Case Report

Unusual Occurrence of Six Anti-erythrocyte Alloantibodies in an Rh(D)-negative Man with Myelodysplastic Syndrome

Hideki WAKUI, Ikuko TADA, Yasunori KIMURA, Kosaku YOSHIDA, Yasuyuki ENDO and Akira B MIURA

We report an Rh(D)-negative man with myelodysplastic syndrome who produced six anti-erythrocyte alloantibodies (anti-D, -C, -E, -Di, -Jka and -S) in succession. Three of these antibodies (anti-E, -Jka and -S) were not noted until delayed hemolytic transfusion reactions occurred. Treatment with cortico-steroids was effective in preventing both further formations of antibodies and other transfusion reactions. It was very difficult to find blood compatible with the patient, but repetitive blood transfusions were required for his progressive anemia and thrombocytopenia. Several problems concerning the transfusion of blood in such a case are discussed.

Key words: Alloimmunization, Anti-D, -C, -E, -Di, -Jka, -S, Delayed transfusion reactions

The incidence of anti-erythrocyte antibody formation among patients (excluding pregnant women) with various disorders, is about 1%, and most of the antibodies involved are usually less than three kinds in any single patient (1). Only once in a while are cases reported where more than four antibodies have developed in a single patient (2 – 5).

We report here an unusual case of Rh(D)-negative man with myelodysplastic syndrome who produced six anti-erythrocyte alloantibodies (anti-D, -C, -E, -Di, -Jka and -S). Several difficult problems when giving blood transfusions to Rh(D)-negative patients who have multiple alloantibodies are also discussed.

CASE REPORT

A 58-year-old Japanese man was admitted to our hospital because of low grade fever and palpitation on April 5, 1988. During the operation he received a transfusion of three units of Group A, Rh(D)-negative red blood cells. Both screening tests for irregular anti-erythrocyte antibodies and crossmatching tests were negative, and post-transfusion reactions were not observed at this time. Anti-cancer chemotherapy had not been performed following the operation. Thereafter, he was well until four months before entry.

At the physical examination on admission he was pale. Tachycardia and systolic heart murmur were also noted. Lymphadenopathy, hepatosplenomegaly, and hemorrhagic diathesis were not observed.

Laboratory findings on admission showed pancytopenia: the hemoglobin was 5.8 g/dl; the white-cell count was 2,400/μl, with 30% neutrophils, 6% eosinophils, 1% basophils, 12% monocytes, and 51% lymphocytes; the platelet count was 65,000/μl. The serum total bilirubin was 0.8 mg/dl, the aspartate aminotransferase 15 U/l, the lactic dehydrogenase 67 U/l, the serum iron 208 μg/dl, the
vitamin B₄ 363 pg/ml, the folic acid 4.9 ng/ml, and the erythropoietin 597 mU/ml. The serum IgG was 1,406 mg/dl, the IgA 126 mg/dl, and the IgM 169 mg/dl. The direct antiglobulin test was negative, but the indirect antiglobulin test was positive. A bone marrow examination revealed hyperplastic marrow with prominent dyserythropoiesis: the nuclear cell count was 798,000/μl, with 35.4% erythroblasts and 11.2% myeloblasts; the myeloid-erythroid cell ratio was 1.66; the megakaryocyte count was 31.3/μl. On the basis of the above findings, a diagnosis of myelodysplastic syndrome (refractory anemia with excess of blasts) was made according to the FAB classification (6).

His blood types were as follows: A, ccdee, Di (a−b−), Jk (a−b+), MNs, Kp (a−b+), Js (a+b), Fy (a+b−), P₁ (−), U (+), Le (a−b+), Lu (a+b+), Xg (a−), Tj (a+), and Jr (a+).

Fig. 1. Clinical course of the patient. Three anti-erythrocyte alloantibodies (anti-D, -C, and -Dia) were detected in the serum on admission. In addition, other three kinds of antibodies (anti-E, -S, and -Jka) were noted during delayed hemolytic transfusion reactions. The sequential change of these serum antibody titers is shown. Numbers in the column indicate units per month of both red blood cells and platelets which were transfused to the patient. Abbreviations used: DHTTR, delayed hemolytic transfusion reactions; PC, platelet concentrated; RBC, red blood cells.

However, on April 12, hemolytic transfusion reactions occurred, which were successfully treated with a bolus of methylprednisolone. On April 11, another alloantibody (anti-E) was detected in his serum. Furthermore, on April 16, two kinds of alloantibodies (anti-Jka and -S) were detected in his serum in addition to the four antibodies being previously discovered.

He was treated with vitamin D₃, vitamin A, and anabolic steroids for myelodysplastic syndrome. However, these treatments were not effective, and repetitive blood transfusions were required because of both his progressive anemia and his thrombocytopenia. It was very difficult to find donors whose red blood cells did not react with the patient’s serum antibodies in Akita prefecture, but a relatively sufficient amount of compatible red blood cells was supplied through a network of Red Cross Service centers in eastern Japan. When Group A compatible red blood cells were not available for a long interval, the patient received transfusions of washed Group O red blood cells that did not have antigens with which the patient’s serum antibodies reacted. On the other hand, when several units of compatible red blood cells were available for a short interval, part of them were frozen and stored at −80°C until they were used. Platelets transfused to the patient were obtained from A, Rh(D)-positive donors and were washed one more time than usual.

In order to prevent further formations of anti-erythrocyte alloantibodies and other transfusion reactions, methylprednisolone was given just before each transfusion after the first hemolytic episode. The dose of methylprednisolone was gradually decreased from 1,000 mg/time to 40 mg/time. This treatment was effective, and titers of four antibodies (anti-E, -Di², -Jk², and -S) decreased gradually. Among them, anti-Jk² and anti-S became undetectable in the patient’s serum, on August 5 and on September 16, respectively.

Although the patient’s anemia relatively improved by the transfusions, both the white-cell count and the platelet count decreased to 1,500/μl and to 10,000/μl, respectively. After August, he suffered from a persistent fever, bloody sputa, and dyspnea because of pulmonary aspergillosis. A treatment with anti-fungus drugs was started on August 18. However, on September 23, he died from...
respiratory failure due to pulmonary aspergillosis. This was later confirmed by post-mortem examination.

**DISCUSSION**

This case of an Rh(D)-negative man with myelodysplastic syndrome is unusual in that the patient developed six anti-erythrocyte alloantibodies (anti-D, -C, -E, -Di\(\alpha\), -Jk\(\alpha\), and -S) in succession. Myelodysplastic syndrome is a diverse group of clonal diseases arising not only in pluripotent stem cells for erythrocytes, granulocytes, and platelets, but also in lymphocytes, particularly in B lymphocytes (7). Recently, a polyclonal rise in serum immunoglobulins and the development of various autoantibodies (including anti-erythrocyte auto-antibodies) have been reported in some patients with myelodysplastic syndrome (8). Therefore, it is possible that the unusual alloimmunization to multiple blood group antigens in our patient may have resulted from B cell dysfunctions associated with myelodysplastic syndrome. Although the incidence and significance of alloantibodies to red blood cell antigens have been examined in some kinds of hematological disorders (9), these examinations have not been made in a large population of patients with myelodysplastic syndrome (8). Therefore, it is possible that the unusual alloimmunization to multiple blood group antigens in our patient may have resulted from B cell dysfunctions associated with myelodysplastic syndrome. Although the incidence and significance of alloantibodies to red blood cell antigens have been examined in some kinds of hematological disorders (9), these examinations have not been made in a large population of patients with myelodysplastic syndrome (8). Therefore, it is possible that the unusual alloimmunization to multiple blood group antigens in our patient may have resulted from B cell dysfunctions associated with myelodysplastic syndrome. Although the incidence and significance of alloantibodies to red blood cell antigens have been examined in some kinds of hematological disorders (9), these examinations have not been made in a large population of patients with myelodysplastic syndrome (8). Therefore, it is possible that the unusual alloimmunization to multiple blood group antigens in our patient may have resulted from B cell dysfunctions associated with myelodysplastic syndrome. Although the incidence and significance of alloantibodies to red blood cell antigens have been examined in some kinds of hematological disorders (9), these examinations have not been made in a large population of patients with myelodysplastic syndrome (8). Therefore, it is possible that the unusual alloimmunization to multiple blood group antigens in our patient may have resulted from B cell dysfunctions associated with myelodysplastic syndrome.

All the six antibodies in our patient seem to have been formed as a consequence of a blood transfusion during an operation about four years ago, and to be present in his serum on admission. The reason why anti-D was detected in the patient, even in the absence of exposure to D antigen, can be explained by the presence of anti-G (10). Almost all red blood cells carrying D, and all cells carrying C, also carry an antigen G. This patient was probably immunized with C-positive cells transfused at the time of the operation, and subsequently produced anti-G in addition to anti-C. The anti-G is considered to have an anti-D cross-reactivity.

Titers of three (anti-E, -Jk\(\alpha\), and -S) of the six kinds of clinically important antibodies in the patient’s serum were too low to be detected by the regular serological studies made on admission. As a result, incompatible red blood cells were transfused, and delayed hemolytic transfusion reactions were induced in this patient. Because anti-E was first detected in his serum a few days after the incompatible blood transfusion, this is probably the most offending antibody for the hemolysis (11). Both anti-Jk\(\alpha\) and anti-S also appear to cause these hemolytic reactions. It is known that most of anti-erythrocyte alloantibodies seen in patients who have received multiple transfusions are due to the initial 1~10 transfusions (9). Thus, if frequent tests for these antibodies had been performed early in our patient’s transfusion treatment, the three antibodies (anti-E, -Jk\(\alpha\), and -S) would probably have been noted before the incompatible transfusion.

After the episode of transfusion reactions in the patient, methylprednisolone was given prior to each transfusion in order to prevent further antibody formations and other hemolytic reactions. This treatment was effective in these preventions. However, a fungal infection developed in the lungs, perhaps as a side-effect.

For the difficulty to find red blood cells compatible with the patient in our prefecture only, we requested a supply of them from other large Red Cross Service Centers in eastern Japan. When Group A compatible red blood cells were not available for a long interval, and the patient’s anemia progressed, the patient was transfused with washed Group O red blood cells that did not have antigens with which his serum antibodies reacted. On the other hand, when several units of compatible red blood cells were available for a short interval, some of them were frozen and stored until they were used.

A large amount of platelets was also transfused to the patient. Platelets were prepared from A, Rh(D)-positive donors. They were washed one more time than usual in order to remove contaminating red blood cells. No clinical episodes associated with these transfusions were observed, but the platelet count did not rise significantly during the latter part of the patient’s clinical course, probably due to the development of serum anti-platelet antibodies.

There are several difficult problems that require further consideration when giving blood transfusions to Rh(D)-negative patients who have had repetitive transfusions. Should transfusions to such patients be matched for antigens other than ABO and Rh(D)
to prevent alloimmunization? Blumberg et al (9) retrospectively studied the frequency of alloimmunization among patients requiring multiple transfusions, and performed a cost analysis for antigen matching. According to their results, antigen matching for other than ABO and Rh(D) is generally not cost-effective. Therefore, we would like to recommend that blood-group typings, including minor blood groups, among the larger population of Rh(D)-negative subjects should be registered at Red Cross Service centers, and that frozen red blood cells should be used more frequently. Accordingly, when an Rh(D)-negative patient is encountered with multiple alloantibodies, as our patient was, it may be possible to find sufficient units of compatible red blood cells at Red Cross Service centers.

ACKNOWLEDGMENT: We thank Mr. Takeshi Notoya, Blood Transfusion Service, Akita University School of Medicine, for carrying out serological studies.

REFERENCES