Case Report

Rh-Incompatibility-Induced Delayed Hemolytic Transfusion Reaction: Role of Immunologic Reactions in RH-Incompatibility

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Abstract

Blood transfusions cause to increase oxygen-carrying capacity and intravascular volume. Despite all the benefits of transfusion, it may have some complications. When mistransfusion occurs or when no other option is available, incompatible packed-cells may be infused, which puts the patient at risk of experiencing a hemolytic transfusion reaction (HTR). The HTRs are classified as acute or delayed reactions have wide spectrum of clinical presentations. In this report, we present a case of delayed hemolytic reaction due to rhesus factor (Rh) incompatibility in the operation room. Critical incident reporting and evaluation of adverse transfusion reactions may provide data for effective patient management and prevent the occurrence or repetition of these events.

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Introduction

In general, incompatible transfusions should be strictly avoided, as hemolysis of the transfused red blood cells (RBCs) can happen with potentially fatal outcomes, known as hemolytic transfusion reactions (Figure 1) (1).

Clinical presentations of an incompatible transfusion cover a broad spectrum: in mild cases, the patients become immunized with alloantibodies bearing a potential risk for later transfusions or their pregnancies. Sometimes, serological tests become positive after the transfusion without any clinical presentations. In some other cases, the positive effect of the transfusion (e.g. rising of hemoglobin) is missing or too short lasting, but in a number of cases, severe or life-threatening events may occur (2).

According to published statistics (2011-2015), about 14% of all deaths due to blood transfusion were related to non-ABO-dependent types (3-4). In fact, by implementing this process, the serum IgM levels increase sharply. This causes intravascular hemolysis, which ultimately ends in renal dysfunction, shock and death. Although immunoglobulin M hemolytic transfusion reactions (IgM-HTRs) have lower prevalence rates than HTRs (IgG-HTRs), the severity of degradation due to increased IgM-HTRs is more than other types (5-7).

Antibody-induced hemolysis generally occurs by one of these two mechanisms; first, RBCs can be lysed intravascularly when complement is activated to form the Membrane Attack Complex (MAC). (8-11). This is usually due to IgM binding to the RBC membrane but can also occur with IgG (5-7).

Phagocytes can also opsonize the RBCs, a process called as extravascular hemolysis. If activation of complement does not lead to MAC formation to the extent that rapid intravascular hemolysis occurs, then C3 deposited on the RBC surface may convert to C3b and iC3b. In this case, Complement Receptors on phagocytes (i.e., CR1, CR2, and CR3) can consume C3b-coated RBCs. Second, antibody-induced opsonization can occur as a result of Fc domains of IgG bound to RBCs, which are recognized by Fcγ receptors (FcγRs) on phagocytes intravascularly (12-15). There is significant data mostly in animal models, which demonstrates the existence of each of these mechanisms of RBC clearance after binding to antibodies (8-11).

Regardless of the canonical pathways described, alternative mechanisms of IgG-mediated RBC clearance have been suggested, which involve neither complement nor FcγR pathways. These include destabilization of the RBC membrane by antibody binding which can induce eryptosis (programmed RBC death) (12-18).

Several in vitro investigations suggested that IgM and IgG antibodies interact with complement in different ways; it showed that one molecule of IgM on a cell surface is sufficient to initiate complement fixation, but a doublet (two molecules side by side) of the IgG in serum is required to form a complement-fixing site. Nevertheless, electron microscopic and molecular studies have suggested that IgG antibody, although inefficient at initiating fixation of complement, may produce more membrane damage in comparison to IgM. Meanwhile, a series of cell surface receptors have been described which improve the adherence of antibody and complement-coated erythrocytes to macrophages and lymphocytes. Receptors specific for IgM, IgG and complement on macrophages and for complement on lymphocytes; these cellular receptors play an important role in both sequestration and clearance (19-23).

Reporting the adverse transfusion reactions is not to find a guilty person but to reveal the cause of a transfusion reaction in order to treat the patient adequately and to prevent the occurrence or repetition of an adverse event (24).

Clinical Report

A 16-month old boy with left lateral neck mass (rhabdomyosarcoma) was brought to our operating room by the ear, nose, and throat (ENT) surgeons for palliative resection of the mass (Figure2). He had had the swelling of his left lateral neck for 9 months and underwent surgery in respect of the mass when he was 11-month old which was diagnosed as rhabdomyosarcoma in pathological studies. It started to grow again and became 62*31*52 millimeters involving facial muscles, candidate for palliative resection.

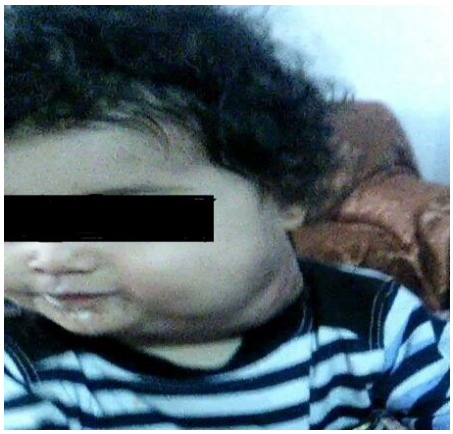

Figure 1. The patient with mandibular rhabdomyosarcoma.

On preoperative assessment, the patient weighed 12 kilograms. No other problem was found in history and physical examination except for being passive-smoker. The anteroposterior and lateral neck X-ray showed intact airway with small deviation of trachea to the right side (Figure 3). His blood group and Rh was B-negative and laboratory data was within normal range (hemoglobin = 11 gr/dL, hematocrit = 33.7%).

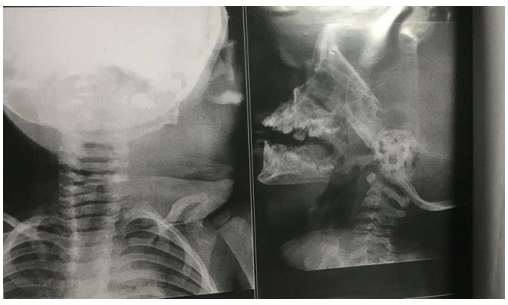

Figure 2. Anteroposterior and lateral neck X-ray.

Anesthesia induced using Sevoflurane 8% inhalation in oxygen; under basic monitoring (electrocardiogram, pulse oximetry, noninvasive blood pressure). Administering 0.25 mg atropine intravenously after about two minutes, the patient was successfully intubated in the first try by direct laryngoscopy using a #3.5 cuffed endotracheal tube. Then, 4 mg Atracurium and 25 microgram Fentanyl were infused through the intravascular (IV) line and maintenance of anesthesia was continued with Sevoflurane 2.5%.

After 30 minutes of surgery, according to estimated blood loss (140 cc), we prescribed 20 cc of packed-cell for the infant. Soon after blood transfusion, blood bank informed us about sending the wrong unit of O-negative blood to the operation room.

The transfusion was stopped. 200 mL of saline 0.9% was administered over 15 minutes; Foley catheter was inserted,10 gr of mannitol was infused over 15 minutes; 5 mg of Furosemide was injected; 10 mEq sodium bicarbonate was administered to alkalize the urine; the packed-cell and blood sample of patient was sent to the laboratory to repeat the crossmatch. Blood and urine samples were sent to the laboratory to check the blood cell count, partial thromboplastin time, fibrinogen level, direct coombs and urine analysis. Axillary temperature was 37.8ºC.

Surgery lasted for about 90 minutes. He was extubated and taken to recovery when able to cry and according to lab results there was no hemoglobinuria, coagulation profile was normal and direct coombs was reported negative; but after six hours, the lab results were changed as below:

Hemoglobin: 6.3 g/dL, Platelet: 307000, Hematocrit: 20%, Reticulin count: 0.2% (corrected=1%), partial thromboplastin time: 30, prothrombin time: 12, International Normalized Ratio: 1.1, Urine Analysis: RBC: 3-5, pH 7.5, Hemoglobin: +, total Bilirubin: 0.6 mg/dL, direct Bilirubin direct: 0.2 mg/dL, Direct coombs: negative, Lactate Dehydrogenase: 870 U/L, Fibrinogen: 190 mg/dL.

Fifteen cc/Kg of iso-group and iso-Rh packed-cell was infused over 4 hours and 5 mg of furosemide was prescribed. Three hours after transfusion hemoglobin concentration was 9 gr/dL and no hemoglobinuria were found in urine sample. All other lab data was normal. He was discharged in a stable condition two days later, after removing the drain and hemovac. In a weekly follow-up of our patient during the next 2 months, no serum antibodies appeared.

Discussion

Human error is a substantial factor in iatrogenic injury (1). Fortunately, most of these errors do not result in patient injury, but a small number can have catastrophic effects and lengthen the hospital stay.

The reasons for mistransfusions may occur in the pre-analytical, laboratory and/or clinical periods of transfusion. Examples of pre-analytical errors are incorrect patient identification, donor mix-ups, and incorrect blood bag labelling. Laboratory errors may cause incorrect blood grouping or cross-matching. Clinical errors may happen at bedside testing or when the units are being transfused. Electronic data processing systems and various hemovigilance systems have been established during recent years to prevent these mistakes (25).

Chiaroni et al, found that during a 5-year period in France, the incidence of ABO discrepancies was 1 per 3,400 tests performed. In their experience, most discrepancies (58%) were secondary to phlebotomy errors in which the samples were obtained from the wrong patient, whereas the second common cause of discrepancy was error during patient registration (30%) (25). In comparison, in a study that Figueroa et al. have done, 90% of errors were due to patient identification at the time of phlebotomy, and only 10% were due to admission or registration errors (26).

MacDougall and co-workers have attempted to mitigate the risk of ABO mismatch associated with knowledge gap. Based on the findings, they found that the use of adaptive methods (for blood compatibility in ABO system) is helpful in blood donors and recipients. In fact, this can be done as a "forcing function" before the release of blood from the blood bank and before transfusion at the bedside to reduce transfusion mismatch associated with gaps in ABO compatibility knowledge especially in Fresh Frozen Plasma and Platelet transfusion (25).

Some options include easy access to standard operating procedure instructions in work areas (25), a blood-component lock system that will not allow the issuance of a component unless there is a patient wristband and blood component match (26), and

computerized inventory control that will not permit issuance of a blood component that does not match the written request. Ultimately, automation may be the best solution. Handheld bar-code devices that may be used at the bedside can prevent the need for visual matching of data (26-28).

Ahrens et al. reported that of 21 transfusion-related errors, one (4.8%) was a pre-analytical error, 4 (19.0%) were laboratory errors and 16 (76.2%) were clinical errors (28). Their results confirm that bedside testing is the weakest link in the safety chain of transfusion in medical practice (26-29).

Delayed hemolytic transfusion reactions have been studied widely in the setting of sickle cell disease and beta-thalassemia, emphasizing the risk of adverse events in patients with baseline hematologic deficiencies (26-29). Chadebech et al, reported two cases of sickle cell disease with delayed hemolytic transfusion reaction in the absence of detectable antibody. Even in monthly follow-up of the serum of these patients in 6 months, no antibodies appeared (26).

Within the pediatric population, allergic reactions to platelets and RBCs were the most common reported reaction types. As said by Vossoughi et al. the rate of allergic reactions to platelets was more than three times, and the rate of allergic reactions to RBCs was more than seven times the adult rate (26).

Irani et al, reported a case of a delayed hemolytic transfusion reaction due to anti-e, an antigen in the Rh blood group system, after a liver transplant that was a consequence of receiving emergent incompatible RBC transfused during surgery that was treated successfully using an automated red cell exchange. According to this study, they stated that how a red cell exchange can reduce the potentially harmful effects of a delayed hemolytic transfusion reaction caused by anti-e or any clinically significant red blood cell antibody (26).

Werch et al, reported two women in child bearing age who had D2 blood type and received two units of D1 RBCs. Prompt delivery of intravenous RHIG (Rh Immunoglobulin) prophylaxis could prevent alloimmunization and associated complications in those two patients (27).

Arneja et al, have combined a recently developed mouse model for transfusion mediated RBC alloimmunization with mice genetically deficient in interleukin-6 receptor (IL-6Rα) to determine the role of IL-6Rα signaling in regulating RBC alloimmunization. The findings indicated that IL-6Rα signaling plays a key role in the generation of anti-RBC alloantibodies in response to transfused RBCs. Based on these results, available biologics targeting IL-6Rα can be a therapeutic option for the prevention of RBC alloimmunization (27).

While much remains to be learned, better concept of the cellular and molecular mechanisms that govern the course of HTRs, will undoubtedly lead to better therapy and improved survival for patients suffering this life-threatening complication of transfusion and shorten the duration of their hospital stay.

Conclusion

By decreasing the incidence of human errors we can prevent complications of mistransfusion. There are so many unknown aspects of cellular and molecular pathophysiology of mistransfusion which could be a good target for future researches. By preventing human errors and improving our knowledge and skill to face these kind of complications, we can hopefully improve survival of our patients.

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

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