Case reports: red blood cell autoantibodies mimicking alloantibodies

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The phenomenon of autoantibodies mimicking alloantibodies is rare and challenging. This report describes several unusual cases of mimicking autoantibodies and reviews the literature. ***Immunohematology*** 1991;7:98–101.

The specificity of autoantibodies in warm autoimmune hemolytic anemia is most frequently related to the Rh system, and the autoantibodies often demonstrate "panhemagglutinating" reactivity.[1,2] Autoantibodies mimicking a simple specificity have been rarely reported.[2–4] This report describes five cases of autoantibodies that mimicked alloantibodies.

Materials and Methods

Serologic procedures were performed with commercially available panel red blood cells (RBCs) and reagents. The procedures included direct antiglobulin testing (DAT), indirect antiglobulin testing (IAT), adsorptions, and grading of agglutination by standard techniques.[5] DAT testing was performed with polyspecific antihuman globulin (AHG) and/or monospecific anti-IgG and anti-C3b, -C3d. Antibody identification panel red cells were incubated at 37°C for 30 minutes in LISS, 22 percent bovine albumin, or 0.9 percent sodium chloride, as indicated in each case, and anti-IgG AHG was used at the antiglobulin phase. Some autoadsorption procedures were performed with ZZAP-treated RBCs using W.A.R.M. (Warm Autoantibody Removal Medium, Organon Teknika, Durham, NC). Homologous adsorptions incorporated the use of selected donor RBCs drawn in CPDA-1 and pretreated with papain (Freeze Dried Papain, Organon Teknika), unless otherwise specified. In cases requiring eluates from DAT-positive RBCs the eluates were prepared using the Elu-Kit II (Gamma Biologicals, Inc., Houston, TX). Chemically modified antisera were used in Rh phenotyping tests. In cases requiring the IAT for antigen typings of DAT-positive RBCs, chloroquine-treated (Gamma-Quin, Gamma Biologicals, Inc.) cells were prepared. Rh_{null} RBCs were not used.

Individual Case Reports and Results

Case one

The patient was an 8-year-old black male with anemia due to sickle cell disease. Initial serologic evaluation indicated blood group O, Rh positive, and the serum antibody screen was negative. He was transfused with two units of compatible RBCs as part of a hypertransfusion protocol. One month later, the serum antibody screen was weakly positive and the DAT was mixed-field positive. Anti-E was identified in the serum and in an eluate. The patient's RBCs phenotyped as E–, and the anti-E in both the serum and the eluate could be completely adsorbed onto E– RBCs. He was transfused intermittently over the next 4 months with E– RBCs. However, the DAT remained positive, and anti-E was still in the eluate. Eventually the eluate became reactive with all cells tested, and the patient was placed on glucocorticosteriod therapy, and he continued to receive E– RBCs for transfusion. The serum antibody screen and DAT eventually became negative. One year later, an anti-Kp^a alloantibody was identified in the serum.

Case two

The patient was a 16-year-old black female with anemia due to sickle cell disease. She was blood group O, Rh positive, and was also a participant in a hypertransfusion protocol. Her initial serum antibody screen was negative, and many units of

compatible RBCs were transfused during the course of her therapy. The serum antibody screen and DAT became positive, and anti-K1 was identified in the serum. The patient's red cells were K:–1, and an eluate was also negative. The anti–K1 could be completely adsorbed from the serum using K:–1 RBCs. The DAT remained persistently positive and the eluate persistently negative. The patient was transfused with K:–1 RBCs.

Case three

The patient was an 82-year-old female with anemia who had received multiple units of RBCs. The patient was blood group B, Rh positive (R_2R_2). The initial DAT was 3+ with anti-IgG and 1+ with anti-C3b, C3d; 3 months later the DAT was 1+ with anti-IgG. Serologic evaluation at the albumin-antiglobulin phase demonstrated apparent 1+ anti-C, 2+ anti-e, plus microscopic reactivity with all C–, e– RBCs, suggestive of warm autoantibodies of undetermined specificity. Three adsorptions of the patient's plasma with ZZAP-treated autologous (R_2R_2) RBCs removed the microscopic reactivity of undetermined specificity and the anti-C and reduced the anti-e reactivity from 2+ to 1+. Suspecting that the antibodies were not truly alloantibodies, homologous adsorptions were performed. Adsorption (x2) with R_2R_2 cells removed the microscopic reactivity as well as the anti-C, and the anti-e reactivity was reduced to $+^w$. Adsorption (x4) with R_2R_2 cells completely removed the anti-e. Therefore, the anti-C and anti-e appeared to be autoantibodies mimicking alloantibodies, since both were adsorbed by red cells lacking C and e antigens.

Case four

The patient was a 19-year-old pregnant black female with sickle cell disease. She was blood group O, Rh positive (probable R_or); weak mixed-field reactions noted with anti-C and anti-E were due to transfusion of four RBC units 6 weeks before this testing. Initially, a delayed hemolytic transfusion reaction was suspected; the DAT was microscopically positive with anti-IgG. In a serum study, microscopic reactivity at the LISS-antiglobulin phase demonstrated apparent anti-C specificity only. Elution studies demonstrated microscopic reactivity of apparent anti-C plus anti-S specificities at the antiglobulin phase. Homologous adsorption studies using untreated rr, S–, and R_1R_1, S+ RBCs were undertaken. The anti-S was removed by once adsorbing the patient's serum with S– RBCs as well as with the S+ RBCs, while the anti-C reactivity was absorbed only by the C+ adsorbing cells. These serologic results suggested the presence of alloanti-C plus a mimicking autoanti-S.

Case five

The patient was an 83-year-old white male with anemia who had received chronic RBC transfusions since 1985. He was blood group O, Rh positive. In 1988 a 3+ albumin-antiglobulin anti-E was found. The patient's RBCs typed as E–, and the anti-E was thought to be an alloantibody. In September 1990 an anti-S was also identified, reacting 2+ at the antiglobulin phase. The DAT was negative, and the RBCs typed as S–. In October 1990 the DAT became positive, and the anti-E and anti-S were still present 2+ by the LISS-antiglobulin technique. In November 1990 the DAT remained positive (with IgG only), and the eluate demonstrated 2+ IgG agglutination against all 16 cells tested. Since October 1990 the patient has received only E–, S– RBCs for transfusion. In January 1991 the DAT was still positive, and the eluate continued to demonstrate panagglutinin activity. The serum was reactive $1+^s$ with S+, E– RBCs, $1+^s$-2+ with S–, E+ RBCs and $+^w$ with all S–, E– RBCs at the albumin-antiglobulin phase. Homologous adsorptions were performed; all three adsorbing cells (two were S–, one was S+) removed the reactivity against S–, E– panel cells in two adsorptions. The anti-S reactivity was removed in four adsorptions with S– as well as with S+ RBCs. Four adsorptions with E– RBCs failed to remove the anti-E reactivity, which had been removed in two adsorptions with E+ RBCs. We concluded that this case demonstrated an alloanti-E and an autoantibody mimicking anti-S.

Discussion

Autoantibodies with mimicking specificities are uncommon. When present, the specificity is most often related to the Rh system.[6] Autoantibodies mimicking specificities in the ABO, Kell, Kidd, Gerbich, MNSs, Ii, and Duffy blood group systems have been described.[3,4,7–12] Rarely, more than one specificity may be mimicked by one apparent autoantibody.[2,13]

Characteristically, mimicking autoantibodies can be adsorbed to exhaustion by RBCs lacking the specific antigen in question. When an individual's RBCs lack the antigen that appears to be defined, the mimicking nature of the autoantibody may not be readily recognized. Indeed, the confusing serologic picture of positive DAT, antibody in serum and eluate, and negative antigen typing may lead to the erroneous diagnosis of delayed hemolytic transfusion reaction.[3,4] However, alloantibody formation to the antigen in question may occur concomitantly with, or following, autoantibody formation.[14,15] Clinically, it is important to distinguish between an alloantibody and a mimicking autoantibody so that appropriate decisions can be made concerning transfusion or other therapy. Autoantibody with mimicking specificity may also occur in an individual whose red cells contain the antigen.[2]

The pathophysiology underlying the production of mimicking autoantibodies is not well understood. In some instances, the transfusion of RBCs may stimulate the recipient's immune system to produce antibodies against any foreign red cell antigens.[16] During the course of this antibody reaction, alloantibody, autoantibody, or both may be produced; and some individuals are able to produce antibodies very rapidly and efficiently.[17] In conjunction with stimulation of the immune system, any RBC destruction that occurs, whether it is of autologous or homologous cells, may cause the antigens of the destroyed cells to be presented to the immune system in a slightly altered form.[14,16] In the absence of RBC destruction, an underlying disease may cause alteration of red cell membrane antigens.[16]

In the case of a mimicking autoantibody, the patient's immune system may pick up some subtle difference in an altered red cell membrane and produce an autoantibody showing simple specificity.[16] It would appear that patients with sickle cell disease, as a group, seem more prone to produce mimicking autoantibodies than any other single group. Indeed, for unclear reasons, patients with sickle cell anemia seem to have an increased incidence of antibody production against transfused red cells.[18]

As illustrated in case one above, the appearance of a mimicking autoantibody following RBC transfusion may be associated with a mixed-field positive DAT. Other cases have been reported simulating a delayed transfusion reaction.[3,19] However, hemolytic red cell destruction by the mimicking autoantibody may range from none to severe.[7,10,11]

Autoantibodies may be associated with a wide variety of clinical and laboratory disorders. Mimicking autoantibodies are one facet of this interesting and challenging spectrum.

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Author's note: The intent of this report is to emphasize the diversity of mimicking antibodies. The data available for each case is presented; however, these five cases do not represent complete serologic workups for mimicking antibodies.

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