Case Report

Role of daratumumab in transfusion medicine: a must know entity

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A R T I C L E  I N F O

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Introduction

Drug interference in serological assays is a well-known phenomenon. Therapeutic monoclonal antibodies (MoAbs) have been successful in treating a variety of malignancies. Some of these MoAbs interfere in day-to-day laboratory tests. Recently, a novel targeted immunotherapy, daratumumab (MoAb against CD38 antigen) was approved for treating advanced stage multiple myeloma (MM). Herein, we describe the interference of daratumumab in the red blood cell (RBC) compatibility testing of a patient with refractory relapsed MM.

Case description

A 72-year-old gentleman previously diagnosed with immunoglobulin (Ig)A MM presented with complaints of pain in both the hip joints for three weeks. Hematological parameters at the time of admission were: hemoglobin 6.8 g/dL, platelet count: 95 x 10^9/L; total leukocyte count: 2.7 x 10^9/μL. Magnetic resonance imaging (MRI) showed spinal cord compression at L4-L5 level. On the second week of admission, we received a request for one RBC unit. His blood grouping was B RhD positive. Initially, one RBC unit was incompatible in the anti-human globulin (AHG) phase using a LISS/Coombs gel card (Biorad, Cressier, Switzerland). Immediate spin (IS) crossmatch using the tube technique was compatible. A direct antiglobulin test (DAT) of the patient was negative for IgG and C3d using monospecific Coombs gel card (Biorad, Cressier, Switzerland). Subsequently, we performed an indirect antiglobulin test (IAT) using LISS/Coombs gel card with commercial three cell panel, DiaCell I-II-III (Biorad, Cressier, Switzerland), which was panreactive (2+) while the auto control was negative. RBC antibody identification was panreactive (2+) using the ID-Diapanel (Biorad, Cressier, Switzerland). We suspected multiple alloantibodies or an antibody to a high-prevalence antigen. Extended phenotyping could not be done as the previous transfusion was within three months. RBC antibody identification was repeated using a papain treated 11-cell panel (single stage assay). However, no variation in the grade of agglutination was observed. Acid
elution was performed using the commercial kit (Diacidel, Biorad, Cressier, Switzerland) and the IAT of the eluate was negative. We further performed AHG crossmatch with 18 group specific RBC units and all were incompatible. Previously, the patient had been transfused on different occasions at our center with five group specific packed RBCs (AHG compatible) due to anemia. We reviewed his compatibility profile prior to the first transfusion. His blood group was B RhD positive, while his DAT and IAT were negative. Retrospective examination of his treatment records revealed that the patient had received one cycle of daratumumab (dose: 16 mg/kg – 1200 mg) three days before the crossmatching was requested. Since the RBC units were AHG compatible prior to the initiation of daratumumab, we suspected that daratumumab interfered in pretransfusion testing. Dithiothreitol (DTT) treatment of the reagent RBCs has been shown to eliminate the effects of daratumumab. So, we attempted crossmatching with DTT treated donor RBCs as described by Chapuy et al. DTT (0.2M) was prepared by dissolving 1 g of DTT in 32 mL of phosphate buffered saline (PBS) at pH 8.0. Two K-negative RBC units were taken for crossmatching. K⁺ and E⁺ RBCs were used as controls. Donor cells and control cells were washed with PBS (pH 7.3) four times. A quantity of 400 μL DTT at pH 8.0 was added to 100 μL (5% suspension) of RBCs. The mixture was incubated at 37 °C for 30 min. Following incubation, the cells were washed with PBS (pH 7.3) four times. A 0.8% suspension was prepared with PBS (pH 7.3) and the crossmatch was repeated on a LISS/Coombs gel card. After DTT treatment, the two RBC units were AHG-compatible. IAT was negative with DTT-treated reagent RBCs. The patient was transfused with one compatible RBC unit and no transfusion reaction was observed. Post-transfusion, the patient’s hemoglobin level improved to 7.6 g/dL.

Discussion

Daratumumab is the first-in-class human IgG1κ anti-CD38 MoAb approved by the FDA in 2015 for the treatment of patients with MM who are double refractory to immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs). CD38 is a transmembrane glycoprotein which is involved in cell adhesion and signal transduction in a variety of cells. It plays a key role in intracellular calcium mobilization through its enzymatic activity. It is normally expressed at low levels on precursor and activated T and B cells, myeloid cells, natural killer cells, RBCs, platelets and plasma cells. It is strongly expressed on myeloma cells, a fact which underlies the treatment of MM with targeted immunotherapy. False positive IAT results were first observed in patients receiving daratumumab during phase I and II clinical trials. However, the drug does not affect the patient’s ABO blood grouping and immediate spin crossmatch. It binds to endogenous CD38 on RBCs. Such sensitized RBCs agglutinate in the Coombs phase resulting in panreactivity in vitro (DAT, antibody screening/identification, crossmatching).

Routine serological methods are ineffective in circumventing the interference in compatibility testing, thereby resulting in an unexpected delay in finding suitable blood for these patients. Also, it may mask the underlying alloan-
Daratumumab, Also, blood unnecessary identification. 21 for cells false antibodies than are investigation provided their response patient with MM. However, they are not without limitations. These drugs interfere with compatibility testing thereby leading to misinterpretations of test results and delay in blood transfusions. Time-consuming special techniques are needed to nullify the drug’s interference. Every center should recognize its mode of testing based on the accessibility of reagents, availability of manpower and expertise, antigen-matched blood and its inventory and turn around time. Of note, the DTT-based method has been accepted worldwide. Communication to the Transfusion Medicine Department regarding treatment with such drugs is mandatory to ensure safe transfusions in these patients. Knowledge related to these inadvertent adverse effects is essential for optimizing transfusion requirements in these patients.

Conflicts of interest

The authors declare no conflicts of interest.

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