CORRESPONDENCE

Importance of Clinically Significant Anti-M Antibody in Hematopoietic Stem Cell Transplantation

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Abstract Naturally occurring anti-M antibodies are mostly of the IgM class, however, an IgG component can also be present along with IgM. The IgM anti-M antibodies can be ignored if they are not reactive at 37 °C, but the patient should receive M antigen-negative red blood cells if the antibody is reactive at 37 °C or if it is of IgG class. Here we discuss a case of clinically significant naturally occurring anti-M antibody had both IgM and IgG components in a 3 years old child who was a hematopoietic stem cell donor for her 6 years old sister suffering from beta-thalassemia major. The specificity and immunoglobulin class of the antibody was confirmed by antibody screening at wide thermal range, dithiothreitol treatment of serum and reaction of serum with enzyme treated panel cells.

Keywords Anti-M · Naturally occurring · Clinically significant

To The Editor

The MNS system was discovered in 1927. It was the second blood group system to be recognized following the discovery of ABO blood group system. The anti-M antibody was first discovered by Wolf and Johnson in 1933 [1]. This is a relatively common, naturally occurring antibody, usually of IgM type [2]. Most of them are not active at 37 °C and generally

are ignored in transfusion practice as clinically insignificant antibody [3]. Though it is a cold reactive saline agglutinin; but sometimes the anti-M antibody can be reactive at 37 °C or at antiglobulin phase and can behave like a clinically significant antibody [4]. Anti-M antibody can cause delayed hemolytic transfusion reaction and hemolytic disease of newborn [5]. It can also cause anemia and reticulocytopenia in newborn by suppressing the M antigen-positive erythroid precursor cells [6]. The anti-M antibody does not react with papain- or ficin-treated red cells and is known to show a ‘dosage effect’ [7]. Naturally occurring anti-M antibodies are more commonly found in children than in adults. Here we discuss a case of clinically significant naturally occurring anti-M antibody in a 3 years old child who was a hematopoietic stem cell donor for her 6 years old sister suffering from beta-thalassemia major.

A 6-year-old female child was diagnosed as beta-thalassemia major at the age of 1 year based on thalassemia mutation analysis (IVS:1-5;G-C). The patient was on regular transfusion and required one unit of packed red cell once in every 20–25 days. The patient’s red cells were typed before first episode of blood transfusion and she was receiving phenotype matched blood transfusion since her childhood to avoid RBC alloimmunization. Iron chelation was started since the age of 2 years with oral iron chelating agent and serum ferritin was monitored in every 3 months interval. Subsequently she was taken for allogeneic stem cell transplantation. The stem cell donor was her 3 years old sibling sister who had a complete 6/6 HLA matched with the patient done on intermediate resolution DNA typing technique. The pre-transplant work-up was performed in the immuno-hematology laboratory for the patient and for her sibling donor.

The blood grouping, antibody screening and compatibility testing between the patient and the donor were

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performed by column agglutination technique (Ortho Biovue System, Ortho clinical diagnostics, High Wycombe, UK) during the pre-stem cell transplant work-up. The stem cell donor's red cells were also typed for extended Rh, Kell, Duffy, Kidd and MNS systems according to the institutional protocol. The blood groups were typed as B positive in both the cases without any obvious grouping discrepancy. Major cross-matching was compatible in this case. However, minor cross-matching with patient's red cells showed incompatibility. The antibody screening of stem cell donor showed a pattern of reaction with three-cell panel and the antibody identified on using an 11-cell panel was anti-M. It was showing 'dosage effect' as it showed agglutination only with cells homozygous for 'M-antigen' not with the cells those had heterozygous expression of 'M-antigen' in panel cells. On testing the thermal amplitude, the antibody was found to be 2+ reactive at 37 °C, but also showed 4 + reactivity at 4 °C. The DAT and autocontrol were negative. Indirect antiglobulin tests were performed with M antigen-negative O group red cells and papain-treated M antigen-positive O group red cells. The serum showed no reactivity either with M antigen-negative red cells or papain-treated red cells, thus confirming the antibody to be anti-M [7]. To determine the immunoglobulin class of the antibody, the serum was treated with 0.01(M) dithiothreitol (DTT) at 37 °C for 1 hour and an antibody screening was subsequently performed. The reactivity persisted even after DTT treatment, but the reaction strength decreased, suggesting the presence of IgG along with IgM type of anti-M in this case. Red cell phenotyping of the stem cell donor revealed that it was negative for M antigen. Her parents informed that she had not received any kind of transfusion since birth. So the anti-M antibody was naturally occurring in this case which had both IgM and IgG components. As the antibody was reactive at 37 °C and showing incompatibility during cross-matching; the antibody should, therefore, be considered as potentially clinically significant. The situation became complicated when the previous record of stem cell recipient's red cell phenotyping revealed that it was M-antigen positive.

The stem cells were harvested from the marrow in this case due to young age of the donor; therefore she required one unit of red cell transfusion during that invasive procedure. So one 'M-antigen' negative, group specific, leucocyte-reduced, irradiated PRBC was transfused to the stem cell donor to combat with the red cell loss during the procedure. The transfusion proceeded without any complications. As the patient's phenotype was 'M-antigen' positive and the naturally occurring antibody was potentially clinically significant the harvested product from marrow was plasma depleted as much as possible to reduce

the chance of hemolytic transfusion reaction during the stem cells infusion [8]. The stem cell bag was kept in a hanging position for 1 hour and due to the difference of specific gravity between different blood components plasma was separated from the product. Then the plasma was depleted by the manual blood component extractor to a transfer bag with the help of sterile tube connecting device [7]. The centrifugation of stem cell bag was avoided to reduce the stem cell loss during plasma depletion [7]. The stem cell infusion was uneventful and proceeded without any complications in the recipient.

Naturally occurring anti-M antibody is present in 1 in 2500 normal, healthy donors when tested with M+N– cells, but is detected in 1 in 5000 when tested with M+N+ cells [9]. Anti-M antibodies are mostly of the IgM class, however, an IgG component can also be present along with IgM. The IgM anti-M antibodies can be ignored if they are not reactive at 37 °C, but the patient should receive M antigen-negative red blood cells if the antibody is reactive at 37 °C or if it is of IgG class [10]. Anti-M antibody can show various clinical presentations as discussed by Das et al. [11]. Tondon et al. [12] also reported two cases of anti-M, one presenting as cross-match incompatibility and the other as a blood group discrepancy. Therefore, in this case M antigen-negative PRBC was issued to the stem cell donor for safe transfusion and anti-M containing plasma was depleted from the harvested stem cell product to avoid transfusion reaction in recipient.

To conclude, complete pre-stem cell transplant work-up should be performed in every case of hematopoietic stem cell transplantation and the antibody screening should be done meticulously using the wide thermal range. The immunoglobulin class should, therefore, be identified in each case and antigen-negative red cells should be given to avoid any transfusion reactions. The harvested stem cell product may need modification according to the type and character of antibody detected in the immuno-hematology laboratory.

Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interest.

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