Case report: massive postpartum transfusion of Jr(a+) red cells in the presence of anti-Jr^a

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Jr^a is a high-prevalence antigen. The rare Jr(a–) individuals can form anti-Jr^a after exposure to the Jr^a antigen through transfusion or pregnancy. The clinical significance of anti-Jr^a is not well established. This study reports a case of a 31-year-old woman with a previously identified anti-Jr^a who required massive transfusion of RBCs after developing life-threatening postpartum disseminated intravascular coagulopathy. Despite the emergent transfusion of 15 units of Jr^a untested RBCs, she did not develop laboratory or clinical evidence of acute hemolysis. The patient's anti-Jr^a had a pretransfusion titer of 4 and a monocyte monolayer assay (MMA) reactivity of 68.5% (reactivity > 5% is considered capable of shortening the survival of incompatible RBCs). The titer increased fourfold to 64 and the MMA reactivity was 72.5% on Day 10 posttransfusion. Review of laboratory data showed evidence of a mild delayed hemolytic transfusion reaction by Day 10 posttransfusion. Despite rare reports of hemolytic transfusion reactions due to anti-Jr^a in the literature, most cases, including this one, report that this antibody is clinically insignificant or causes only mild delayed hemolysis. Clinicians should be advised to balance the risks of withholding transfusion with the small chance of significant hemolysis after transfusion of Jr(a+) RBCs in the presence of anti-Jr^a. ***Immunohematology* 2005;21:97–101.**

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Jr^a is a high-prevalence antigen in all populations. The Japanese population has the highest frequency of the Jr(a–) phenotype. However, even in that population, the incidence is reported to be only 0.03 to 0.12 percent.[1] Because of its rarity, the clinical significance of anti-Jr^a is not well established. Reid and Lomas-Francis[2] describe anti-Jr^a as being capable of causing decreased RBC survival. In the obstetric setting, the authors note that although the DAT can be positive, anti-Jr^a is not associated with HDN.

Jr(a+) RBCs have been transfused to individuals with anti-Jr^a without incident.[3–5] On the other hand, there exist in the literature a dozen or so reports highlighting the ability of anti-Jr^a to cause both mild to moderate HDN and delayed hemolytic transfusion reactions.[6] The typical hemolytic reaction associated with anti-Jr^a is delayed, extravascular, and self-limited, and the decreasing Hct is usually accompanied by transiently increased antibody titers.[7] More recently, Kwon et al.[6] reported a case of anti-Jr^a causing acute hemolysis. In this report, we describe the case of a patient with anti-Jr^a who developed postpartum disseminated intravascular coagulopathy (DIC) and received 15 units of incompatible Jr(a+) RBCs. Subsequently she had no overt clinical signs of hemolysis, and laboratory findings suggested only mild delayed hemolysis.

Case Report

A 31-year-old multiparous Vietnamese woman with history of three previously uncomplicated pregnancies (with a different partner from the current pregnancy) presented for prenatal care at an outside facility in the 32nd week of her fourth pregnancy. ABO/D typing showed the patient's RBCs to be Group A, D+. The antibody screen test showed that the patient's serum reacted weakly with all reagent RBCs in the antiglobulin phase of testing. RBC treatment using either DTT or ficin had no effect on reactivity. The autologous control and DAT were negative; thus an antibody directed at a high-prevalence antigen was suspected. The patient's serum was then tested with several RBC samples lacking various high-prevalence antigens, including k, Kp^b, and Ch, and RBCs with very weak U expression. All RBCs tested reacted with the patient's serum. The specimen was subsequently referred to our laboratory, where phenotyping of the patient's RBCs for high-prevalence antigens showed that her RBCs possessed Vel, Di^b, k, and Kp^b antigens but lacked Jr^a antigens. Jr(a–) RBCs from two different donors located through Serum Cells and Rare Fluids Exchange (SCARF) were not agglutinated by the patient's serum, which was consistent with the presence of anti-Jr^a. Allogeneic adsorptions were

performed with W.A.R.M-treated RBCs (W.A.R.M.; Immucor Inc., Norcross, GA) that were also phenotypically matched for Rh and Kidd antigens. No additional alloantibodies were detected in the serum. The anti-Jr^a was shown to have a titer of 4. Because of the difficulty in locating Jr(a–) RBCs, and the possibility of shortened survival of transfused Jr(a+) RBCs, we recommended autologous donation or screening family members in the hope of finding a compatible donor if there was a reasonable concern that the patient or the baby might need transfusion during the pregnancy and delivery.

The patient went into labor during the 38th week of her pregnancy and vaginally delivered a healthy male infant without evidence of HDN. Her postpartum course was complicated by development of DIC and profuse, life-threatening vaginal bleeding, which necessitated an emergent abdominal hysterectomy. Intraoperatively, she received four units of uncrossmatched Group O, D– RBCs and 11 units of crossmatch-incompatible Group A, D+ RBCs. Because of the high incidence of Jr^a, all of the RBC units were presumably Jr(a+). Her hemorrhage was eventually brought under control after the surgery. Clinically, there was no evidence of acute intravascular hemolysis during the resuscitation effort.

Approximately 15 days after the initial surgery, the patient was found to have developed abdominal abscesses. Because surgery with possible significant blood loss was anticipated, and because of the case report from Kwon et al.[6] reporting acute hemolysis after repeated exposures to Jr(a+) RBCs, two frozen units of Jr(a–) RBCs were imported from Blood Bank of Hawaii. Of note, the only other possible source of units of Jr(a–) RBCs at that time was from Japan. However, these units would not have been immediately available and would not have been fully tested for transfusion-transmissible diseases according to FDA guidelines. Initial attempts at computerized tomography–guided drainage of the abscesses were complicated by perforation of the colon. This necessitated a laparotomy for hemicolectomy and abscess drainage. Both units of Jr(a–) RBCs were transfused intraoperatively without incident. The patient did not require further transfusions. Twelve days after the second surgery, her Hct was stable at 36.8%.

Materials and Methods

Antibody detection and identification were performed by tube method. Antibody detection tests were performed using reagent RBCs (Immucor, Inc.). Antibody identification was performed using panels of reagent RBCs (Ortho-Clinical Diagnostics, Inc., Raritan, NJ, and Immucor, Inc.). Panels of ficin-treated RBCs (Immucor, Inc.) were also used. DTT-treated RBCs were prepared using 0.2 M solution (DTT, Sigma-Aldrich Corp., St Louis, MO). Alloadsorption was performed using W.A.R.M.-treated RBCs (W.A.R.M.; Immucor, Inc.), which were also phenotypically matched for Rh and Kidd antigens.

Polyspecific and monospecific DATs were performed (Bioclone Anti-IgG, Bioclone Anti-C3d, and Bioclone AHG, Ortho-Clinical Diagnostics) by standard tube method. The elution was performed using the rapid acid method (Elukit II, Gamma Biologicals, Inc., Houston, TX). Two different enhancement media (PEG, Gamma Biologicals, and O.A.E.S., Ortho-Clinical Diagnostics) were used to enhance antibody agglutination. Antibody titer was determined with serial dilutions of patient's serum using IAT.

Patient's RBCs were phenotyped using conventional methods for the common antigens. Rare antisera and reagent RBCs were prepared in-house or provided through SCARF. Monocyte monolayer assay (MMA) was performed by the American Red Cross Blood Services of Southern California Region, Los Angeles, California. The method was described in detail elsewhere.[8]

Results

Anti-Jr^a was not detectable in the serum immediately after the transfusion of the 15 units of uncrossmatched (presumably Jr[a+]) RBCs. This was not surprising because of the large volume of crystalloid solutions and blood components administered during the resuscitation. The DAT using polyspecific anti-human globulin at this time was weakly positive (1+), but the patient's RBCs were negative in the DAT using anti-C3d or anti-IgG. An eluate was performed and tested and found to contain anti-Jr^a. Allogeneic absorption of the eluate, using W.A.R.M-treated RBCs that were also phenotypically matched for Rh and Kidd, did not show any additional alloantibodies.

Because of the concern for a significant delayed hemolytic transfusion reaction, we recommended that the clinicians give intravenous fluids as necessary to maintain adequate renal perfusion and monitor laboratory values, including Hct, bilirubin, LDH, and haptoglobin. Additionally, a sample was sent daily to our reference laboratory for DATs and evaluation for

hemolysis. The patient's Hct decreased from 38.6% on Day 5 posttransfusion to 30.9% on Day 10. Of note, during this period the patient also developed syndrome of inappropriate antidiuretic hormone secretion and hyponatremia. The resulting fluid retention and dilutional anemia contributed to the decreasing Hct and made it unlikely that it was solely due to hemolysis. On Day 10 posttransfusion, the total bilirubin increased from 0.4 mg/dL at the time of transfusion to 1.6 mg/dL (normal range 0.2–1.0 mg/dL) and LDH increased from 307 to 431 IU/L (normal range 91–180 IU/L). Haptoglobin levels were obtained only on Days 4 and 5 posttransfusion; both were well within normal range. Anti-Jr[a] became detectable in the serum again on Day 6 posttransfusion and the titer had risen from a pretransfusion titer of 4 to 64. Concurrently, the reactivity of the polyspecific DAT increased from 1+ to 2+, and both the monospecific DATs (using anti-IgG and anti-C3) reacted 2+ at 6 days posttransfusion. Both the prenatal pretransfusion serum sample and a serum sample obtained on Day 10 posttransfusion were sent for MMA testing, which showed 68.5% and 72.5% reactivity respectively (reactivity > 5% is considered capable of shortening the survival of incompatible RBCs). However, visual check of serial serum samples showed no evidence of hemolysis, and the patient continued to have no overt clinical evidence of intravascular hemolysis during the posttransfusion period. Select laboratory values are shown in Table 1.

Table 1. Results of select pertinent laboratory tests pretransfusion and in the days after massive transfusion of 15 units of presumably Jr(a+) RBCs in the presence of anti-Jr[a].

Day (posttransfusion)	Hct (%)	Na (135–145 mmol/L)*	LDH (91–180 IU/L)*	Total bilirubin (0.2–1.0 mg/dL)*	DAT	Anti-Jr[a] titer	Other lab values
–30 (pretransfusion)	–	–	–	–	Negative	4	MMA reactivity: 68.5% (≤ 5%)*
0	24 50.7 7.4	131	307	0.4	–	–	Prothrombin time = 36.5, International normalized ratio = 3.53, Partial prothrombin time =138.8 Fibrinogen = 72 mg/dL D-dimer > 10,000 ng/mL Platelet = 13 × 10^9/L
1	33.2	139	–	0.9	Polyspecific: 1w anti-IgG: 0 anti-C3: 0	–	–
4	33.4	138	261	–	–	–	Haptoglobin 121 (43–212 mg/dL)*
5	38.6	125 118 123	333	–	Polyspecific: 2+ anti-IgG: 2+ anti-C3: weak	–	Haptoglobin 101 (43–212 mg/dl)* Urine bilirubin negative
6†	38.2	123	391	–	Polyspecific: 2+ anti-IgG: 2+ anti-C3: 2+	64	–
8†	33.6	132	386	2.2 Direct 0.5	Polyspecific: 1+ anti-IgG: 1+ anti-C3: 1+	64	–
10†	30.9	132	431	1.6	Polyspecific: 2+mf anti-IgG: 1+mf anti-C3: 1w mf	64	MMA reactivity: 72.5% (≤ 5%)*
15‡	28.8	133	–	–	Polyspecific: 2+ anti-IgG: 1+ anti-C3: 2+	–	–
17	25.2	132	372	0.7 Direct 0.1 (0.0–0.2 mg/dL)*	–	–	Haptoglobin 201 (43–212 mg/dl)* Urine bilirubin negative
20	30.0	128	–	0.6	–	–	–
27	36.8	134	–	–	–	–	–

*Normal range values

†Results from Days 6 to 10 show evidence of onset of mild delayed hemolysis. Visual checks of serum showed no evidence of hemolysis through this period.

‡On Day 15, patient underwent abdominal surgery and received two units of Jr(a–) RBCs intraoperatively.

Discussion

Because of the rarity of anti-Jr^a, its clinical significance is not clear. Several reports of anti-Jr^a causing mild to moderate HDN[9,10] exist in the literature, but others have questioned the validity of the diagnoses in such cases.[11] Mild to moderate delayed hemolytic transfusion reactions[9,12,13] have also been reported in association with anti-Jr^a. More recently, Kwon et al.[6] reported a concerning case of acute hemolytic transfusion reaction due to this antibody in the setting of repeated exposures to the antigen within a week. On the other hand, others have reported no clinical evidence of hemolysis after incompatible transfusions, even in the face of rising antibody titers.[4] Studies using monocyte phagocytosis[14] and MMA[8,15] suggested that most anti-Jr^a are not clinically significant. The lack of clinical significance in most cases could be in part accounted for by the low antigen density of Jr^a on the RBC membrane.[14,16]

Additional data are needed to fully establish the clinical significance of anti-Jr^a. The MMA has been proposed as a valuable tool for predicting the clinical significance of antibodies to high-prevalence antigens such as anti-Jr^a.[8,15] A recent retrospective review of 20 years of MMA data by Arndt and Garratty[8] showed that only results greater than 5% are potentially clinically significant. Furthermore, one-third of patients with MMA results between 5.1% and 20% had clinical signs of hemolysis (defined as jaundice, fever, chills, change in blood pressure, back pain, vomiting, tachypnea, and hemoglobinuria[8]), and two-thirds of patients with MMA results greater than 20% reactivity had such symptoms. When clinical signs of hemolysis were absent, patients from both groups often had laboratory indications of hemolysis, which included decreased Hb, Hct, and haptoglobin, increased bilirubin or LDH, hemoglobinemia, or the presence of bilirubin in the urine. In the same review, only 5 out of 14 (36%) cases of anti-Jr^a examined showed MMA reactivity greater than 5%, two of which had reactivity greater than 20%. But the positive predictive value of the MMA result for hemolysis is not established specifically for anti-Jr^a because of the small number of cases and the lack of associated clinical information. Through a personal communication with these authors, we learned that clinical information was available on 4 of the 15 cases. Two of these cases had MMA results greater than 20%. Of these, one experienced a transfusion reaction with the infusion of a third unit of Jr(a+) RBCs. This is the same case reported by Kwon et al.[6] In the other case, flow cytometry showed normal RBC survival compared with the calculated expected RBC survival rate. Clinically the patient did not have signs of hemolysis. Clinical information on the other 11 patients is unavailable. In our case, despite the strong MMA reactivity both before and after the transfusion of a total of 15 units of incompatible RBCs, we found no clinical evidence of hemolysis and only laboratory evidence of very mild, well-tolerated, delayed hemolysis. The decrease in Hct was at least in part due to dilutional anemia and postoperative surgical blood loss.

It is likely that most transfusions of Jr(a+) RBCs will not result in significant acute or delayed hemolysis in the presence of anti-Jr^a. However, because anti-Jr^a can cause significant acute hemolysis at least in rare cases after repeated exposures to Jr(a+) RBCs[6], it is prudent to make a reasonable attempt to locate Jr(a–) RBC units when anti-Jr^a is identified, especially in those cases with strongly positive MMA results. If blood loss can be anticipated, as in the case of an elective surgery or delivery, autologous donations should be encouraged. It may also be necessary to look into family members and rare donor registries as potential sources of compatible units because of the extreme scarcity of the Jr(a–) phenotype in North America. It is important to weigh the availability of Jr(a–) RBCs against the cost and the infectious disease risks when importing such units from countries outside the United States or older units frozen before the availability of the most current infectious disease testing. In our opinion, the risks of acquiring an infectious disease appear to outweigh the risks of transfusing Jr(a+) units, and clinicians should be guided in this way. Additionally, clinicians should be advised of the available serologic results, which might include antibody titer, DAT reactivity, and MMA results. The limitations of these data and the lack of conclusive information in the current literature regarding the clinical significance of anti-Jr^a must be made clear as well. The clinical decision to transfuse Jr(a+) RBCs and the risks of hemolysis after transfusion of incompatible RBCs must also be evaluated against the risks of withholding transfusion. The recent guidelines of the UK National Blood Service[17] recommended transfusing serologically least-incompatible RBCs to patients with anti-Jr^a and antigen-negative RBCs to patients with strong anti-Jr^a when transfusion is necessary. We feel this approach is reasonable given the rarity of Jr(a–) RBC units, the lack of data we have about anti-Jr^a, and the lack of laboratory assays that can reliably predict its clinical significance.

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