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Case Report

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# Prolonged Thrombocytopenia and Severe Transfusion Reaction after ABO-Incompatible Allogeneic Hematopoietic Stem Cell Transplantation in a Patient with Chronic Myelomonocytic Leukemia

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**Keywords**
Transfusion reaction · ABO-incompatible allogenic hematopoietic stem cell transplantation · Hematopoietic stem cell transplantation

**Abstract**
***Introduction:*** Major ABO-incompatible allogeneic hematopoietic stem cell transplantation (allo-HCT) is a common practice and represents a challenging transfusion scenario. Prolonged thrombocytopenia with increased platelet transfusion needs is one of its reported adverse effects, and this has been linked to the persistence of recipient anti-donor isoagglutinins. ***Case Presentation:*** A 55-year-old male patient, O Rh(D)-positive, with chronic myelomonocytic leukemia underwent major incompatible allo-HCT from a A Rh(D)-negative donor. He presented with prolonged thrombocytopenia and multiple transfusion reactions after A Rh(D)-negative platelet transfusions. Considering the outcomes of numerous examinations, we tested the anti-A1 titers, finding a significant persistence of anti-donor isoagglutinins. We limited platelet transfusions to blood group O Rh(D)-negative donors, which significantly decreased the requirement for platelet transfusions. In addition, the transfusion reactions ceased. ***Conclusion:*** In case of transfusion reactions against platelet products in major ABO-incompatible allo-HCT patients, isoagglutinin monitoring should be considered and a change in the platelet transfusion protocol may be beneficial in patients presenting high isotiters against recipient's blood type.



## Introduction

Major ABO-incompatible allogeneic hematopoietic stem cell transplantation (allo-HCT) is a common practice. However, its impact on the clinical outcome of recipients is controversial, with studies reporting increased platelet transfusion requirements, delayed red blood cell (RBC) engraftment, and pure red cell aplasia (PRCA) [1, 2]. These adverse effects have been associated with the persistence of host anti-donor isoagglutinins after transplantation and of its producing plasma cells [3]. Transfusion support of major ABO-incompatible allo-HCT recipients is therefore challenging. To this end, international guidelines are available, recommending transfusion of RBC according to recipient type, and plasma and platelet support

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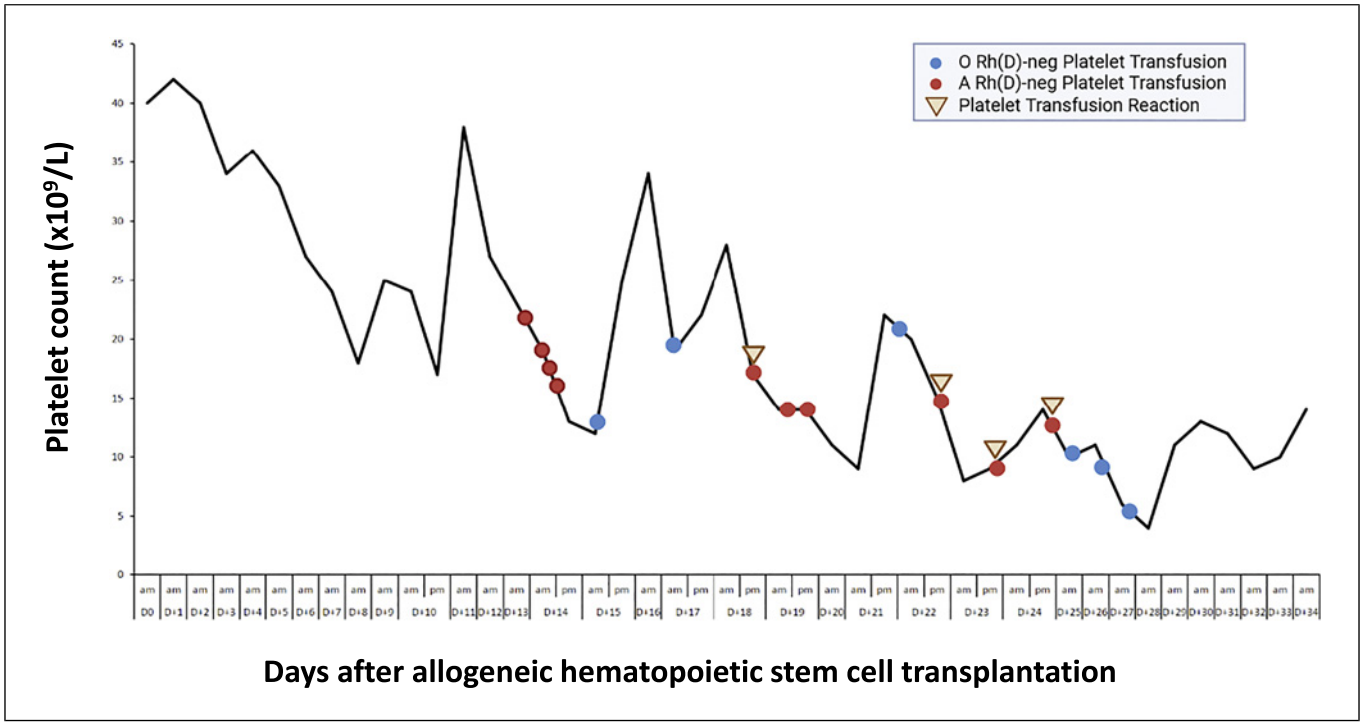


**Fig. 1.** Platelet count and transfusion reactions during hospitalization.

according to donor type [4]. Here, we present a case report of prolonged thrombocytopenia and multiple transfusion reactions after platelet transfusions in a major ABO-incompatible allo-HCT recipient. The patient provided written informed consent for publication of the details of the medical case.

## Case Presentation

A 55-year-old male patient was diagnosed with chronic myelomonocytic leukemia in March 2022. Bone marrow evaluation showed ≤5% myeloid blast cells. Cytogenetic analysis revealed a normal karyotype, and molecular diagnostics showed *ASXL1, RUNX1, SRSF2* (VAF 40%), *KRAS* (VAF 7%), and *TET2* (VAF 97%) mutations. He was intermediate-risk 2 according to the chronic myelomonocytic leukemia-specific prognostic scoring system. Clinically, the patient suffered from thrombocytopenia, requiring repeated platelet transfusions. Unfortunately, a spontaneous intracerebral hemorrhage with perifocal edema occurred in July 2022 during thrombocytopenia. The patient suffered from intermittent aphasia, but the symptoms resolved within a few days. Besides the previous intracerebral hemorrhage, his medical history was unremarkable, and his ECOG performance status was 1. Thus, he was a candidate for allo-HCT. Due to the lack of a matched donor, a haploidentical allo-HCT (HLA-A-mismatch) was performed in August 2022 after conditioning with total body irradiation (8 Gy) and fludarabine. Furthermore, there was a major blood group incompatibility, since the patient's blood group was O Rh(D)-positive, whereas the donor was A Rh(D)-negative. Post-transplant cyclophosphamide and tacrolimus/mycophenolate mofetil were used as graft-versus-host disease prophylaxis. The transfused dose of CD34+ stem cells was 7.5 × $10^6$/kg/body weight of the recipient, and the stem cell transfusion was uneventful. After allo-HCT, the patient developed splenomegaly and platelet transfusion refractoriness (PTR), requiring platelet transfusion almost daily. Likewise, multiple RBC transfusions, O Rh(D)-negative, were performed. Due to the unavailability of A Rh(D)-negative platelets, he occasionally received O Rh(D)-negative platelets. So far, none of them caused a transfusion reaction. Eighteen days after allo-HCT, the patient received one unit of irradiated apheresis platelet blood group A Rh(D)-negative, due to a platelet count of 28 × $10^9$/L (reference, 150–450 × $10^9$/L). Besides, no further medications or fluids were given. Before the transfusion, the patient was hemodynamically stable and afebrile. Roughly 10 minutes after the initiation of the transfusion, the patient complained of palpitations and chills. The systolic blood pressure declined from 110 to 80 mm Hg, and he developed sinus tachycardia (110/bpm). The transfusion was stopped immediately, and glucocorticosteroids and antihistamines were given intravenously, relieving the symptoms within 15 min. Altogether, the patient had received 135 mL (50%) of the platelet product. A transfusion reaction work-up was initiated. The minor compatibility test was negative. No eluate was performed due to the absence of detectable IgG on the post-transfusion direct antiglobulin test sample. Microbiological evaluation of the remaining platelets revealed no bacterial contamination. His post-transfusion platelet count (taken the next morning) was 17 × $10^9$/L. Further platelet transfusions, including both apheresis and pooled platelet products from blood groups A and O Rh(D)-negative donors, were well tolerated after premedication with antihistamines. However, there was no increment in platelet count after transfusions (shown in Fig. 1). A similar episode occurred 4 days later,

during the transfusion of a pooled platelet product blood group A Rh(D)-negative. Besides chills, fever, hypotension, and tachycardia, the patient had dyspnea with a decline in oxygen saturation to 85%. Again, the transfusion was stopped immediately, and glucocorticosteroids and antihistamines were given intravenously. Thus, the adverse reaction could be terminated within 15 min. The post-transfusion work-up revealed no abnormality. Again, no platelet increase was achieved after the transfusion (Fig. 1). Repeated transfusion reactions with the same clinical symptoms after platelet transfusions of the blood group A Rh(D)-negative occurred within the next 3 days. HLA work-up revealed HLA antibodies class I versus HLA B76 in weak reaction strength. Due to the rarity of the HLA trait, HLA-matched platelet transfusions were not possible. An additional platelet work-up was performed. No platelet-specific antibodies were detected. Finally, the patient's anti-A1 IgM levels were examined by conducting a column agglutination test using the automated immunohematology analyzer IH-500 (Bio-Rad, CA, USA), showing a titer of 2,048. Based on this result, platelet transfusions were restricted to blood group O Rh(D)-negative donors. Thereafter, the need for platelet transfusions decreased over the next few days, and a stable platelet count of >20 × $10^9$/L was achieved 1 month after allo-HCT.

The levels of anti-A1 IgM were consistently high following the transfusion reaction. The highest level observed was 4,096, which occurred 2 days after the last reaction (D + 27). Even by the time of discharge, the anti-A1 IgM remained at a titer of 4,096. One month after discharge (D + 69), the titer declined to 2,048. Fifteen days later, the titer dropped to 1,024. No further transfusion reaction occurred until the patient could be discharged. Neutrophil engraftment was achieved on day 18 after the transplant. However, the platelets did not raise further until the patient was discharged (D + 34). In total, transfusions of 61 platelets and 21 RBCs were performed during hospitalization. After discharge, platelet counts remained below 50 × $10^9$/L. Bone marrow evaluation 5 months after allo-HCT revealed a complete remission with incomplete hematological recovery and a chimerism of 100%. None of the molecular abnormalities, which were seen at diagnosis, could be detected. However, due to a poor graft function with ongoing bicytopenia the patient received a CD34+ selected stem cell boost 9 months after allo-HCT. Since last follow-up, the disease of the patient is in an ongoing remission, but still with incomplete hematological recovery.

## Discussion

We report repetitive transfusion reactions, as well as PTR, to A Rh(D)-negative platelet products, in a blood group O Rh(D)-positive patient after allo-HCT from a A Rh(D)-negative donor. Several studies have assessed PRCA as one of the main complications in major incompatible transplant recipients. In this case, however, the main clinical concerns were thrombocytopenia and PTR. PTR is a common complication in patients undergoing allo-HCT with an incidence of 38% [5]. Additionally, patients receiving a major ABO-incompatible allo-HCT show an increased platelet transfusion requirement in comparison with those receiving a compatible one [6]. Some factors associated with PTR are sepsis, splenomegaly, and the development of HLA or HPA antibodies [5]. Our patient had mild splenomegaly but no signs of sepsis, and our work-up excluded relevant HLA or HPA antibodies. Furthermore, there was no evidence of hemolysis or fragmented RBCs, which would suggest a microangiopathic hemolytic anemia. An acute graft-versus-host disease of the skin (Stage I) was evident 1 month after allo-HCT, which responded promptly to glucocorticosteroids. In the context of multiple transfusion reactions in a major ABO-incompatible HCT recipient, we hypothesized that the recipient's ABO antibodies could be reacting against the ABH antigens of the platelet product. The patient's high-level isoagglutinin A supported this premise. In addition, the transfusion reactions stopped after switching platelet transfusion to blood group Rh(D)-negative donors. In line with a previous report, our patient's isoagglutinin A levels remain elevated until discharge [2]. Unfortunately, the recipient's isoagglutinin A levels were not evaluated prior to allo-HCT. Consequently, it was not possible to compare the elevated levels of isoagglutinin A detected after the transfusion reactions with any previous measurements. Despite the change in transfusion strategy to O Rh(D)-negative platelet donors, PTR remained as a common complication after allo-HCT.

Finally, the risk of Rh(D) alloimmunization following Rh(D)-positive platelet transfusions seems to be rather low [7]. Given the low risk, some centers advocate the use of platelets without consideration of Rh(D) status and without Rh immune globulin prophylaxis [8, 9]. Nevertheless, according to the German cross-sectional guidelines for therapy with blood components and plasma derivatives we use Rh(D)-negative products if the donor's blood group is Rh(D)-negative, whenever available.

In conclusion, a deviation of transfusion support recommendations should be considered in case of transfusion reactions against platelet products in major ABO-incompatible allo-HCT patients with high isoagglutinin levels. Thus, isoagglutinin monitoring is a relevant tool to assess which patients could benefit from this switch [2]. Additionally, the significance of isoagglutinin monitoring becomes even more apparent when considering its association with the risk of relapse, PRCA, and delayed recovery of RBCs [10].

## Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The patient provided written informed consent for data collection. Written informed consent was obtained from the patient for publication of the details of the medical case.

## Conflict of Interest Statement

All authors declare no competing conflict of interest.

## Author Contributions

L.S.-B. and S.K. were responsible for the concept of this paper, contributed to the literature search data collection, analyzed and interpreted data, and wrote the manuscript. D.H. and S.A.K. treated the patient and critically revised the manuscript. H.K. and P.W. critically revised the manuscript. All authors approved the submission.


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## Data Availability Statement

Questions regarding data sharing should be addressed to the corresponding author.

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