CASE REPORT

Autoimmune Hemolytic Anemia during Adalimumab Treatment for Plaque Psoriasis

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Abstract

Adalimumab is commonly used to treat autoimmune diseases with few reported hematological adverse reactions. We herein describe the case of an 85-year-old Japanese man with plaque psoriasis who developed autoimmune hemolytic anemia (AIHA) after 3 years of adalimumab treatment. The patient suddenly developed hematuria and dyspnea on exertion while receiving adalimumab treatment. Laboratory data showed low hemoglobin levels and slightly increased reticulocyte counts, while direct and indirect antiglobulin tests were positive. The patient was diagnosed with AIHA which resolved after replacing the adalimumab treatment with prednisolone therapy. The findings from this case indicate that AIHA may be caused by long-term adalimumab treatment.

Key words: adalimumab, autoimmune hemolytic anemia, psoriasis

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Introduction

Adalimumab is a fully human recombinant immunoglobulin G1 monoclonal antibody that specifically binds to tumor necrosis factor (TNF) and is indicated for the treatment of rheumatoid arthritis, ankylosing spondylitis, Crohn’s disease, psoriatic arthritis, plaque psoriasis, and juvenile idiopathic arthritis (1). Previous reports indicate that adverse reactions to adalimumab are associated with the hematologic system and include thrombocytopenia and leucopenia (2). However, to the best of our knowledge, no previous cases of autoimmune hemolytic anemia (AIHA) have been reported in patients receiving adalimumab treatment. We herein present the first case of AIHA diagnosed after the patient received 3 years of adalimumab treatment for plaque psoriasis.

Case Report

An 85-year-old Japanese man was admitted to our hospital presenting with an acute onset of hematuria, fatigue, dizziness, and dyspnea on exertion for the previous six days; his symptoms had gradually worsened following the onset. His medical history included plaque psoriasis, diabetes, paroxysmal atrial fibrillation, and an old myocardial infarction. There was no family history of systemic lupus erythematosus, thyroid disease, rheumatoid arthritis, or hematological abnormality. The patient reported that he had been receiving biweekly adalimumab injections for the previous 3 years as a treatment for his plaque psoriasis. In addition, he was prescribedamlodipine, nicardipine, and warfarin treatment for use on a regular basis. He denied any recent changes in the medication or dosages, and he experienced no other systemic symptoms such as arthralgia or abdominal pain.

On the physical examination, the patient’s vital signs were normal, and his skin showed no appreciable petechiae or purpura. Head and neck examinations revealed pale conjunctiva in both eyes. There was no evidence of lymphadenopathy. A cardiovascular examination revealed normal findings, auscultation revealed clear lungs, and an abdominal examination was unremarkable with no hepatosplenomegaly. A neurological examination also revealed normal findings. Laboratoryanalyses on the day of admission revealed a low hemoglobin level (6.9 g/dL) and elevated serum total bilirubin (5.6 mg/dL) and lactate dehydrogenase (487 IU/L) levels. Three days later, the patient’s hemoglobin level decreased to 4.8 g/dL, and a slightly elevated reticulocyte count (3.3×10⁴/μL; 2.2%) and low serum haptoglobin levels were documented.
(<10 mg/dL) were concurrently detected. Antinuclear antibody, rheumatoid factor, and cold hemagglutination tests were all negative, whereas direct and indirect antiglobulin tests were positive. Abdominal computed tomography showed no hepatosplenomegaly, lymphadenopathy, or tumor. As a result, the patient was diagnosed with AIHA. Although idiopathic AIHA was a possibility, an association between AIHA and the adalimumab treatment was undeniable. Therefore, the adalimumab treatment was discontinued, and the patient was treated with prednisolone (50 mg per day). One month later, his hemoglobin levels returned to normal and his symptoms of hematuria, fatigue, dizziness, and dyspnea on exertion disappeared.

**Discussion**

We herein report the first case, to the best of our knowledge, of AIHA during adalimumab treatment for plaque psoriasis. We speculate that AIHA may be associated with adalimumab treatment based on two hypotheses. The first hypothesis is that anti-TNFα drugs can stimulate the production of antibodies, targeting hematologic cells by inducing the apoptosis of Th1 lymphocytes. Immune-mediated thrombocytopenia and neutropenia during treatment with anti-TNFα drugs, including adalimumab, have been reported (3, 4). Although the mechanisms associated with anti-TNFα-induced thrombocytopenia and neutropenia are unclear, a hypothesis suggested that anti-TNFα drugs induce the apoptosis of Th1 lymphocytes and consequently leave a relative excess of Th2 lymphocytes. This excess could subsequently stimulate anti-platelet and anti-neutrophil antibody production, thus leading to platelet and neutrophil destruction (3). Therefore, it is possible that adalimumab stimulates the production of anti-erythrocyte antibodies, thereby causing AIHA.

The second hypothesis is that humanized monoclonal antibody therapies can potentially induce the production of anti-erythrocyte antibodies by stimulating the immune system via drug-antibody complexes on the surfaces of erythrocytes. There have been several reports of AIHA during treatment with humanized monoclonal antibodies such as anti-HM1.24, efalizumab, and infliximab (5-7). According to a study involving the anti-HM1.24 monoclonal antibody, the potential mechanism of AIHA induction following treatment with this humanized monoclonal antibody occurred as follows: initially, the humanized monoclonal antibody binds to erythrocytes via surface factors, after which antibodies against the therapeutic anti-monoclonal antibody bind to the erythrocyte-bound monoclonal antibodies. The modified erythrocytes are then phagocytized by splenic macrophages, and erythrocyte membrane antigens are subsequently released and recognized by the immune system. Finally, anti-erythrocyte autoantibodies are produced and induce AIHA.

In clinical trials of adalimumab, 10.6% of adalimumab-treated patients developed anti-adalimumab antibodies (8); in these patients, drug-antibody complexes could be produced on the erythrocytes during long-term adalimumab use and could cause AIHA by stimulating the immune system to produce anti-erythrocyte antibodies.

Based on these hypotheses, it is possible to speculate that the present case involved AIHA associated with adalimumab treatment. However, we cannot rule out the possibility of idiopathic AIHA because we did not perform a re-challenge test or an enzyme-linked immunospot assay to determine the possibility of T cells reacting to drug-erythrocyte complexes, and we initiated prednisolone treatment as soon as the adalimumab treatment was discontinued. More reported cases are necessary to determine whether adalimumab treatment is associated with AIHA.

In conclusion, AIHA may occur during adalimumab treatment. Because AIHA can be fatal if not treated appropriately, patients who present with persistent symptoms of hematuria, fatigue, and/or dizziness while undergoing adalimumab treatment should be evaluated for AIHA.

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

**References**