Case Report

Successful Management of the Fetal Severe Anemia Associated with Jra Alloimmunization by Intrauterine Transfusion of Jr(a+) Red Blood Cells

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Objective. We present a case of fetal severe anemia associated with Jra alloimmunization, which was managed using Doppler measurement of the peak systolic velocity of the fetal middle cerebral artery (MCA-PSV) and intrauterine transfusion (IUT) of Jr(a+) red blood cells (RBCs). We also review the previous case reports on fetal or neonatal anemia associated with Jra alloimmunization.

Case Report. A woman with Jra alloimmunization was referred to our department at 29 weeks of gestation. As fetal MCA-PSV exceeded 1.55 multiples of the median, fetal blood sampling was performed and demonstrated severe anemia. During the course, a total of two IUTs were performed using Jr(a+) RBCs. The neonate was delivered by repeated cesarean section at 35 weeks of gestation and showed no apparent signs of hemolysis.

Conclusion. Based on the literature review, fetal anemia associated with Jra alloimmunization becomes severe during mid-gestation and may not develop during late gestation. The severity of fetal anemia is predicted by MCA-PSV Doppler assessment rather than the maternal anti-Jra titers. Timely IUT of Jr(a+) RBCs can help to prolong the pregnancy to term in emergency situations wherein compatible blood of Jr(a-) RBCs is not available soon.

1. Introduction

Fetal anemia can cause fetal high-output cardiac failure, fetal hydrops, iatrogenic preterm delivery, and fetal demise [1]. Therefore, fetal anemia is still an important cause of fetal and neonatal mortality and morbidity in modern obstetric practice.

The Jra antigen, which is a high-incidence red blood cell (RBC) antigen, is known to be involved in hemolytic anemia of the fetus and newborn [2, 3]. The expression of Jra antigen is regulated by the ATP-binding cassette G2 (ABCG2) gene on chromosome 4q22.1 and Jra antigen is located on ABCG2 transporter, which is highly expressed on cells of the erythroid lineage [3, 4]. The Jr(a-) phenotype results from the inheritance of ABCG2 null alleles caused by frameshift or nonsense mutations such as c.1515delC (p.Ala505fs), c.376C>T (p.Gln126Ter), c.421C>A (p.Gln14Lys), and c.1723C>T (p.Arg575Ter), particularly in Japanese individuals [3, 5, 6]. Furthermore, the variation in the Jra antigen density on RBCs among Jr(a+) individuals with genetic mutations at 376 and 421 has also been reported [7].

Although anti-Jra can be produced in Jr(a-) women due to pregnancy or incompatible Jr(a+) RBC transfusion and cross the placenta, the effect of anti-Jra on fetal anemia remains unclear [4, 7–11]. For example, the fetal anemia associated with anti-Jra positivity is reported to be mild [8, 9]. In contrast, several reports have shown an association between Jra alloimmunization and fetal or neonatal severe anemia requiring intervention [4, 10, 11]. In addition, in one case, neonatal death occurred due to Jra alloimmunization [10].

We report a case of fetal severe anemia associated with Jra alloimmunization that was successfully managed by close fetal monitoring and intrauterine transfusion (IUT) of Jr(a+)
were obtained by searching PubMed or Medical Online for the terms “Jr(a)”, “hemolytic disease”, “fetus”, and “anemia”. All reports and publications in English or Japanese from 2006 to 2016 were reviewed. Cases at Nagara Medical Center, a tertiary center in Japan, were also included.

2. Clinical Case

The patient was a 34-year-old Japanese woman (gravida 5 para 2, including 2 miscarriages) with blood group O type RhD (+). She was referred to our department in the 29th week of her fifth pregnancy for perinatal management. She had no relevant medical history and had never received a blood transfusion. Screening performed when she was pregnant with her first child revealed Jr(a-) and anti-Jra with a titer of 1:512. Her Jr(a-) genotype was c.376T/T and c.421C/C. Her partner was Jr(a+) with c.376C/C and c.421C/A. Her first child of 2590g was delivered at 36 weeks of gestation due to previous CS at the referring hospital. The neonate of 2114g had anemia (Hb 9.2g/dL, Hct 28.4%) with jaundice (total bilirubin 1.7mg/dL) based on a positive direct antiglobulin test DAT, without jaundice (total bilirubin 1.7mg/dL) (Table 1). On the sixth day after the first IUT (30 weeks and 6 days), the titer of anti-Jra increased from 1:256 to 1:512. The IgG subclass was found to be IgG1 and IgG3. Her partner was Jr(a+) with c.376C/C and c.421C/A. Her first child of 2590g was delivered at 36 weeks of gestation due to previous CS at the referring hospital. The neonate of 2114g had anemia (Hb 9.2g/dL, Hct 28.4%) with jaundice (total bilirubin 1.7mg/dL) based on a positive direct antiglobulin test DAT, without jaundice (total bilirubin 1.7mg/dL) (Table 1). On the sixth day after the first IUT (30 weeks and 6 days), the titer of anti-Jra increased from 1:256 to 1:512. The IgG subclass was found to be IgG1 and IgG3. The seventh day after the first IUT, the MCA-PSV level remained within the normal range and that the CTAR level had normalized to 31.6% (Figure 1). Her return to her referring hospital, where she was managed from 32 weeks of gestation due to previous CS at the referring hospital. The neonate of 2114g had anemia (Hb 9.2g/dL, Hct 28.4%) with a positive DAT, without jaundice (total bilirubin 1.7mg/dL) (Table 1). On the second day after birth, the neonatal anemia worsened (8.0g/dL) and a blood transfusion was performed.

RBCs. We also analyzed the clinical characteristics and perinatal outcome of fetal anemia due to Jra alloimmunization. Cases were obtained by searching PubMed or Medical Online for the terms “Jr(a)”, “hemolytic disease”, “fetus”, and “anemia”. All reports and publications in English or Japanese from 2006 to 2016 were reviewed. Cases at Nagara Medical Center, a tertiary center in Japan, were also included.

Table 1: The fetal blood analysis.

| GA Weeks + days | Pre-IUT Hb(g/dL)/Hct(%) | Post-IUT Hb(g/dL)/Hct(%) | Volume of IUT (ml) | T-bil (mg/dL) | DAT |
|----------------|--------------------------|--------------------------|--------------------|---------------|-----|
| 30+0 (first IUT) | 3.5/9.9 | 7.2/22.1 | 70 | N/A | N/A |
| 31+2 (second IUT) | 6.1/18.6 | 9.5/29.1 | 35 | N/A | N/A |
| 35+1 (at birth) | 9.2/28.4 | - | 1.7 | + |

GA: gestational age; Hb: hemoglobin; Hct: hematocrit; IUT: intrauterine transfusion; T-bil: total bilirubin; DAT: direct antiglobulin test; N/A: not available.

**Table 1:** The fetal blood analysis.

| GA Weeks + days | Pre-IUT | Post-IUT | Volume of IUT | T-bil | DAT |
|----------------|---------|----------|---------------|-------|-----|
| 30+0 (first IUT) | 3.5/9.9 | 7.2/22.1 | 70 | N/A | N/A |
| 31+2 (second IUT) | 6.1/18.6 | 9.5/29.1 | 35 | N/A | N/A |
| 35+1 (at birth) | 9.2/28.4 | - | 1.7 | + |

**Figure 1:** The peak systolic flow velocity of the fetal middle cerebral artery during pregnancy. (—) The median MCA-PSV level in normal pregnancies; (**) 1.55 MoM; (*) our case. MCA-PSV: the peak systolic flow velocity of the fetal middle cerebral artery; MoM: multiple of the median.
Neither neonatal anemia nor jaundice developed after the single blood transfusion. The neonate was discharged from the hospital without phototherapy.

To investigate the phenotype and the Jra antigen density of the neonate, an analysis of the ABCG2 gene was performed at Japanese Red Cross Tohoku Block Center. Genomic DNA was extracted from the peripheral blood and PCR-SSP was used to examine the genetic base substitutions at positions 376, 421, 1515, and 1723, which are most common in Japanese Jra(–) individuals [7]. The neonate’s phenotype was classified as Jra(a+); the neonate was heterozygous for c.376C/T with no mutation at position 421 (c.421C/C), which was the same genotype of the second child.

3. Discussion

We presented a case of fetal severe anemia associated with Jra alloimmunization in which the pregnancy was successfully prolonged by Doppler measurements of the MCA-PSV and timely IUT. This is also the first case report describing the performance of IUT using Jra(a+) concentrated RBC units. In the present case, fetal anemia did not develop after the IUT of Jra(a+) RBCs and the neonate’s blood exam did not show any evidence of hemolysis.

Several clinical investigations and experimental studies have been performed to elucidate the precise pathogenesis of fetal anemia associated with Jra alloimmunization [4, 7, 9–17]. There are ten reports, including our own, describing fetal or neonatal anemia in association with Jra alloimmunization (Table 2). A review of the literature revealed several features of the clinical course of fetal anemia with Jra alloimmunization (Table 2). First, the cases that required IUT suggested that the fetal anemia becomes severe during mid-gestation; however, it is unclear when anemia occurs. Furthermore, the fetal anemia was not exacerbated during late gestation. In the present case, fetal anemia did not develop after the second IUT of Jra(a+) RBCs and the neonate’s blood exam did not show any evidence of hemolysis.

In this review, the majority of clinical data analyzed are derived from Japanese women (9 women were Japanese and 1 was Caucasian of Gypsy Spanish origin [10]), so it is necessary to be cautious about applying our results to other racial groups.

Experimental studies have demonstrated that the ABCG2 is expressed on not only cells of the erythroid lineage but also the placenta and that it is a plasma membrane protein extruding endogenous and exogenous substrates, such as xenobiotics, heme, porphyrin, and uric acid [15–17]. The maintenance of cellular porphyrin and heme homeostasis, which constitute an essential component of hemoglobin, by ABCG2 is thought to perform a vital physiological function in erythropoiesis [17]. Taken together, these clinical and experimental findings suggest that anti-Jra antibodies may directly affect the function of ABCG2 and may cause fetal anemia due to ineffective erythropoiesis.

One of the important findings in our case was that pregnancy could be prolonged by incompatible IUT with Jra(a+) RBC units. In the present case, we were not able to obtain Jra(a-) RBC units because of the low incidence of Jra(a-). As a result, a total of 105 ml of Jra(a+) RBCs were transfused and fetal anemia did not develop after the second IUT. The sufficient efficacy of incompatible transfusion using adult Jra(a+) RBCs may be partly due to a low expression of ABCG2 on adult RBCs compared with fetus [4]. In the setting of incompatible transfusions in adults, whereas most reported cases showed a mild and delayed hemolytic transfusion reaction, an acute hemolytic transfusion reaction also has been reported, suggesting that anti-Jra is a possible cause of transfusion-related hemolysis [18–20]. Therefore, IUT of Jra(a+) RBCs may be considered, especially in emergency situations wherein compatible blood of Jra(a-) RBCs is not available soon [20].

Another important finding in our case was the different outcomes between the second child who did not require IUT and the present child who required IUT. Since the severity of fetal anemia may be independent of the maternal anti-Jra, we hypothesized that the Jra antigen density on fetal RBCs contributes to the severity of anemia. In contrast to
### Table 2: The clinical details and outcomes of the reported cases of Jra alloimmunization, including the present case.

| Case | GA at first PUBS or IUT (weeks) | MCA-PSV at first PUBS (MoM) | Hb (g/dL)/Hct (%)/T-bil (mg/dL) at first PUBS | Number of IUTs | Type of blood transfusion | GA at birth (weeks) | Interval between the last IUT and birth (weeks) | Hydrops fetalis | Hb (g/dL)/Hct (%)/T-bil (mg/dL) at birth | Maximum anti-Jra titer | Neonatal transfusion | Neonatal outcome |
|------|--------------------------------|-----------------------------|-------------------------------------------|----------------|--------------------------|-------------------|---------------------------------------------|---------------|------------------------------------------|-------------------|---------------------|-------------------|
| **Cases with IUT (n = 6)** | | | | | | | | | | |
| Present case | 30 | >1.55 | 3.5/9.9/ N/A | 2 | Jr(a+) | 35 | 5 | - | 9.2/28.4/1.7 | 512 | + | Alive |
| Case 2 (unrelated) | 29 | >1.55 | 5.3/15.7/1.4 | 1 | Jr(a-) | 37 | 8 | - | 9.4/29.0/1.1 | 256 | - | Alive |
| Ishihara et al. [11] | 30 | >1.55 | 3.5/7.9/1.0 | 4 | Jr(a-) | 35 | 1 | + | 7.2/ N/A/1.0 | 512 | + | Alive |
| Fujita et al. [4] | 30 | >1.5 | 8.5/26.8/ N/A | 1 | Jr(a-) | 37 | 7 | - | 11.8/35.4/2.0 | 512 | - | Alive |
| Aikou et al. [12] | 30 | >1.5 | 5.4/15.7/2.3 | 1 | Jr(a-) | 38 | 8 | - | 10.8/31.8/2.1 | 32 | - | Alive |
| Yahara et al. [13] | 27 | N/A | 3.4/11.4/1.9 | 2 | Jr(a-) | 37 | 6 | + | 12.2/37.0/1.0 | 16 | - | Alive |
| **Cases without IUT (n = 4)** | | | | | | | | | | |
| Sasamoto et al. [14] | - | - | - | 0 | - | 33 | - | - | 8.2/25.4/0.9 | 1024 | - | Alive |
| Peyrard et al. [10] | - | - | - | 0 | - | 36 | - | + | 6.4/ N/A/2.5 | 1024 | + | Neonatal death |
| Endo et al. [7] | - | - | - | 0 | - | 37 | - | - | 8.4/25.8/1.9 | 256 | - | Alive |
| Masumoto et al. [9] | - | - | - | 0 | - | 37 | - | - | 11.5/ N/A/ N/A | 64 | - | Alive |

GA: gestational age; Hb: hemoglobin; Hct: hematocrit; PUBS: percutaneous umbilical cord blood sampling; IUT: intrauterine transfusion; T-bil: total bilirubin; N/A: not available. Case 2 is unrelated to ours. The clinical data of case 2 was provided by the Department of Fetal-Maternal Medicine, Nagara Medical Center.
our hypothesis, the Jr(a+) genotype was the same in both children, suggesting that their Jr antigen density was similar and implicating the impact of ABCG2 on erythropoiesis and compensatory mechanisms when ABCG2 is inhibited by anti-Jra. There are several possibilities that could explain the intrafamilial phenotypic variability in the perinatal outcomes. One possibility is that increasing sensitization due to a previous Jr positive child may be involved in the development of fetal severe anemia. It is known that the degree of fetal anemia due to red cell alloimmunization depends on the number of affected pregnancies. Another possibility is anti-Jra titer variability. Intra- and interlaboratory variability in the titer measurement constitute a major point of concern. In addition, antibody titration, a semiquantitative method to detect the reactivity, may not reflect true biological activity in the Jra alloimmunization. Although our main goal in the management of pregnancies complicated by Jra alloimmunization is to detect fetuses that are at higher risk of developing severe anemia in order to prevent fetal hydrops [21], the clinical course of fetal anemia may be affected by various factors, such as the Jr antigen density of cells of the erythroid lineage and placenta, the maternal antibody titer, and the numbers of affected pregnancies. It is important to recognize that fetal severe anemia can occur, even if a previous child did not develop anemia.

In conclusion, it is necessary to recognize Jra alloimmunization as a possible cause of fetal severe anemia, and that this may occur through ineffective erythropoiesis and hemolysis. We think that careful obstetric management is needed, including routine Doppler measurements of the fetal MCA-PSV to detect anemia, the sampling of fetal blood by PUBS when fetal anemia is detected, and when necessary timely IUT to improve the neonatal outcomes by preventing fetal hydrops and fetal anemia-associated prematurity.

Conflicts of Interest

The authors declare no conflicts of interest in association with the present study.

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