Persistent anti-Dr^a in two pregnancies

N. Rahimi-Levene, A. Kornberg, G. Siegel, V. Morozov, E. Shinar, O.Asher, C. Levene, and V. Yahalom

The Drori (Dr^a) antigen is one of the ten high-prevalence antigens of the Cromer blood system, which are carried on decay-accelerating factor (DAF, CD55). The Dr(a–) phenotype was first described in a 48-year-old Jewish woman from Bukhara. Her serum contained an antibody to a high-prevalence antigen named anti-Dr^a. Most known individuals with the Dr(a–) phenotype are Jews from the geographic area of Bukhara, but individuals from Japan have also been described. Antibodies in the Cromer blood group system, including anti-Dr^a, have never been reported to cause HDN. In most of the cases with anti-Dr^a examined in Israel, the antibodies have been subtyped as IgG2 and IgG4. This report is of a woman with Dr(a–) phenotype and an anti-Dr^a titer of 256 to 512 in her serum, observed during two successive pregnancies. At birth, the RBCs of the first- and second-born child were negative and positive in the DAT, respectively, and neither manifested clinical signs of HDN. The disappearance of Cromer system antibodies, including anti-Dr^a in midpregnancy, has been described in a previous study. In that study, it was theorized that the antibodies in the serum of the women were adsorbed onto placental DAF. The finding of a high anti-Dr^a titer in two successive pregnancies in this patient, with a positive DAT for the RBCs of one of the two babies at term, differs from published reports, suggesting that a different mechanism might be involved. ***Immunohematology* 2005;21:126–128.**

Key Words: Anti-Dr^a, titers in pregnancy

The Drori (Dr^a) antigen is part of the Cromer blood group system, which includes ten high- and three low-prevalence antigens.[1] The Cromer antigens are carried on the complement regulatory glycoprotein decay-accelerating factor (DAF; CD55). The Dr(a–) phenotype was first described in a 48-year-old Jewish woman of Bukharian origin by Levene et al.[2] More cases have been published; most of them were of Jewish women born in Bukhara, a few were of individuals from Japan.[3,4]

Antibodies in the Cromer system have not been reported to cause clinical HDN.[1] There are reports in the literature of women with Cromer antibodies in which the titer fell during pregnancy and the baby carrying a Cromer antigen was born with a negative DAT.[5,6] DAF is expressed strongly on the apical surface of trophoblasts, more so in the second and third trimesters.[7] The placental trophoblasts possess the DAF polymorphism of the fetus, which is inherited from both parents and is most likely positive for the high-prevalence Cromer antigens, including Dr^a. Reid et al.[8] suggested that antigen-positive trophoblasts may absorb maternal antibodies with DAF specificity such as anti-Dr^a, causing their disappearance from maternal blood and explaining the lack of HDN secondary to this antibody. They reported two cases with Cromer antibodies, one of them anti-Dr^a, which disappeared during pregnancy, supporting their hypothesis.

In this report two successive pregnancies in a Dr(a–) woman with anti-Dr^a in her serum are described. The anti-Dr^a titers did not change significantly throughout either pregnancy. At birth, a DAT performed on the RBCs of the first baby was negative and that performed on those of the second baby was positive. Neither baby had clinical evidence of HDN.

Case Report

A 28-year-old Jewish woman of Bukharian origin in her second pregnancy was admitted to the Assaf Harofeh Medical Center delivery room in labor in March 1998. A RBC sample was sent to the blood bank for blood type and antibody screen. An antibody to a high-prevalence antigen was found in her serum and investigated. Her RBCs were typed as Group A^1, D–, C–, E–, c+, e+, C^w–; M–, N+, S–, s+; P_1–; Lu(a–b+); K–, k+, Kp(a–b+); Le(a–b+); Jk(a+b+); Yt(a+), and Dr(a–) and the DAT was negative. During testing for the Cromer antigens, weaker reactions were observed with anti-IFC and -Cr^a when compared with the positive controls. A sample from her husband was tested and his RBCs were determined to be Group A^1, D+, C+, E–, c–, e+, C^w–; M+, N+, S–, s+; P1+; Lu(a–b+); K–, k+, Kp(a–b+); Fy(a+b+); Jk(a+b–); Yt(a+b–),and Dr(a+). His antibody screen and DAT were negative.

The patient was found to have anti-D (low titer from passive immunization in pregnancy) and anti-Le^{bH}. An antibody to a high-prevalence antigen was found in her serum, which was characterized as anti-Dr^a, and her RBCs typed as Dr(a–). The titer of the antibody by

saline indirect antiglobulin test was 512 (Table 1). The patient's serum was examined with two known Dr(a–) RBCs and the presence of anti-K, anti-M, anti-S, and anti-P1 were excluded.

Table 1. Anti-Dr^a titers

Date	Titer
May 1998	512
April 1999	256
May 2000	256
June 2000	512
July 2000	256
August 2000	256
September 2000	256

Materials and Methods

Standard tube hemagglutination tests were used for antigen typing, antibody screening, and panels. Antibodies and rare RBCs used in the testing were from the Israeli National Blood Group Reference Laboratory and SCARF. Column agglutination tests (DiaMed AG, Switzerland) were also used for antibody screening and panels. The RBCs were examined with anti-DAF (CD55) and anti-MIRL (CD59) in column agglutination tests (DiaMed AG). The elution was performed using the rapid acid method (Elukit II, Gamma Biologicals, Inc., Houston, TX).

Results

The RBCs of the newborn were negative in the DAT and there was no clinical evidence of HDN. In May 2000, during her next pregnancy, anti-Dr^a was identified with a titer of 256 (Table 1). In June 2000, the anti-Dr^a titer was 512 and in July 2000 the titer was 256. The pregnancy was uncomplicated and RhIG was again administered antenatally. The patient gave birth in October 2000 to a full-term healthy baby, the titer remaining stable throughout pregnancy. The infant's RBCs were typed as Group A, D+; the DAT was positive with anti-IgG resulting in 2+ to 3+ reactivity in tubes and 4+ by the column agglutination test (DiaMed AG). The positive DAT precluded Dr^a typing. An elution was performed on the baby's RBCs and anti-Dr^a was identified. The eluate did not react with RBCs from the mother, Dr(a–) RBCs, or RBCs treated with alpha-chymotrypsin. There was no clinical evidence of HDN. The titer of the anti-Dr^a in the mother's serum was 256. Testing of maternal RBCs by the column agglutination test (DiaMed) was negative with anti-DAF (CD55) and positive with anti-MIRL (CD59).

Discussion

DAF is a protein connected to the membrane via a glycosylphosphatidylinositol anchor. It protects cells against destruction by autologous complement by inhibiting formation and acceleration of the decay of C3 and C5 convertases, thus preventing the complement cascade from causing hemolysis. DAF is a member of the regulators of complement activation gene family encoded by a gene on the long arm of chromosome 1.[9] It is widely distributed throughout the body and expressed on epithelial cells, endothelial cells, blood vessels, and the apical surface of trophoblasts.[7,10] The Cromer antigens are carried on DAF and the different phenotypes provide a basis for biochemical and functional investigation of alternate forms of DAF. Dr(a–) is a rare Cromer phenotype, lacking expression of the Dr^a antigen, with reduced levels of DAF and weak expression of other Cromer antigens, including Cr^a, Tc^a, Tc^b, Tc^c, Es^a, IFC, Wes^b, and UMC.[10] No hematological abnormalities have been described in Dr(a–) individuals. The molecular change associated with Dr(a–) has been characterized.[9] Four pregnancies in a woman who had Cr(a–) RBCs and anti-Cr^a, in which the titer of the anti-Cr^a declined during pregnancy and remained low until term, were described by Sacks and Garratty.[6] The decline in the titer was thought to result from absorption of the antibody by white cells or platelets or be due to neutralization by plasma of the fetus. Another case of anti-Cr^a in a pregnant woman in which the titer of the anti-Cr^a decreased was described by Dickson et al.[5]

Reid et al.[8] described two patients with repeat pregnancies who had Cromer blood group system antibodies (anti-Cr^a and anti-Dr^a) with titers of 128 or greater at the beginning of pregnancy. These antibodies became undetectable in the serum from the second trimester onward. RBCs from the babies tested positive for the relevant Cromer antigens but were negative by the DAT. The antibodies would reappear in the serum of the mother after delivery or at the beginning of a subsequent pregnancy.

Holmes et al.[7] showed the preferential expression of DAF at the feto-maternal interface of the placenta, increasing quantitatively during placental development. DAF at this site plays a protective role against maternal complement-mediated attack. DAF can absorb the Cromer antibodies produced by the mother, more so in the second and third trimesters when the expression of DAF increases. This hypothesis is supported by reappearance of these antibodies after

pregnancy when the placenta is no longer present. Most of the patients with anti-Dr^a found in Israel have been multiparous women. Subclasses of IgG examined in these cases during the years 1989–1991 were IgG2 and IgG4. The anti-IgG subtype antibodies used were from the Netherlands Red Cross and tests were performed in tube or capillary tests. None of the offspring had HDN (C. Levene, unpublished data, 1989–1991). The patient reported here was Dr(a–). She developed anti-Dr^a and was monitored during two subsequent pregnancies. The anti-Dr^a titer remained consistently at 256 or above during both pregnancies. RBCs from the first baby typed as Dr(a+) and the DAT was negative. RBCs from the second baby were positive in the DAT; they could not be typed for the Dr^a antigen, but anti-Dr^a was identified in the eluate, with no clinical signs of HDN. Our findings differ from previous[5,6,8,11] reports, where anti-Cromer antibody titer declined during pregnancy. Reid et al.[8] suggested that the titer decreased due to Cromer blood group system antibodies binding to the placental DAF. In the case described here, presumably the anti-Dr^a was not adsorbed by the placental DAF, which might happen if the placental DAF was Dr(a–), if Dr^a was poorly expressed, or due to another unexplained mechanism.

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Naomi Rahimi-Levene MD, Director of the Blood Bank; Abraham Kornberg MD, Chief of the Hematology Institute; Gabriela Siegel, High Risk Pregnancy Unit; and Valery Morozov, MD, Blood Bank, Assaf-Harofeh Medical Center, Zerifin, 70300, Israel; Eilat Shinar MD, Director; Orna Asher PhD, Director Immunohematology Laboratory; Cyril Levene MD, Consultant National Blood Group Reference Laboratory (NBGRL); and Vered Yahalom MD, Deputy Director & Medical Director NBGRL Magen David Adom (MDA)-National Blood Services, Ramat Gan, Israel.