Case Report / Olgu Sunumu

Mycophenolate Mofetil Induced Remission in Steroid-Refractory Autoimmune Hemolytic Anemia

Mikofenolat Mofetil ile Remisyon Sağlanan Steroide Dirençli Otoimmün Hemolitik Anemi

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Abstract

Autoimmune hemolytic anemia (AIHA) is a disease that is seen in 1/10.000 people and characterized by forming antibodies against red blood cells and degradation of these red blood cells in reticuloendothelial system. Even autoimmune diseases can accompany, it is seen usually idiopathic. Paleness due to anemia, jaundice, tachycardia, darkening in urine color, hepatosplenomegaly are frequently seen clinical findings. Clinically normochrome and normocytic anemia, reticulocytosis, polychromasia in peripheral smear, spherocytes, indirect hyperbilirubinemia and increased lactate dehydrogenase are seen. Direct coombs test is the diagnostic test. Steroids are the first line drugs in treatment. The dosage and the treatment duration is formed according to patient's clinical situation. The treatment is checked by complete blood count, reticulocyte and Coombs test. Immunosuppressor treatments are given to patients that don't respond to treatment in 4-6 weeks or less patients who has recurrence at the time of decreasing the treatment dosage of corticosteroids. In few patient, that did not respond steroids, immunosuppressive treatments are used. Here, we present a patient, who is diagnosed with AIHA that we couldn't manage remission by steroid treatment, and no response to rituxumab as an immunosuppressor, but treated successfully with microphenolat mofetil.

Öz

Otoimmün hemolitik anemi (OİHA), eritrosit antijenlerine karşı antikor oluşması, antikorla kaplanmış eritrositlerin retiküloendotelyal sistemde yıkımı ile karakterize, 1/10,000 sıklıkta görülen bir hastalıktır. Otoimmün hastalıklar eşlik edebileceği gibi genelde idiyopatik olarak görülmektedir. Anemiye bağlı solukluk, sarılık, taşikardi, idrar renginde koyulaşma, hepatosplenomegali sık görülen klinik bulgular arasında yer almaktadır. Genellikle normokrom ve normositer anemi, retikülositoz, periferik yaymada polikromozi, sferosit, indirekt hiperbilirubinemi, laktat dehidrogenaz artışı görülmektedir. Direkt Coombs testi tanısal tetkiktir. Tedavide steroidler ilk tercihtir. Tedavinin dozu ve süresi hastanın kliniğine göre düzenlenmektedir. Tam kan sayımı, retikülosit ve Coombs testi ile tedavi takip edilmektedir. Dört-altı haftada yanıt alınamayan hastalarda veya kortikosteroid tedavisinin azaltıldığı dönemde tekrar nüks eden daha az olguda ise immünosüpresör tedaviler uygulanmaktadır. Burada, OİHA tanısı konulan ve steroid tedavisi ile remisyon sağlayamadığımız immünosüpresif tedavilerden rituksimab tedavisine cevap alamadığımız mikofenolat mofetil ile tedavi edilen gören bir olgu sunulmuştur.

Keywords
Steroid, autoimmune hemolytic anemia, mycophenolate mofetil

Anahtar Kelimeler
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Introduction

Autoimmune hemolytic anemia (AIHA) is a disease that is characterized with the antibody production against erythrocyte antigens and degradation of the antibody coated erythrocytes by the reticuloendothelial system. The prevalence is 1 out of 100.000. In general, normochromic, normocytic anemia, indirect hyperbilirubinemia and hepatosplenomegaly are observed. Steroids are the first choice in the treatment. In the rare cases of unresponsiveness to the steroids, immunosuppressive treatments are applied. Herein, we present a case in which a hemolytic anemia diagnosis presents a steroid resistance, but immunosuppressive treatment was beneficial.

Case Report

A 2-year old male was brought in our hospital with the complaints of lassitude and paleness. Physical examination revealed a pale skin and jaundice, spleen was palpable for 3 cm and liver was impalpable. Urinary darkening was reported for two days pre-hospitalization. Biochemical studies revealed the levels of hemoglobin: 4.8 g/dL, mean corpuscular volume: 103 fL, white blood cell (WBC): 8950 K/µL, thrombocyte: 256.000 K/µL, lactate dehydrogenase (LDH): 683 U/L, indirect bilirubin: 3.4 mg/dL, direct bilirubin: 1.2 mg/dL, direct Coombs (++++). Peripheral smear revealed a widespread schistocytes, dacrocytes, spherocytes, normoblasts and macrocytosis. Number of reticulocyte was 29%, and vitamin B12, folic acid and ferritin levels were normal. Serology analyses for toxoplasma, Rubella, cytomegalovirus, Herpes virus, hepatitis A and B, Epstein-Barr virus were consistent with the infection. After the patient was diagnosed with AIHA, prednisolone treatment was started with the dose 2 mg/kg/day divided in 3 doses. On day 10, after remission of hemoglobin to 12 g/dL, the steroid dose was decreased, and the patient was discharged. The patient was returned to the hospital 6 months after discharge with paleness and lassitude, hemoglobin was 7.6 g/dL, direct Coombs immunoglobulin G was (++), reticulocyte number was 3%. Peripheral smear was consistent with the hemolysis. Cold agglutinin (-) was detected. Prednisolone (2 mg/kg/day) treatment was started. Because the hemoglobin levels did not increase after 3 days of hospitalization, prednisolone dose was increased to 3 mg/kg/day. On day 10 of prednisolone treatment, hemoglobin was 9.4 g/dL, direct Coombs immunoglobulin G (++), reticulocyte number was 10%, total bilirubin was 1.2 mg/dL and indirect bilirubin was 0.8 mg/dL, and the patient was discharged with a steroid decrement programme. Seven months later, the patient returned to the hospital with lassitude, paleness and weakness, and analyses revealed that hemoglobin: 4.7 g/dL, widespread schistocytes, spherocytes, polychromasia. Direct Coombs was 4+ positive and total bilirubin was 5.4 mg/dL, direct bilirubin was 1.2 mg/dL, C3, C4, antinuclear antibody, anti-dsDNA and immunoglobulin levels were normal. The was accepted as relapse and steroid treatment (2 mg/kg/day) was started. Because the hemoglobin levels did not increase, the dose of steroid treatment is gradually increased to 6 mg/kg/day. The hemoglobin level increased to 10.2 g/dL. During the process of the gradual decrease of the steroid treatment, the hemoglobin levels decreased to 8.6 g/dL. Therefore, we treated the patient with the immunosuppressive drug Rituximab (375 mg/m^2/week) for 4 weeks. However, the remission did not occur. Along with the erythrocyte transfusion with intervals, treatment with mycophenolate motefil (MMF) was started with the two doses of 15 mg/kg/day. Because of the failure assessing the remission, the dose of MMF was increased to 30 mg/kg/day. On the day 21 of the treatment, the analyses revealed that WBC: 9.200 K/µL, hemoglobin: 10.6 g/dL, thrombocyte counts: 422.000 K/µL, reticulocyte number: 8%, total bilirubin: 1.4 mg/dL, and the patient was discharged on the day 60. Hemoglobin levels on post-discharge day 30 was measured as 10.8 mg/dL. Measurement for hemoglobin was in remission on post-treatment month 4 and was measured as 13.6 mg/dL, and is continued to be followed up.

Discussion

AIHA is a disease characterized by the degradation of the erythrocytes in the intravascular or reticuloendothelial system that is initiated by the immunoglobulin G and/or immunoglobulin M type of antibodies that bind to the surface antigens of the erythrocytes (1). Its etiology consists of collagen tissue diseases, lymphoproliferative diseases, non-Hodgkin lymphoma, drugs (especially penicillins, cephalosporins etc.) and viral infections (2,3). In a

study including 285 children (age: 2.4-5.6) diagnosed with AIHA, 53% of the patients had immunological disorders, 37% of the patients were idiopathic and 10% of the patients had infection (4). None of the factors were observed in our 2-year old patient. Autoantibodies are classified based on their types against the AIHA erythrocyte antigens. Our case is warm indirect haemagglutination that is characterized by the immunoglobulin G autoantibodies and is the most common type of the disease (4). Complaints such as anemia symptoms including weakness, fatigue, shortness of breath, dizziness and paleness, as well as jaundice and hematuria are observed (1). Those evidences are also present in our case. In laboratory evidences, normochromic and normocytic anemia, normalized number of reticulocytes formed by reticulocytosis, which the response of the bone marrow to the increased peripheral degradation, is >5% (2). In our case, reticulocyte number was 17%. In peripheral smear, widespread schistocytes, polychromasia, spherocytes, as well as high serum levels of indirect bilirubin and LDH were observed in our case. Direct Coombs test positivity is a diagnostic test. It indicates the antibodies bound to the antigens on the erythrocyte surface. As the standard Coombs reactant anti-human immunoglobulin G causes agglutination in the presence of antibody and test gives (+) result (5). Response rate to the steroid treatment of the AIHA cases is 70-80% (2). However, abovementioned case is rare case because of the relapse and unresponsiveness to the steroid. Initial steroid dose 1-2 mg/kg/day and dose can be increased depending on the hemoglobin levels, as it was in our case (6). When the hemoglobin levels reach to the desired levels, dose is decreased slowly. Generally, the dose reaches down to 0.5 mg/kg/day within 4-6 weeks. As it was in our case, the responsiveness to the treatment is checked regularly by the complete blood counts, reticulocyte counts and Coombs test. In the cases of either unresponsiveness within 4-6 weeks or not being in remission during the period of the steroid dose is decreased, alternative treatment options should be considered, as it was in our case. On the patients who are either unresponsive to the steroids or cannot tolerate, immunosuppressant treatment is also advised in order to continue the remission (3). In our case, our first-choice rituximab is an anti-CD 20 monoclonal antibody and is used either in the resistant or glucocorticoid-dependent cases with the dose of 375 mg/m^2/week for 4 weeks via intravenous infusion (7). In a study, responsiveness was found to be 50-60% (8). Side effects, such as fever, trembling, headache, dizziness, nausea, vomiting, hypotension and sinus tachycardia, can be observed in response to the rituximab treatment (9). However, we did not observe either any response or complications in response to the 4-week treatment in our case. Other immunosuppressive treatment choices include MMF, danazol, azathioprine and cyclosporine (1). In our case, we chose MMF as an immunomodulator after rituximab treatment. MMF can be applied with a dose of 2x30-40 mg/kg/day. In our case, we did not observe either any complications or side effects in response to the MMF, initial dose was 15 mg/kg/day, then escalated to 30 mg/kg/day. In previous studies, MMF treatment gives in successful results in the steroid-resistant AIHA, and in our study, patient was found to be in remission at 6-month post-treatment (10,11). In conclusion, AIHA is a type of anemia that successfully responds to the steroid treatment. However, it can continue with the relapses. When the steroid treatment is not responsive during relapses, there are various immunosuppressant treatment choices. MMF is one of the immunosuppressant drugs that we preferred in our case and obtained positive response.

Ethics

Informed Consent: It was taken.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.Ö., Y.I.B., H.E., G.S., T.B., E.K., A.P., Concept: E.Ö., Y.I.B., H.E., G.S., T.B., E.K., A.P., Design: E.Ö., Y.I.B., H.E., G.S., T.B., E.K., A.P., Writing: E.Ö.

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