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Intravascular Hemolytic Transfusion Reaction due to Anti-Vw+Mi^a with Fatal Outcome

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Abstract. Because of the increasing use of type, screen and hold protocols and minimal surgical blood order protocols in transfusion services, a number of patients are receiving un-cross-matched blood in elective situations. There are many low-frequency red blood cell antigens which are lacking on reagent cells used for antibody screening procedures, and alloantibodies directed against these antigens are relatively common and occur in either natural or immune forms. A case of an intravascular hemolytic transfusion reaction resulting in death is reported. The patient had a naturally occurring anti-Vw+Mi^a and received 1 U of Vw+Mi^a-positive donor red cells. It is the 1st documented case of a hemolytic transfusion reaction due to this incompatibility. The potential threat of transfusion reactions due to low-frequency antigens must be recognized by the physicians who design type, screen and hold protocols and it has particular reference to the selection of possible recipients for whom the protocols are applied.

Introduction

The purpose in reporting this case after a delay of 11 years is to document an intravascular hemolytic transfusion reaction due to Vw+Mi^a incompatibility, the 1st such case to be reported. Unless cases like this are reported, the physicians who design the type, screen and hold protocols or minimal surgical blood order protocols, and the physicians who designate the patients to whom the protocols are applied will not be fully aware of the potential dangers of using un-cross-matched blood. There are scores of red blood cell antigens which are routinely lacking from reagent red cells used in screening for unexpected antibodies. Antibodies, often natural in origin, directed against many of these antigens are relatively common. The risk of a hemolytic transfusion reaction due to an antibody undetected on screening is present whenever un-cross-matched blood is transfused. This risk is acceptable in true emergency situations. This risk must also be recognized when un-cross-matched blood is transfused in elective situations.

Case Report

The patient was a 57-year-old Caucasian man who was admitted to hospital on January 17, 1969, for treatment of anemia and weakness. He had had a subtotal gastric resection and gastrojejunostomy performed in 1949 for duodenal peptic ulcer and had received transfusions at that time. Between 1949 and 1969 he was admitted to hospital twice for treatment of gastrointestinal hemorrhage, and there were additional admissions for treatment of anemia. On January 17, 1969, the patient's hemoglobin was 6.4 g/dl and the hematocrit 26%. He received one unit of packed red blood cells on January 17, 1969, and a second unit on January 18, 1969, without untoward incident. On January 20, 1969, a third unit of packed red blood cells, No. 15697, was started at 13.30. At 14.00 he suffered nausea and vomiting which was recorded by the nurse. The transfusion was allowed to complete itself and this occurred by 15.10. At 15.30 the patient again suffered nausea and vomiting, this time accompanied by chills. A physician was notified and Tigan prescribed. Later that evening the temperature rose to 39.7 °C. Severe pains developed in the legs and joints. At 22.00 notation was made that the patient was jaundiced and had difficulty in breathing. His temperature was 40.3 °C and the pulse was rapid. On January 21, 1969, the laboratory was notified of a possible transfusion reaction. By this time the patient was 'very shocky' with difficult breathing, was in an oxygen tent, and was listed in critical condition. There had been no output of urine.

The patient died at 14.00 on January 22, 1969, 47 h after completion of the transfusion. The gross autopsy findings included massive aspiration of gastric contents; an old functional subtotal gastric resection with gastrojejunostomy, a marginal gastric ulcer, 3.5 cm in diameter with thrombosed artery in the base, perforation, and focal peritonitis; acute and chronic pyelonephritis. No significant underlying cardiac, pulmonary, or hepatic diseases were described. The cause of death was stated as due to massive intravascular hemolysis following transfusion of one unit of packed red blood cells incompatible on the basis of a low-frequency antigen.

Blood samples obtained 17 and 24 h after transfusion had negative direct antiglobulin tests, plasma hemoglobins of 90 and 83 mg/dl, direct bilirubin of 3.5 mg/dl, total bilirubin of 7.4 mg/dl, prothrombin time of 15%, SGPT over 1,300, and blood urea nitrogen of 90 mg/dl. The pretransfusion sample had a negative direct antiglobulin test, plasma hemoglobin of 1.1 mg/dl, prothrombin time of 100%, and was Group A. Crossmatches performed at the hospital on January 21, 1969, using the pretransfusion and posttransfusion patient sera, showed incompatibility in saline and albumin with the red blood cells of the implicated donor, No. 15697. Because of anuria, no urine studies were performed.

Serologic Results

Posttransfusion samples dated January 22, 1969, obtained approximately 40 h after transfusion of unit No. 15697, were received by the author on January 28, 1969. The patient's red blood cells typed as Group A_1, Rh-D-positive, and the direct antiglobulin test was negative with polyspecific reagent. The patient's serum contained neither anti-A nor anti-A_1 and no reactions were obtained when the serum was tested against a commercial 10-cell panel. Integral segments of donor unit No. 15697, a Caucasian, were received with the patient's samples. The donor's red blood cells typed as Group A_1, Rh-D-positive, Verweyst-positive, Miltenberger-positive using three sources of anti-Vw and three sources of anti-Mi^a. The patient's serum was tested against the donor's red cells and the reactions were $+4^s$, a solid agglutinate (score 12), in saline at room temperature, $+4^s$ (score 12) in albumin after incubation at 37 °C, and $+1^s$ (score 3) at antiglobulin phase using polyspecific reagent. A fresh additional sample from the donor was received on February 11, 1969. Identical typing and cross-match results were obtained. Samples of the patient's serum and the donor's red blood cells were forwarded to the consultation service of Spectra Biologicals where the patient's antibody specificities were confirmed as anti-Vw+Mi^a (type ii se-

rum) and the donor's antigen specificities were confirmed as Verweyst-positive and Miltenberger-positive (class I cells) [1]. The patient's serum reacted strongly against 3 class I red cells including those of Miltenberger, the original class I proband. Class I cells reacted strongly at room temperature, at 37 °C, and by the antiglobulin technique. The red blood cells of 3 Vw-negative Mi(a+), class II, individuals and those of 1 Mur.-positive, class III, person were less reactive at room temperature and at 37 °C and those cells did not react by the antiglobulin technique. The consultation service found no other unexpected alloantibody in the patient's serum.

Additional testing of the patient's serum was performed in February, 1980, with freshly obtained class I and class II red blood cells. Both cell samples were agglutinated in saline at 24 °C, in polymerized albumin at 24 and 37 °C, and by indirect antiglobulin technique using anti-IgG reagent. The patient's type ii antibody was clearly reactive at 37 °C by this routinely employed four-phase technique. Sulfhydryl cleavage of the antibody using 0.15 *M* 2-mercaptoethanol showed that the anti-Mi^a component was 80% IgM and 20% IgG while the anti-Vw component was 100% IgM. Neither component of the antibody was complement dependent nor complement binding on 'in vitro' testing.

Discussion

The principles involved in the investigation and documentation of a hemolytic transfusion reaction include finding evidence of increased red blood cell destruction and then identifying the cause. The evidence of increased red blood cell destruction in the case described is documented by the fact of normal plasma hemoglobin level pretransfusion and elevated plasma hemoglobin levels of 90 and 83 mg/dl at 17 and 24 h after transfusion of the implicated donor unit. Hyperbilirubinemia was also present after transfusion. The cause of the reaction in this case was donor unit No. 15697, proven to be incompatible with the patient's pre- and posttransfusion sera. The specificity of the incompatibility was Verweyst-Miltenberger and the immunoglobulin class of the patient's alloantibody was predominantly IgM. The immediate cause had to have been human error since the donor unit was found, retrospectively, to be incompatible with the patient's pretransfusion serum. Other errors occurring in hospital included delayed recognition of the reaction by the attending staff and delayed reporting of the reaction to the laboratory staff.

The intravascular hemolysis of one unit of packed red cells resulted in death because of several factors: the patient had preexisting advanced renal disease, pyelonephritis, and had experienced massive aspiration of gastric contents. The latter occurred secondary to the vomiting precipitated by the acute intravascular hemolysis and accounted for the respiratory distress described clinically. Further, the patient had a marginal gastric ulcer with thrombosed artery in the base, perforation, and focal peritonitis. It is unlikely that the outcome would have been fatal had the patient not had these underlying diseases and if aspiration of gastric contents had been prevented.

Class I red blood cells, such as those of donor No. 15697, occur in 1 of 1,755 random Caucasians [2]. Type ii antibodies, however, are not infrequent, having been found in 1–2% of normal sera [3]. They are usually

natural in origin, usually complete, but occasionally develop immune characteristics and have been implicated in hemolytic disease of the newborn. One example of anti-Mi^a was shown to be capable of destroying red cells 'in vivo' [3], but there is no report in the literature of a similar occurrence due to anti-Vw. The antibody in this patient's serum shows serologic characteristics which are typical of other type ii sera. It was predominantly IgM and most of its serologic reactions were complete in nature.

It is exceedingly unlikely that the first two donor units had any role since one was given 3 days before the reaction and the other 2 days prior to the reaction, and nothing untoward was reported. It is also unlikely that any other alloantibody could have been responsible, for it would have had to be a complete IgM type of antibody to have caused an immediate intravascular hemolytic transfusion reaction. The only alloantibody which comes to mind is anti-A or anti-A_1, but it was determined initially and in retrospect that the patient's red blood cells were group A_1. The first two donor units transfused were also group A and elicited no reaction. All the evidence points to the fact that the incompatibility was on the basis of Vw+Mi^a alone.

The significance of documenting and reporting this case at this time relates to the increasing use of type, screen and hold protocols and minimal surgical blood order protocols in hospital transfusion services. The use of these protocols results in a number of patients receiving un-cross-matched blood in elective situations. There are a host of low-frequency red blood cell antigens, such as C^w, V, VS, Go^a, Js^a, Kp^a, Bu^a, Lu^a, Wr^a, Di^a, Yt^b, Co^b, super Sd^a, M_1, Henshaw, Mi^a, and Vw, which cannot routinely be present on screening cells and may be present in donor units. Natural and/or immune alloantibodies directed against these antigens are relatively common. Incompatibilities due to natural antibodies could probably be detected by immediate spin technique if donor blood is required for patients on type, screen and hold protocols. Incompatibilities due to V, VS, Kp^a, and other antigens, where the antibody is immune in nature, will not be detected by an immediate spin technique. This problem must be kept in mind by the physicians in designing type, screen and hold protocols or minimal surgical blood order protocols, and in designating the potential recipients to whom the protocols are applied.

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References

1 Cleghorn, T.E.: A memorandum on the Miltenberger blood groups. Vox Sang. *11*: 219–222 (1966).
2 Race, R.R.; Sanger, R.: Blood groups in man, 6th ed., chapter 3, pp. 92–127 (Blackwell, Oxford, 1975).
3 Mollison, P.L.: Blood transfusions in clinical medicine, 6th ed., chapter 9, pp. 367–368; chapter 13, pp. 557–586 (Blackwell, Oxford, 1979).

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