Case Report

A suspected delayed hemolytic transfusion reaction mediated by anti-Jo^a

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A 32-year-old African-American woman with a history of sickle cell disease presented for surgical evaluation of left total hip arthroplasty due to avascular necrosis of the femoral head. In anticipation of a complex orthopedic procedure, pre-surgical blood work was ordered. The patient's Fenwal blood sample typed as group O, D+. Although the patient had a history of anti-Fy^a, the antibody identification was inconclusive, so the workup was sent to a reference laboratory. The patient was last transfused with red blood cells (RBCs) 2 years earlier, but had no history of transfusion reactions. Due to surgery, the patient's hemoglobin (Hb) decreased from 10.2 g/dL (preoperative) to 8.6 g/dL (postoperative). One unit of weakly crossmatch-incompatible Fy(a–), C–, E–, K–, and sickle cell hemoglobin S (HbS)-negative RBCs was transfused without incident, and the patient was discharged. Several days later, the reference lab reported two new specificities, anti-Jo^a and anti-Jk^b. Fortunately, the transfused RBC unit was Jk(b–). Therefore, the crossmatch incompatibility was attributed to anti-Jo^a, which targets a high-prevalence antigen found in 100 percent of most populations. Two weeks after discharge, the patient returned in sickle vaso-occlusive pain crisis. The patient was clinically stable, but her Hb was 6.7 g/dL. One unit of Fy(a–), Jk(b–), C–, E–, K–, HbS– RBCs, which was weakly crossmatch-incompatible, was transfused. The following day, her Hb was unchanged, lactic acid dehydrogenase increased from 951 to 2464 U/L, potassium increased from 3.7 to 4.6 mEq/L, creatinine increased from 0.60 to 0.98 mg/dL, and the patient developed a 38.4°C fever. These findings are consistent with a delayed hemolytic transfusion reaction (DHTR), mediated by anti-Jo^a, occurring 2 weeks after the first RBC transfusion. Further care could not be provided because the patient left the hospital against medical advice. The purpose of this case study is to report findings consistent with a DHTR attributed to anti-Jo^a, an antibody with relatively unknown clinical significance. ***Immunohematology* 2017;33:73–75.**

Key Words: Jo^a, delayed hemolytic transfusion reaction (DHTR), Dombrock blood group system, high-prevalence antigen

The Dombrock blood group system consists of antithetical antigens, Do^a and Do^b, and the high-prevalence antigens, Gy^a, Hy, Jo^a, DOYA, DOMR, and DOLG.[1,2] The *DO* gene is located on chromosome 12p12.3, contains 3 exons, and encodes a protein comprised of 314 amino acids.[1–3] The Do glycoprotein is an ADP-ribosyltransferase (CD297) that is linked via glycosylphosphatidylinositol (GPI) to the red blood cell (RBC) membrane.[1] The glycoprotein is absent in the Do_{null} phenotype, known as Gy(a–), which is rarely found in persons of white, black, Japanese, and Chinese populations.[2] The Gy(a–) phenotype is not associated with pathology, although the RBCs of patients with paroxysmal nocturnal hemoglobinuria Type III lack the Do glycoprotein.[3] Dombrock antibodies are typically IgG-restricted, weakly reactive, and do not activate complement.[2] Anti-Do^a and -Do^b can cause acute[4] and delayed hemolytic transfusion reactions, but not hemolytic disease of the fetus and newborn (HDFN).[2] Rare literature reports about anti-Jo^a exist, linking this specificity to delayed hemolytic transfusion reactions (DHTRs).[1,5]

The Jo(a–) phenotype is caused by the 350C>T nucleotide substitution, causing an amino acid change from Thr to Ile at amino acid position 117.[1] To date, only rare African-American individuals have been identified with the Jo(a–) phenotype,[2] although more than 99 percent of these individuals express Jo^a.[2] RBC genotyping of ethnic groups in West, Central, and East Africa revealed the allele frequencies for *DO*01.–05,* the Jo(a–) phenotype, to be as high as 15 percent.[6] Jo^a and Hy (ISBT [International Society of Blood Transfusion] allele *DO*02.–04*) show a phenotypical relationship. RBCs that are Jo(a–) have weak reactivity with anti-Do^a, no or weak reactivity with anti-Do^b, reactivity with anti-Gy^a, and weak reactivity with anti-Hy.[2] RBCs that are Hy– often type as Jo(a–), and the proximity of Hy (amino acid 108) and Jo^a (amino acid 117) likely explains this phenomenon.[3] Nevertheless, some Hy– RBCs have been shown to express weak Jo^a.[7] Patients who are Jo(a–) may be either *DO*01.–05/DO*01.–05* or *DO*02.–04/DO*01.–05*.[2] Because of past confusion of anti-Hy as anti-Jo^a, it is best to use reagent RBCs tested by DNA analysis to confirm anti-Jo^a specificity.[2]

Case Report

A 32-year-old African-American woman with a history of sickle cell disease (SCD) was seen for left total hip arthroplasty due to avascular necrosis of the femoral head. Blood type and an antibody detection test were ordered on the day of surgery. The patient's RBCs typed as group O, D+. Previous records showed a known anti-Fy^a, acquired from past transfusion. The

antibody identification panel showed weak to 1+ panreactivity with Fy(a–) cells. The patient was last transfused with RBCs 2 years earlier, was not on a chronic transfusion regimen, and had no history of transfusion reactions. The autocontrol and direct antiglobulin test (DAT) were negative, so a novel alloantibody was suspected. Because the antibody identification was inconclusive, a pre-transfusion blood sample was sent to a reference laboratory for antibody identification and RBC genotyping. Later that day, the surgery was performed with an estimated blood loss of 450 mL, reducing the hemoglobin (Hb) from 10.2 to 8.6 g/dL (reference range 14.0–18.0 g/dL). One unit of RBCs was ordered emergently. One unit of Fy(a–), C–, E–, K–, HbS– RBCs was selected, but was weakly crossmatch incompatible. The unit was released with a risk form with orders to "transfuse with caution." The transfusion proceeded without incident, and the patient was discharged in stable condition.

Several days after discharge, the reference lab reported their findings. Anti-Fy^a and new anti-Jo^a and anti-Jk^b were identified. The RBC unit transfused during the hospitalization was known to be Jk(b–). Thus, the crossmatch incompatibility was attributed to anti-Jo^a, which targets a high-prevalence antigen found in 100 percent of most populations. The anti-Jo^a was reactive by indirect antiglobulin test (IAT), polyethylene glycol (PEG)-IAT, and ficin-IAT. Genotyping predicted the patient's RBCs to be Fy(a–b–), Do(a+b+), Jo(a–), and Hy+. In addition, the patient was homozygous for the Duffy null promoter *FY*02N.01* and for *RHCE*01.01,* which is associated with altered expression of e and the presence of a variant e allele.[8]

The patient was non-compliant with her prophylactic medications, and 2 weeks after discharge, the patient was admitted to the hospital because of a sickle-related vaso-occlusive pain crisis. Although the patient was clinically stable, her Hb was 6.7 g/dL, so 1 unit of RBCs was emergently ordered. One unit of Fy(a–), Jk(b–), C–, E–, K–, HbS– RBCs, which was weakly crossmatch incompatible, was transfused. The crossmatch incompatibility was attributed to anti-Jo^a. Several hours after completion of the transfusion, the patient's temperature peaked at 38.4°C, which was 37.1°C pre-transfusion. On the following day, the Hb was unchanged. Lactic acid dehydrogenase (LDH) increased from 951 to 2464 U/L (reference range 120–246 U/L), potassium (K+) increased from 3.7 to 4.6 mEq/L (reference range 3.5–5.5 mEq/L), and creatinine (Cr) increased from 0.60 to 0.98 mg/dL (reference range 0.6–1.60 mg/dL). The clinical team suspected a hemolytic transfusion reaction. The patient was informed about the suspected transfusion reaction; however, the patient was upset and left the hospital against medical advice.

Discussion

This case report serves to contribute to the rare literature implicating anti-Jo^a in DHTRs.[1,5] Jo^a is a high-prevalence antigen in the Dombrock blood group system, which is found in 100 percent of most populations. Only African-American individuals have been identified as being Jo(a–); although the antigen is still present in greater than 99 percent of individuals in this population. Because finding Jo(a–) units can be nearly impossible in an emergent setting, it is important to understand the clinical significance of anti-Jo^a.

The patient presented in this case report demonstrated findings consistent with that known about the Jo(a–) phenotype. The patient was African American, and her RBCs typed as Do(a+b+) and Hy+. On two separate occasions, the patient was transfused with 1 unit of RBCs, each of which was weakly crossmatch incompatible, attributed to anti-Jo^a. Transfusion of the first RBC unit was not immediately associated with symptoms of a transfusion reaction. However, 2 weeks later, the patient returned with an Hb of 6.7 g/dL. The patient received a second RBC unit that was weakly crossmatch incompatible, also attributable to anti-Jo^a. On the following day, the Hb remained unchanged, LDH spiked, K+ and Cr increased, and the patient experienced a new-onset fever. These findings are consistent with a DHTR, occurring 2 weeks after transfusion of the first RBC unit. DHTRs typically occur days to weeks after transfusion and are mediated by non-brisk extravascular hemolysis. Patients may be asymptomatic, but with unexplained anemia. Fortunately, most DHTRs have a benign course and require only supportive care, with monitoring of the hematocrit.

In retrospect, the transfusion reaction was potentially avoidable. Both RBC transfusions could be categorized as overtransfusion because the patient was clinically stable before being transfused. On the day after the first transfusion of 1 RBC unit, the patient was discharged because she was clinically stable, just as she had been prior to transfusion. In addition, the second transfusion of 1 RBC unit could have been avoided. In general, patients with SCD who are clinically stable with a high reticulocyte count do not need RBC transfusions.[9] This patient was in sickle pain crisis in stable condition with a 6.7 g/dL Hb and reticulocyte count of 11.9%. From the perspective of judicious transfusion medicine practice, the risk of a hemolytic transfusion reaction from a crossmatch-incompatible RBC unit outweighed the potential benefits.

Other transfusion management options could have been considered in a non-urgent/non-emergent setting. Rare donor registries, such as the American Rare Donor Program (ARDP), are an effective tool for finding antigen-negative RBC units. Although they are even more rare than Jo(a–) units, Gy(a–) units would also be compatible because Gy(a–) represents the Do_{null} phenotype. Family members of the patient could have been tested to identify those who were ABO compatible, Fy(a–), Jk(b–), C–, E–, K–, HbS–, and possibly Jo(a–). Another option to ensure the safety of transfusion therapy is the monocyte monolayer assay (MMA).[10] This could have been used to predict the clinical significance of the anti-Jo^a. An MMA with a monocyte index of more than 5 percent would have supported avoidance of transfusion in this case. Lastly, hemoglobin-based oxygen carriers (HBOCs) may become an alternative therapy for patients requiring RBCs that are difficult to obtain. Some patients may be able to receive HBOCs through clinical trials.[11]

Conclusions

This case report presents findings that are consistent with a DHTR due to anti-Jo^a, a rare antibody of relatively unknown clinical significance. The transfusion medicine service should be aware that anti-Jo^a has been implicated in DHTRs. The risks and benefits of transfusing an incompatible unit should be assessed for each patient. Because Jo^a is a high-prevalence antigen, securing Jo(a–) blood can be nearly impossible in an urgent/emergent setting. In a non-emergent setting, accessing the ARDP, testing likely Jo(a–) blood donors, such as persons of African-American ethnicity and family members, and the use of hemoglobin-based oxygen carriers are possible options to avoid hemolytic reactions. Fortunately, several weeks after the transfusion reaction, the patient returned to our hospital as an outpatient in stable condition.

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