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CASE REPORT

High Dose Corticosteroid Therapy for Anti-Thymocyte Globulin Associated Severe Serum Sickness in an Adult Patient with Aplastic Anemia

Mürüvvet Seda Aydın[1], İsmail Doğan[2], Funda Ceran[1], Simten Dağdaş[1], Gülsüm Özet[1]

[1]Department of Hematology, Ankara City Hospital, Ankara, Türkiye
[2]Department of Rheumatology, Ankara City Hospital, Ankara, Türkiye

Abstract

Classical serum sickness is a type III immune complex-mediated hypersensitivity disease caused by immunization of the host by non-human serum proteins. Anti-thymocyte globulin is one of the agents mostly responsible. Prophylactic steroids are used in the treatment protocol of aplastic anemia in addition to anti-thymocyte globulin. A 33-year-old female patient diagnosed with aplastic anemia developed severe serum sickness with anti-thymocyte globulin, despite the administration of a prophylactic dose of methylprednisolone. The patient responded dramatically to a single dose of pulse steroid therapy. There are reports that high-dose steroids (1-2 mg/kg/day to 500-1000 mg/day methylprednisolone) and/or therapeutic plasma exchange are beneficial treatment options. Our report shows the benefit of a single pulse dose of steroid and gradual tapering of the dose in this case.

Keywords: Aplastic Anemia; Anti-thymocyte globulin; Immunology; Methylprednisolone; Serum Sickness.

Classic serum sickness is a type III immune complex-mediated hypersensitivity disease caused by immunization of the host by non-human serum proteins[1]. Anti-thymocyte globulin (ATG) is one of the agents mostly responsible[2]. Steroids are mainly added to the treatment protocol of aplastic anemia (AA) in order to prevent ATG-associated serum sickness[3].

Case Report

In March 2021, a 33-year-old female patient applied to our clinic with the complaint of fatigue with unremarkable personal medical history. Physical examination revealed pallor and vulvar erythema. The patient's hemoglobin level was 7.5 g/dl, white blood cell count was 1000/µl and platelet count was 5000/µl. The bone marrow cellularity was 10% and hereby the patient was diagnosed as very severe AA. Fluorescein-labeled proaerolysin test revealed 11% paroxysmal nocturnal hemoglobinuria clone at granulocytes. Diepoxybutane test was normal. Equine ATG (40 mg/kg/day for four days) and cyclosporine (5 mg/kg/day to be added on the 14th day) protocol was initiated as there was no readily available HLA (human leukocyte antigen)-matched sibling donor. Both epicutaneous and intradermal skin testing were performed before ATG administration. In order to prevent serum sickness, 2 mg/kg/day intravenous methylprednisolone was applied. After four days of 40 mg/kg/day ATG administration, methylprednisolone dose was reduced to 1 mg/kg/day on the 5th day. However, on the 8th day of the treatment, the

Correspondence: Mürüvvet Seda Aydın, M.D. Department of Hematology, Ankara City Hospital, Ankara, Türkiye
Phone: +90 530 117 63 99 **E-mail:** drmseda84@gmail.com
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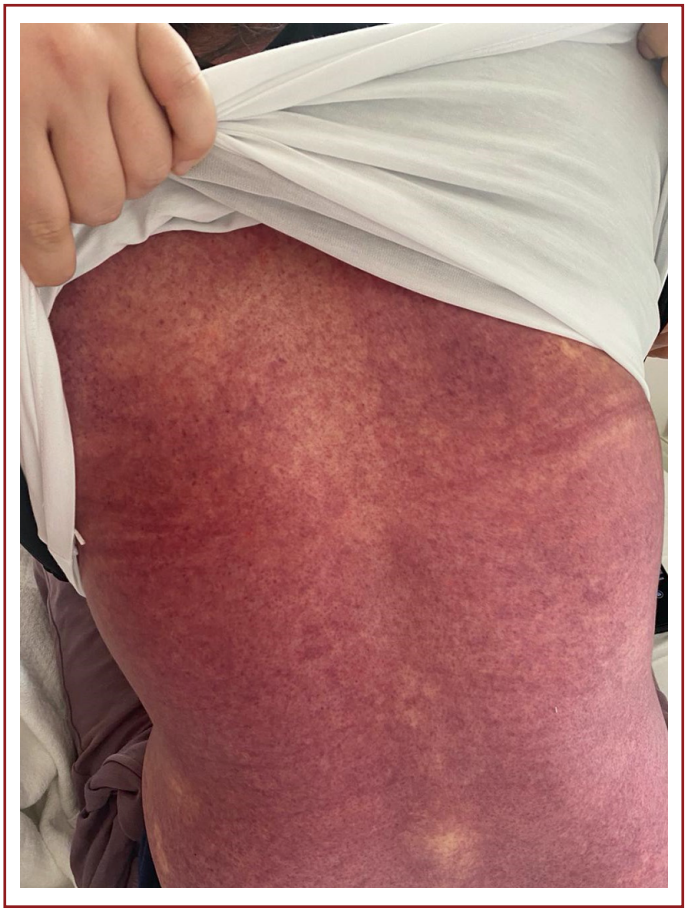

Figure 1. Severe itchy rash.

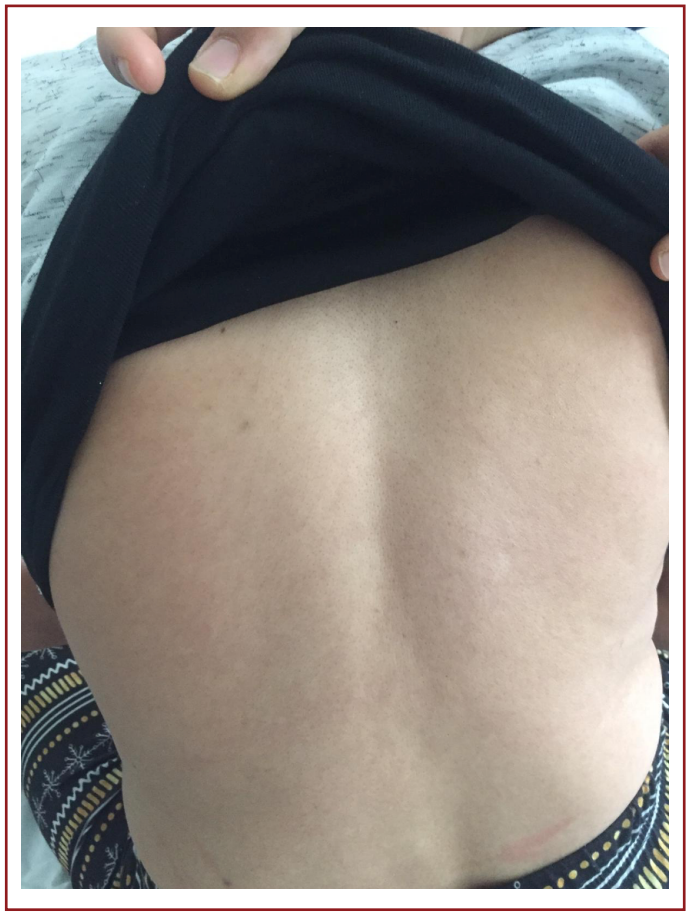

Figure 2. Fading of the rush.

patient developed significant pruritic skin rashes, starting from the anterior lower trunk, groin and spreading to the back (Fig. 1). Mucous membranes were not involved. Skin eruptions did not regress with the steroid dose increment to 2 mg/kg/day and anti-histamine administration. Symptoms worsened as fever, arthralgia, pain in the jaw, impaired oral intake and altered general status were also added. Complement measurements (C3, C4) were normal and proteinuria was not observed. Skin biopsy could not be performed due to thrombocytopenia. A single dose of 1 gram/day methylprednisolone was administered to the patient at 9th day. Broad-spectrum antibiotics (meropenem and teicoplanin) were also started for neutropenic fever without any specific infectious sign. We planned therapeutic plasma exchange (TPE) for the patient but we had to cancel it because of short-standing hypotension which responded to boluses of fluids. Improvement in oral intake and general performance status were observed and fever subsided the next day. Acute phase reactants (C-reactive protein and procalcitonin) were improved. Blood and urine cultures resulted negative and antibiotics were discontinued. The patient's rashes significantly faded in five to seven days (Fig. 2). Methylprednisolone dose was then reduced to 1 mg/kg/day and it was discontinued by tapering the dose gradually in four weeks. The patient is now on oral cyclosporine and eltrombopag treatment at outpatient clinic with good clinical status and improving hematological parameters.

Discussion

Equine ATG with methylprednisolone and cyclosporine is the recommended regimen for young adults with AA without a readily available hematopoietic stem cell donor[3]. Equine ATG was the offending agent of the classical serum sickness (type III immune complex-mediated hypersensitivity) in our case despite prophylactic steroid administration. Diagnosis is clinical and anti-heterologous antibodies can aid confirming diagnosis; however, special laboratories are needed for testing[4]. Decreased levels of complement, increased levels of the C1q and mild proteinuria support diagnosis of serum sickness but in our case, complement (C3 and C4) levels were normal and proteinuria was not

seen[2]. The Naranjo Adverse Drug Reaction Probability Score was calculated as 6 points (probable reaction) [5]. Antihistamines and low-dose steroids are generally sufficient to alleviate the symptoms but there are reports that higher doses of steroids (1–2 mg/kg/day to 500–1000 mg/day methylprednisolone) were needed [6,7,8]. Therapeutic plasma exchange could also be beneficial considering previous reports [7,9,10]. Our first plan was to give pulse dose steroids for three consecutive days but taking only one day of pulse dose steroid was noticeably enough to relieve the patient's symptoms.

Conclusion

As conclusion, pulse dose steroids can serve as an effective relieving treatment option for severe serum sickness, but when deciding to use high-dose corticosteroids, clinicians should take into account the side effects of steroids. Desensitization regimen was successfully used in a case in a previous report and can be necessary in the next ATG administration for this patient.[11]

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