

# Notorious anti-Jk3 in a pregnant woman

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## ABSTRACT

This is a case study of a 23-year-old pregnant Polynesian woman with anti-Jk3 identified in her plasma during her third visit to a hospital. This patient, with a history of mild anemia due to  $\beta$ -thalassemia minor and two known transfusion of packed red cells came to an emergency room complaining of severe abdominal cramps. Her hemoglobin during her second hospital visit was 7.5g/dL and her antibody screen was negative. Two units of crossmatch compatible packed cells were transfused with no adverse reaction and she was discharged. Four days post transfusion, she returned to the hospital complaining of back pain and fatigue and she was running a fever (101°F). Her antibody screen was positive, direct antiglobulin testing was also positive and the eluate showed pan-agglutination with a red cell panel. Anti-Jk3 was identified in her plasma by the Red Cross and a delayed transfusion reaction was suspected. As a result, Kidd null crossmatch compatible units were obtained from relatives. The patient was successfully transfused and was discharged with a hemoglobin of 10.1g/dL. The fetus appeared to be unaffected by the antibody. This case reiterates the hard-to-identify characteristics of Kidd antibodies and highlights the need for medical laboratory personnel to be informed on the prevalence of the Kidd null phenotype among various populations. Educating ethnic populations with rare phenotypes and organizing targeted blood drives may increase inventories of these rare blood phenotypes.

**ABBREVIATIONS:** HDFN: Hemolytic disease of the fetus and newborn, IgG: Immunoglobulin G.

**INDEX TERMS:** Anti-Jk3, Kidd null phenotype, Jk (a-b-), Kidd blood group.

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## INTRODUCTION

The Kidd blood group system is a small system with three antigens, which include, Jk<sup>a</sup>, Jk<sup>b</sup> and Jk3. The Jk<sup>a</sup> and Jk<sup>b</sup> antigens are co-dominant alleles and the Jk locus is found on chromosome 18. These antigens are well developed in fetuses.<sup>1</sup> Jk3 is considered a high frequency antigen expressed on red blood cells expressing Jk<sup>a</sup> and/or Jk<sup>b</sup> antigens.<sup>2</sup> Individuals not expressing Jk<sup>a</sup> or Jk<sup>b</sup> also do not express Jk3, and these are individuals with the null phenotype. This null phenotype, Jk(a-b-), is extremely rare in most populations, but occurs in up to 1.4% among Niueans, which is one of the Polynesian ethnic groups.<sup>3</sup> Kidd antigens have been reported to disappear and there is a high chance of a patient producing anti-Jk3 during the period of antigen disappearance. A case was reported on an 85-year old woman of Russian Jewish descent whose Kidd antigen phenotype changed from Jk(a+b-) to Jk(a-b-). The patient produced anti-Jk3 during the period that Jka was undetectable.<sup>4</sup> The anti-Jk3 identified had weak reactivity, but was able to destroy Jka positive cells. This further elucidates the peculiar characteristics of this blood group.

The Kidd antigens are not only found on the urea transporter glycoprotein of red blood cells, but they are also on the endothelial cells of the vasa recta and the renal medulla vascular vessels of the kidneys.<sup>5</sup> The Kidd glycoprotein transports urea in and out of the red blood cells and helps in concentrating urea in the kidneys.<sup>6</sup> Lack of the glycoprotein seems to have no adverse effect in Kidd null individuals although they are unable to effectively concentrate urine.<sup>5,6</sup> Kidd null individuals have a high chance of developing anti-Jk3 when exposed to antigen positive red blood cells.

The phenotypes in this system include: Jk(a+b+), Jk(a+b-) and Jk(a-b+). The null phenotype Jk(a-b-) is

extremely rare in most populations. The molecular basis for the null phenotype differs in different ethnic groups. Inheritance patterns include the inheritance of the dominant inhibitor gene *In(JK)* and the inheritance of the recessive silent allele *Jk*.<sup>1,2,5</sup> Individuals who inherit the inhibitor gene have a suppressed expression of the Kidd antigens; so they do not produce Kidd antibodies.<sup>2</sup> Mechanisms of the null phenotype attributed to the inheritance of the silent allele include: mutations in *JK\*B* alleles, mutation in a *JK\*A* allele and the deletion of two exons in a *JK\*A* allele.<sup>7</sup> Kidd antigens are poorly expressed on the red cells of individuals who inherit the dominant suppressor gene *In(JK)*; therefore they cannot produce anti-Jk3.

### What is known about Kidd antibodies?

Kidd blood group antibodies have been associated with mild to severe acute and delayed transfusion reactions. On the other hand, anti-Jk<sup>a</sup>, anti-Jk<sup>b</sup>, and anti-Jk3 rarely cause severe hemolytic disease of the fetus and newborn.<sup>5</sup> These antibodies exhibit certain characteristics which are not frequently observed in other blood group antibodies. They develop after exposure from a previous transfusion or pregnancy and are typically difficult to detect; as such, they are a common cause of delayed hemolytic transfusion reaction.<sup>1,2</sup>

Anti-Jk<sup>a</sup> and anti-Jk<sup>b</sup> rarely react with heterozygous cells; hence rule outs are performed using homozygous antigen expressions. Anti-Jk3 antibody hemolyzes donor cells having the Jk<sup>a</sup> and/ or Jk<sup>b</sup> phenotypes since Jk3 is expressed on both Jk<sup>a</sup> and/or Jk<sup>b</sup> cells.<sup>8</sup> Kidd antibodies are primarily IgG1 and IgG3 with about half of these antibodies capable of activating complement. When complement is activated, hemolysis of the transfused red blood cells ensues. The Kidd antibodies are usually weakly reactive and are always found together with other antibodies, making them notoriously difficult to detect in the laboratory.<sup>1,2,5</sup> Anti Jk3 is comparable to anti-Fy3 in the Duffy blood group system, which is produced by individuals lacking the Duffy glycoprotein; including Fy<sup>a</sup> and Fy<sup>b</sup> antigens. Anti-Fy3 also reacts with all red cells expressing Fy<sup>a</sup> and Fy<sup>b</sup> positive red cells but not Fy(a-b-) red blood cells. The Duffy antigen has also been associated with hemolytic transfusion reactions. Titers of Kidd antibodies also rapidly decrease in plasma and may not be detected at all during a pretransfusion work up.<sup>2,8</sup> Undetectable levels can be

reached as early as a few weeks or months following an antigen exposure occurrence which is what probably happened to the patient discussed below; hence, highlighting the need to always check patients' transfusion histories.<sup>1</sup>

### Case study presentation

A 25-year-old pregnant Polynesian woman with a history of mild anemia attributed to  $\beta$  thalassemia minor presented to a hospital emergency room with severe abdominal cramps and fatigue. This patient was three months pregnant with her first child and appeared jaundiced. This visit was the patient's second visit to this hospital where she had been transfused with two units of packed red blood cells four months prior to the current hospital visit. Information on possible prior transfusions at other hospitals was unavailable.

During this second visit, her hemoglobin was 7.5g/dL (Table 1), hence the physician ordered three units of blood. The patient's blood type was B positive and the antibody screens during her previous and current visits were both negative. Two units of crossmatch compatible packed red blood cells were transfused uneventfully resulting to an increase in hemoglobin (9.2g/dl). This patient started exhibiting signs of a transfusion reaction four days after receiving the packed cells. She returned to the hospital complaining of back pain, fatigue, chest discomfort and she was running a fever (101°F). This was the patient's third visit to this hospital. The patient's bilirubin and lactate dehydrogenase levels increased with a decrease in hemoglobin and hematocrit (Table 1). The physician ordered three units of blood again for this patient. The antibody screen this time was positive which was previously negative. A direct antiglobulin panel was positive with both anti-IgG and anti-C3. The eluate obtained after an acid elution tested against a red blood cell panel showed pan-agglutination. Pan agglutination was also observed with the patient's plasma. The patient's specimens were sent to the Red Cross reference laboratory where an antigen profile revealed that this patient was Kidd null and c negative (Table 2). The patient's eluate reacted with Jk<sup>a</sup> and/or Jk<sup>b</sup> positive cells, but not with Jk(a-b-), c+ cells. The patient was determined to have made anti-Jk3 and no other alloantibody was present when the eluate was tested against Kidd null cells. The transfusion reaction was attributed to anti-Jk3.

**Table 1.** Laboratory results for each hospital visit.

Hospital Visit	Hb(g/dL)	Hct(%)	RBC units Transfused	Total bilirubin Range 0.2-1.3 mg/dL	LD(U/L)	Antibody Screen	Antibody Identified
<b>Visit 1</b>							
Day 1	7.6	23.1	2	1.1		Negative	Not applicable
Day 2	9.8	29.2		0.8			
<b>Visit 2</b>							
Four months later							
Day 1	7.5	22.2	2	1.3		Negative	Not applicable
Day 2	9.2	28		0.7			
<b>Visit 3</b>							
Four days later							
Day 1	8.0	23.5		1.7		Positive	
Day 2	7.5	21.5		1.9	600		Anti-Jk3
Day 3	6.7	20.2	3	2.2			
Day 4	8	24.8		1.4			
Day 5	10.1	30.5		0.9	150		

**Table 2.** Antigen typing results

Antisera	Results
Jka	-
Jkb	-
D	+
C	+
c	-
e	-
K	+

The Red Cross did not have any compatible units for this patient, so they had to resort to other ways of getting compatible blood. Siblings and other blood relatives in the area were tested and three units of compatible blood were collected. The patient was successfully transfused with a resultant rise in the hemoglobin and hematocrit levels over the next few days. The patient was discharged with a final hemoglobin value of 10.1 g/dL and hematocrit of 30.5%. The fetus was reported to be unaffected by the anti-Jk3 antibody despite the ongoing hemolytic process in the patient. This patient's case confirms previous reports that anti-Jk3 rarely associated with hemolytic disease of the fetus and newborn or may cause very mild disease in cases where anti-Jk3 has been associated with the HDFN.<sup>9</sup> The father of the baby was unavailable for phenotype testing. The patient gave birth to a healthy baby six months later.

## DISCUSSION

The possible sources of sensitization are by transfusion and pregnancy. This patient must have been exposed to Kidd positive red cells in a previous transfusion and it is less likely that her current pregnancy is a source as she was just three months pregnant at the time. Kidd antigens, which are not very immunogenic, have been reported to reach detectable levels in fetuses at around eleven weeks gestation for Jk<sup>a</sup> and seven weeks for Jk<sup>b</sup>.<sup>1</sup> There is a higher chance of immunization with the Kidd antigens from previous transfusions compared to pregnancy as a potential source.<sup>9</sup> A case study was reported on anti-Jk3 which was identified in a multiparous woman who had been transfused four months prior to a recent emergency room visit.<sup>10</sup> The patient had an uneventful transfusion four months prior, but anti-Jk3 was identified during her next pretransfusion tests. The authors did not believe that the patient had been sensitized by her five pregnancies. If she had been sensitized by the pregnancies, she would have had a reaction during the first transfusion. The sensitization was therefore attributed to the transfusion which she had four months prior.

Strong secondary responses are common with Kidd antibodies, hence the higher occurrences of delayed hemolytic transfusion reactions.<sup>8</sup> Delayed hemolytic transfusion reactions usually occur days or up to four weeks post transfusion, although they may also occur a few hours post transfusion when re-exposure to foreign

antigen occurs. In addition, the titers of these antibodies are known to decrease shortly after being exposed; this again, was observed when the antibody screens of this patient were negative. A possible explanation is that the IgG titer must have been very low to be detected during pretransfusion testing hence, a compatible crossmatch result obtained.<sup>5</sup> This patient was thought to have experienced a delayed hemolytic reaction with a drop in hemoglobin and hematocrit (Table 1). Finding a match for patients with anti-Jk3 is very difficult just as was the case with this patient where compatible units were obtained from blood relatives.

Individuals with  $\beta$ -thalassemia minor do not depend on multiple blood transfusions for survival as they are heterozygous for the  $\beta^0$  or  $\beta^+$  thalassemia gene. These patients have a copy of the normal gene and a copy of the mutated gene. These patients usually have asymptomatic to mild hypochromic microcytic anemia not typically requiring blood transfusions. It is likely that this patient was symptomatic for anemia due to pregnancy since individuals with  $\beta$ -thalassemia minor are reported to be symptomatic when faced stressful situations such as pregnancy.<sup>11</sup>

This case reiterates the complex attributes of Kidd blood group antibodies and the need to pay close attention to the prevalence of rare antibodies observed among different ethnic groups. As a result of the rarity of Kidd null units of blood, individuals from the ethnic groups concerned need to be encouraged to provide autologous units for future use.

Autologous blood donations for long term storage should be encouraged in populations with a high incidence of rare antibodies. In addition, these populations also need to be educated on the advantages of autologous donations as well as allogeneic donations, which will not only boost the supply of rare units of blood, but also prevent alloimmunizations and prevent some adverse transfusion reactions.

Ethnic populations with rare antibodies, including anti-Jk3, need to be educated on the antibody present in their plasma that can be of help in future hospital visits; hence the need for a national electronic health information system. Clinicians and laboratory personnel are able to provide better services during future hospital visits if they have access to patient's history. Patients

without histories have a high chance of being sensitized after which transfusion reactions might ensue with subsequent transfusions.

More blood centers serving diverse ethnic groups are encouraged to carry out ethnic targeted education on the importance of donation as well as targeted blood drives. This would enable blood centers to increase their inventory for patients with rare antibodies by recruiting rarer phenotype blood donors. With the high influx of diverse immigrant populations, medical laboratory science personnel need to be more informed on the prevalence of the null phenotypes among various populations in order to provide quality and timely services.

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## CLINICAL PRACTICE

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