the BCR-ABL gene was detected in blood real-time polymerase chain reaction test. Iron, total iron binding capacity, ferritin and vitamin B12 were, respectively, 107 μg/dL (reference, 33 to 193 μg/dL), 312 μg/dL (reference, 264 to 448 μg/dL), 223.3 ng/mL (reference, 6 to 282 ng/mL) and 851.3 pg/mL (reference, 160 to 970 pg/mL), respectively. The patient was diagnosed with myeloproliferative neoplasm (MPN), consistent with ET according to the World Health Organization's (WHO) diagnostic criteria (2008) [6]. Therefore, adalimumab was discontinued because of the potential risk for inducing malignancies and hydroxyurea at a dose of 500 mg was started. Four months from the ET diagnosis, his PLT count had decreased to 613,000 cells/mm^3 and his back pain remained at tolerable levels.

DISCUSSION

ET is a type of chronic MPNs, which are characterized by stem cell-derived clonal myeloproliferation and an increased risk of leukemic transformation. To date, there is no published report in the literature regarding MPNs in patients with AS. Our patient with AS was diagnosed with ET according to diagnostic criteria of WHO (2008), which included following: a PLT count of more than 450,000 cells/mm^3, a BM biopsy revealing proliferation of megakaryocytes with an enlarged and mature morphology, not meeting the WHO criteria for other MPNs, and no evidence of reactive thrombocytosis. Additionally, the patient had not taken any medications that could cause reactive thrombocytosis and there was no evidence of infection or hematologic disorders (e.g., iron deficiency anemia or other MPNs).

The association between the PLT count and disease activity in patients with AS is somewhat contradicting. Romero-Sánchez et al. [2] showed significant reduction in the PLT count after using infliximab treatment in patients with AS and Kisacik et al. [1] reported a similar finding. However, Yazici et al. [3] did not observe any relationship between the BASDAI score and the PLT count. Of note, the PLT counts of most patients with AS were within normal range [1-3]. Therfore, extremely high PLT counts in patients with AS cannot be fully explained by disease activity *per se* and warrants further exploration. Furthermore, despite low BASDAI scores and a normal range of acute phase reactants, the PLT count of our patient was consistently higher than 2 times the upper normal limit (800,000 cells/mm^3). Thus, we believe that the high PLT count of our patient was caused by ET rather than 'reactive' thrombocytosis induced by the transient inflammatory burden of AS.

HLA-B27 is the most important gene in AS and contribute the initiation of the disease. HLA-B27 was also detected in our patient. Although the association between HLA-B27 in AS patients and ET has not been elucidated, Au et al. [7] reported that HLA-B27 carriers among healthy volunteers had increased risk of acute leukemia. The exact role of HLA-B27 in hematologic malignancies including acute leukemia is not fully understood, but diminished immune surveillance, molecular mimicry by oncogenic microbes, putative linkage disequilibrium with unidentified susceptibility gene has been proposed [7]. Further research is needed to investigate the relationship between HLA-B27 and hematologic disorders including ET.

Adalimumab, an anti-TNF-α agent, is widely used for the treatment of rheumatic diseases including AS. Although it is still under debate, there have been some concerns regarding the risk of hematologic malignancies especially lymphoma when using anti-TNF-α agents in patients with rheumatic diseases. Thus, in our case, consideration should be given to the possibility that adalimumab may cause thrombocytosis, eventually leading to ET. However, to the best of our knowledge, there are few reports on the development of ET or severe thrombocytosis after adalimumab treatment. Recent long-term safety data from clinical trials using adalimumab supports this notion [8]. Otherwise, although uncommon, several cases of thrombocytopenia secondary to anti-TNF-α agents have been reported [9]. Triggering anti-PLT antibodies by using anti-TNF-α agents is proposed to

cause thrombocytopenia, but the exact pathogenesis is not fully understood [9]. In addition, the initial PLT count in our patient before adalimumab treatment was upper than normal limit (475,000 cells/mm^3), suggesting that the patient already had ET by the time he was diagnosed with AS. Therefore, adalimumab may not be the direct cause of ET. Considering that ET is associated with an increased risk of secondary cancer and that adalimumab may contribute to the risk of hematologic malignancies, we promptly discontinued adalimumab upon the diagnosis of ET after discussing it with the patient.

The JAK2V617F mutation is highly prevalent among patients with MPNs. Although most patients with polycythemia vera have this mutation, the frequency of a positive JAK2V617F mutation in ET is approximately 50% [10]. Thus, detection of the JAK2V617F mutation confirms the presence of ET in subjects with thrombocytosis, but its absence does not rule out the diagnostic possibility of ET. Although our patient was not positive for the JAK2V617F mutation, we established a diagnosis of ET based on the PLT count, BM biopsy findings and no evidence of reactive thrombocytosis or other MPNs according to the WHO diagnostic criteria (2008).

The pathogenesis of MPNs has not been fully elucidated. It is assumed that genetic factors such as the JAK2V617F mutation trigger the initiation of MPNs. Subsequently, dysregulation of the signaling pathway in clonal stem cell may promote the development of MPNs. Recently, it has been hypothesized that chronic inflammation may contribute to the pathogenesis and progression of MPNs [11]. The production of TNF-α and interleukin-6 during the inflammatory process can increase oncogenic transcription factor such as the nuclear factor kappa beta and signal transducer and activator of transcription 3, ensuring the inhibition of apoptosis and increased myeloproliferation [11]. Accordingly, chronic inflammatory diseases such as AS may be considered as a risk factor for MPNs, but further investigation for evaluating the association between rheumatic diseases and MPNs is obviously needed.

SUMMARY

We report a case of ET in patient with AS without evidence of reactive thrombocytosis. Since longstanding inflammation accompanied by rheumatic diseases may increase the risk of MPNs, great attention should be paid to hematologic abnormalities including thrombocytosis, during the management of patients with AS.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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