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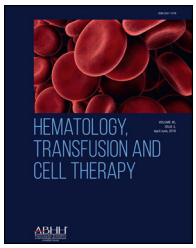

Case Report

Non-RhD (anti-E) red cell alloimmunization following platelet transfusion: a case report and implications on quality of the platelet concentrates and antibody screening protocols

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Introduction

Acute myeloid leukemia (AML) and myelodysplastic syndromes are amongst the commonly encountered hematological disorders in clinical practice. The myelodysplastic patients become transfusion-dependent in due course of the disease and blood transfusion with disease-modifying agents remains the mainstay of management. It is estimated that 15–59% of individuals with hematological malignancies become alloimmunized after transfusions. The risk of red cell alloimmunization (RCA) is proportional to the number of transfusions.[1] It occurs mainly due to antigen mismatched packed red cell (PRC) transfusions. A minor proportion of cases is attributed to platelets. Unlike red cells, platelets do not express antigens of Rh (D,C,c,E and e) and other minor blood group systems like Kell, Kidd, Duffy, MNS, and Lutheran. The residual red cells, which are inevitable in the preparation of platelet concentrates are presumed to be the cause of alloimmunization.[2] RhD alloimmunization following transfusion of platelet concentrates, including buffy coat derived platelet concentrates (BC-PCs) and apheresis platelets (AP-PCs) is well documented in the literature with an estimated incidence of 0-7%.[3] However, platelet induced non-RhD alloimmunization is very uncommon. Here, we describe a case of newly detected anti-E alloantibody following BC-PCs transfusion in a multi-transfused patient who previously had anti-D and anti-C alloantibodies.

Case report

A 72-year-old gentleman, a known case of AML with myelodysplasia-related changes and multi-transfused was referred to our center for symptomatic anemia on 21.6.2019. The laboratory investigations at the time of admission were as follows:- hemoglobin: 6.3 g/dL; platelet count: 48000/μL; white blood cell count: 2000/μL; reticulocyte count: 0.5%; bilirubin levels were within normal limits. In view of anemia, we received a request for crossmatching on the day of

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admission. His past medical records revealed his blood group to be B RhD negative. His indirect coombs test was positive for anti-D with probable Rh extended phenotype being dce/dce (rr-phenotype, K negative) and his last red cell transfusion was 15 days ago. We confirmed his blood group to be B RhD negative and crossmatching with B RhD negative PRC using Coombs gel card was found incompatible. The sample was further evaluated for the presence of additional red cell antibodies using commercial red cell antibody screening (Diacell, Biorad, Cressier, Switzerland) and identification panels (Diapanel, Biorad, Cressier, Switzerland) using Coombs gel card. The patient had developed a new alloantibody (anti-C) in addition to anti-D, auto control being negative. The direct antiglobulin test (DAT) was negative done by monospecific anti-human globulin anti-IgG and anti-C3d gel card (DC screening II, Biorad, Cressier, Switzerland). The patient was transfused with one unit of crossmatch compatible Rh-K matched PRC (rr phenotype, K-negative). Rh-K phenotyping of donor red cells was performed in the gel card (Diaclon Rh subgroups + K, Biorad, Switzerland). His post-transfusion Hb was 8.1 g/dL and he was started on decitabine chemotherapy. Since then, the patient had received 22 units of crossmatch compatible Rh-K matched (rr phenotype, K-negative) B RhD negative PRCs and 12 units of B RhD positive BC-PCs on various occasions at our center for a period of 6 months. The patient was admitted again at our center for low blood counts on 13.1.2020. During this visit, crossmatch with D and C antigens-negative (r"r phenotype, K-negative) PRC was found incompatible. Red cell antibody identification was performed as mentioned above to look for the presence of any new antibody in addition to the previously detected antibodies (anti-D and anti-C). The current panel revealed a third alloantibody (anti-E). The DAT and auto control were both negative. The patient was provided with crossmatch compatible B RhD negative, Rh-K matched PRCs (rr phenotype, K-negative). All the blood transfusions that the patient had received so far were only from our center. Hence, the only source of E antigen for alloimmunization is likely to be the residual red cells in the transfused BC-PCs. Fresh EDTA blood samples were collected from the 12 donors who were the source of the platelets transfused and Rh-K phenotyping was performed. It was observed that four samples were tested positive for E antigen.

Discussion

Our case highlights the potential role of platelet concentrates in RCA. Many examples of naturally occurring anti-E have been described in the literature. Depending upon the sensitivity of the technique used, solely IgM, solely IgG or a mixture of IgM + IgG anti-E antibodies have been detected.[4] Nevertheless, immune anti-E is not infrequent. A ten-year study by Cid et al. found that 2.9% of RhD negative patients developed non-RhD antibodies following RhD positive platelets transfusion.[5] However, RhD positive patients were not included in this study, who can also develop non-RhD alloimmunization. A five-year study based on French hemovigilance database by Moncharmont et al. reported 48 cases of RCA following platelet transfusions (24 cases by BC-PCs and 24 cases by AP-PCs), anti-E being the most common specificity followed by anti-D. The other common non-RhD antibody specificities were anti-C, anti-c and anti-e.[6] Several studies have documented anti-E alloimmunization following platelet transfusions.[2,3,7]

Platelet induced RCA is primarily influenced by two factors viz., the amount of residual red cells in PCs and red cell microparticles.[6] One of the quality indicators of PCs, including BC-PC and AP-PC is the amount of residual red cells. According to the criteria laid by the Directorate General of Health Services, India, the permissible residual red cell content in BC-PCs is less than 0.5 mL.[8] Our institute's estimated mean residual red cell content in BC-PCs is 0.32 mL for the year 2019. The risk of RCA is seemingly higher with the BC-PCs as compared to the AP-PCs due to a significantly larger amount of residual red cells in BC-PCs (0.03 to 0.6 mL in BC-PCs vs 0.00017-0.009 mL in AP-PCs).[3] It has been observed that even a minimal red cell content (<0.5 mL) could elicit a primary immune response to mismatched Rh-K antigens in susceptible individuals.[7] Therefore, there is a definite need to reconsider the immunologically acceptable limit of red cell content in the platelet concentrates.

In addition to the intact residual red cells, red cell-derived microparticles with clinically significant antigens render themselves immunogenic as they can be easily phagocytosed. These microparticles together with the residual red cells could serve as a sufficient trigger for RCA.[2] Although few studies have attempted quantifying these microparticles in PCs, their putative role and safety levels are yet to be established. Currently, the American Association of Blood Banks recommends crossmatching with the donor red cells if the red cell contamination in platelet concentrates exceeds 2 mL. As one of the mitigation strategies for platelet induced RCA, AP-PCs can be transfused wherever feasible.[2]

It is now understood that platelet transfusions increase the risk of RCA in transfusion-dependent individuals. In previously alloimmunized individuals, the rate of additional antibody formation increases by 2–20 fold.[1] As an attempt to reduce the incidence of RCA, many centers have implemented prospective extended antigen matched PRC transfusions for multi-transfused patients to minimize the risk of RCA. However, the patients can still develop alloantibodies despite Rh-K matched PRC transfusions, as seen in our index case. Schonewille et al. demonstrated that extended antigen match transfusion policy would be successful only when the patients do not receive antigen mismatched platelet transfusions.[7] Future recommendations may be directed towards Rh-K matched AP-PCs transfusions in these multi-transfused individuals.[2,3]

Assessing the true magnitude of the problem is paramount to make such necessary changes in transfusion policies which mandates strong suspicion, performing regular antibody screening and meticulous reporting of RCA following platelet transfusions. Red cells in platelets can induce de-novo antibody formation (primary immunization) or act as a booster to an unknown stimulus leading to secondary immunization. Ideally, antibody screening tests should be performed on two different occasions following transfusions i) around 3–7 days to detect early appearing antibodies or booster effect and ii) around 4–8 weeks to detect slowly developing antibodies.[9] This strategy may not apply to many centers due to cost constraints. There is a paucity of data on antibody

screening frequency to detect newly formed alloantibodies following transfusions in multi-transfused patients. As per the French Hemovigilance system, it is mandatory to perform RBC antibody screening 1–3 months after the last red cell transfusion. By and large, identification panel should be performed under these circumstances: i) when the crossmatch is incompatible with antigen-negative units ii) suspected delayed hemolytic transfusion reactions iii) in patients with warm and cold autoantibodies. Based on the previous alloimmunization history, the panel red cells can be used selectively as a cost-effective method.[10] Blood centers should develop their protocols to identify the antibody responders based on the estimated prevalence of RCA (including platelet induced RCA) so that optimal transfusion strategies can be formulated in the future.

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