Mediterranean Journal of Hematology and Infectious Diseases

Letter to the Editor

Hyperbilirubinemia in ABO Minor Mismatch Transplantation

Keywords: Hyperbilirubinemia; ABO Minor Mismatch Transplantation.

Published: July 01, 2024 **Received: June 05, 2024** **Accepted: June 26, 2024**

Citation: Liao G., Wei C., Huang Q., Wei M., Li J., Chen Y., Yin X. Hyperbilirubinemia in ABO minor mismatch transplantation. Mediterr J Hematol Infect Dis 2024, 16(1): e2024050, DOI: http://dx.doi.org/10.4084/MJHID.2024.050

To the editor.

A prerequisite for a successful allogeneic hematopoietic stem cell transplantation (HSCT) is the availability of a human leukocyte antigen (HLA) identical stem cell donor. Due to the fact that the HLA system is inherited independently of the blood group system, approximately 40–50% of all HSCTs are performed across the ABO blood group barrier.[1,2] The expected immune-hematological consequences after transplantation of an ABO-mismatched stem cell graft are immediate and delayed hemolytic complications due to presence of isohemagglutinins or passenger lymphocyte syndrome (PLS).[3] The risks of these complications can partially be prevented by graft manipulation and appropriate transfusion support. Here, we report a rare case of haploidentical HSCT in which a donor's residual high-titer anti-A antibody induced intravascular hemolysis and hyperbilirubinemia during group O RBC transfusion during the blood group transition phase.

An 11-year-old boy was undergoing treatment with dasatinib for chronic myeloid leukemia, onset May 2022. He subsequently underwent acute transformation, and allogeneic peripheral stem cell transplantation from a HLA 5/10-matched donor with ABO incompatibility was performed at our medical center in September 2023. The patient and donor blood groups were A positive and O positive, respectively. The boy was treated with a myeloablative conditioning regimen consisting of fludarabine, busulfan, and melphalan, and a graft-versus-host disease (GVHD) prevention and treatment scheme including post-transplant cyclophosphamide, methotrexate, cyclosporine, and anti-lymphocyte immunoglobulin. The nucleated cell dose infused was 11.8×10^8/kg and the CD34+ cell dose was 8.5×10^6/kg.

On day 6 post-transplantation, the patient's hemoglobin was 63 g/L (normal range, 120–150 g/dL) and he therefore received a transfusion of 2 units of red blood cells (RBCs) with type O-filtered leukocytes, after which he developed fever and hemolysis. Routine blood tests and serum biochemical tests revealed hemoglobin, 54 g/L; total bilirubin (TBIL), 71.8 μmol/L (normal range, 0–23 μmol/L); direct bilirubin (DBIL), 24.4 μmol/L (normal range, 5–18 μmol/L); indirect bilirubin (IBIL), 47.4 μmol/L (normal range, 5–18 μmol/L); alanine aminotransferase (ALT), 656 U/L (normal range, 7–40 U/L); aspartate aminotransferase (AST), 802 U/L (normal range, 13–35 U/L); and lactate dehydrogenase (LDH), 1255 U/L (normal range, 114–240 U/L). Blood analysis at day 8 post-transplantation showed a further drop in hemoglobin to 37 g/L. Coombs test was positive. The anti-A isohemoagglutitin titer of the blood donor was >1:1080. Intravascular hemolytic anemia was considered with elevated bilirubin and aminotransferases caused by hemolysis, and hydration, alkalinization, diuretic therapy, and type O washed RBC transfusion were administered, after which the patient's hemoglobin gradually increased to 94 g/L. Serum biochemical tests at day 10 post-transplantation showed TBIL, 259.7 μmol/L; DBIL, 190.4 μmol/L; IBIL, 69.3 μmol/L; ALT, 1092 U/L; AST, 1068 U/L; and LDH, 2494 U/L (**Figure 1**).

Hepatic veno-occlusive disease, sinusoidal obstruction syndrome, thrombotic microangiopathy, and viral infections were excluded. His bilirubin and transaminase levels gradually decreased to normal after treatment with anti-thymocyte immunoglobulin and basiliximab. The boy had full donor chimerism of 99.8% at day 28 post-transplantation.

Decreased hemoglobin levels are a common complication after transplantation with secondary blood group antigen incompatibility, and may be associated with PLS. PLS is caused by the transfer of B-lymphocytes present in the donor graft into the recipient circulation following HSCT.[4] These cells may produce antibodies against the recipient's RBCs, thereby triggering antibody-dependent cytotoxicity and erythroid clearance, with potential resulting hemolysis and jaundice.[4] ABO and Rh antibodies are the most common antibodies identified in PLS, with a type O donor and type A recipient posing the greatest risk of hemolysis, as in the current patient.[5] Ambulatory

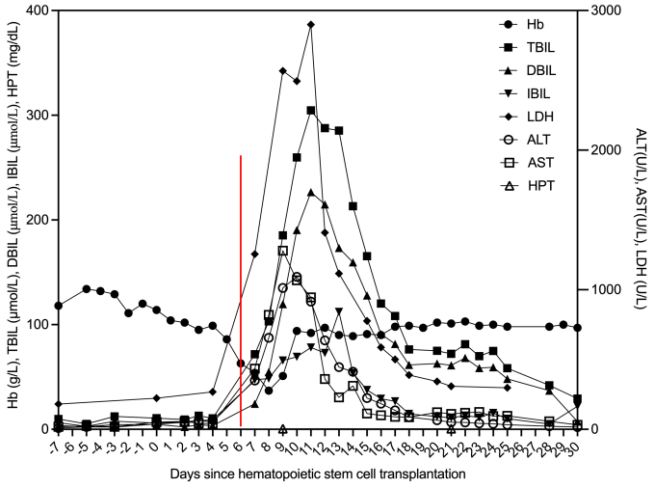

Figure 1. Temporal relationship between hemoglobin (Hb), total bilirubin (TBIL), direct bilirubin (DBIL), indirect bilirubin (IBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and haptoglobin (HPT) during hematopoietic stem cell transplantation in the patient. Red arrow represents transfusion of red blood cells with type O-filtered leukocytes.

monitoring of blood group antibody titers can aid patient monitoring and diagnosis.[6] The disease is self-limiting and does not require special treatment, but RBC transfusions may be given in cases of severe anemia. During the transition phase, transfusion of type O RBCs or recipient RBCs is recommended for ABO-incompatible transplants.[7] In the present case, the patient developed intravascular hemolytic anemia after transfusion of type O RBCs, and it was considered that a small amount of residual plasma during RBC preparation contained high-titer anti-A antibodies, which combined with the patient's own group A RBCs by an acute hemolytic reaction. The patient's hemolysis did not worsen after the transfusion of type O washed RBCs and his hemoglobin level increased.

Although the patient's hemolysis resolved and hemoglobin increased, his bilirubin tended to remain stable; however, there was a rapid rise in bilirubin, predominantly direct bilirubin, at day 10 post-transplantation. There was no significant change in the patient's weight at this time and platelet transfusions were effective, which were not consistent with veno-occlusive disease/sinusoidal obstruction syndrome.[8] Although the patient had intravascular hemolysis, he had no symptoms such as hypertension, fragmented RBC, proteinuria, or worsening renal failure, and therefore did not meet the diagnostic criteria for thrombotic microangiopathy.[9] Viral tests, including hepatitis B virus, hepatitis C virus, cytomegalovirus, and Epstein-Barr virus were all negative, and viral infection was therefore not considered. However, his bilirubin and aminotransferase levels decreased rapidly after treatment with anti-thymocyte immunoglobulin and basiliximab, indicating the possibility of hepatic aGVHD. The blood group-associated antigens are expressed, not only in RBC membranes, but also in other tissues. Blood group-associated antigens are widely distributed in intrahepatic and extrahepatic epithelial cells and hepatocytes, and may be adequate to induce rejection.[10] It follows the development of severe hyperbilirubinemia during HSCT may be caused by a combination of the factors.

Conclusions. Hemoglobin and blood group antibody titers need to be measured after HSCT with minor blood group incompatibility, to allow the early detection of PLS. If the recipient's hemoglobin levels decrease, requiring blood transfusion, washed RBCs should be used where possible to avoid the introduction of antibodies. In the event of increased bilirubin and abnormal liver function, it is necessary to be vigilant for aGVHD and to implement early intervention and control as soon as possible.

Acknowledgements. This study was financially supported by the Scientific Research Project of Guangxi Zhuang Autonomous Region Health Committee (Z-A20231086) and the Scientific Research Fund Project of Guangzhou City Life Oasis Public Welfare Service Center (GZLZ-HEMA-008).

Informed Consent. Informed consent was obtained from the participant included in the study.

Guiping Liao[1#], Changqing Wei[1#], Qiuying Huang[1], Manlv Wei[1], Jing Li[2], Yaopeng Chen[2] and Xiaolin Yin1[*].

[1] Department of Hematology, The 923rd Hospital of the Joint Logistics Support Force of the People's Liberation Army, Nanning, China.
[2] Department of Blood Transfusion, The 923rd Hospital of the Joint Logistics Support Force of the People's Liberation Army, Nanning, China
[#]Those authors equally contributed to this work.

Competing interests: The authors declare no conflict of Interest.

Correspondence to: Xiaolin Yin. Department of Hematology, The 923rd Hospital of the Joint Logistics Support Force of the People's Liberation Army, Nanning, Guangxi, China; E-mail: yin-xl@163.com

References:

1. Akkok CA, Seghatchian J. Immunohematologic issues in ABO-incompatible allogeneic hematopoietic stem cell transplantation. Transfus Apher Sci. 2018;57:812-5. https://doi.org/10.1016/j.transci.2018.10.020 PMid:30404742
2. Worel N, Kalhs P. AB0-incompatible allogeneic hematopoietic stem cell transplantation. Haematologica. 2008;93:1605-7. https://doi.org/10.3324/haematol.2008.001057 PMid:18978296
3. Worel N. ABO-Mismatched Allogeneic Hematopoietic Stem Cell Transplantation. Transfus Med Hemother. 2016;43:3-12. https://doi.org/10.1159/000441507 PMid:27022317 PMCid:PMC4797460
4. Moosavi MM, Duncan A, Stowell SR, Roback JD, Sullivan HC. Passenger Lymphocyte Syndrome; a Review of the Diagnosis, Treatment, and Proposed Detection Protocol. Transfus Med Rev. 2020;34:178-87. https://doi.org/10.1016/j.tmrv.2020.06.004 PMid:32826130
5. Peck JR, Elkhammas EA, Li F, Stanich PP, Latchana N, Black S, Michaels A. Passenger lymphocyte syndrome: a forgotten cause of postliver transplant jaundice and anemia. Exp Clin Transplant. 2015;13:200-2.
6. Teshigawara-Tanabe H, Hagihara M, Matsumura A, Takahashi H, Nakajima Y, Miyazaki T, Kamijo A, Yamazaki E, Fujimaki K, Matsumoto K, Nakajima H. Passenger lymphocyte syndrome after ABO-incompatible allogeneic hematopoietic stem cell transplantation; dynamics of ABO allo-antibody and blood type conversion. Hematology. 2021;26:835-9. https://doi.org/10.1080/16078454.2021.1986654 PMid:34672906
7. Shokrgozar N, Tamaddon G. ABO Blood Grouping Mismatch in Hematopoietic Stem Cell Transplantation and Clinical Guides. Int J Hematol Oncol Stem Cell Res. 2018;12:322-8. https://doi.org/10.18502/ijhoscr.v12i4.112 PMid:30774834 PMCid:PMC6375375
8. Ruutu T, Peczynski C, Houhou M, Polge E, Mohty M, Kroger N, Moiseev I, Penack O, Salooja N, Schoemans H, Duarte RF, Schroeder T, Passweg J, Wulf GG, Ganser A, Sica S, Arat M, Salmenniemi U, Broers AEC, Bourhis JH, Rambaldi A, Maertens J, Halaburda K, Zuckerman T, Labussiere-Wallet H, Basak G, Koenecke C, Peric Z. Current incidence, severity, and management of veno-occlusive disease/sinusoidal obstruction syndrome in adult allogeneic HSCT recipients: an EBMT Transplant Complications Working Party study. Bone Marrow Transplant. 2023;58:1209-14. https://doi.org/10.1038/s41409-023-02077-2 PMid:37573397 PMCid:PMC10622315
9. Nusrat S, Davis H, MacDougall K, George JN, Nakamura R, Borogovac A. Thrombotic Microangiopathy After Hematopoietic Stem Cell and Solid Organ Transplantation: A Review for Intensive Care Physicians. J Intensive Care Med. 2024;39:406-19. https://doi.org/10.1177/08850666231200193 PMid:37990516
10. Nakanuma Y, Sasaki M. Expression of blood group-related antigens in the intrahepatic biliary tree and hepatocytes in normal livers and various hepatobiliary diseases. Hepatology. 1989;10:174-8. https://doi.org/10.1002/hep.1840100209 PMid:2744729