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Immunological basis and management of Hemolytic transfusion reactions

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Abstract

Hemolytic Transfusion reaction is an adverse reaction associated with transfusion of blood products; transfusion reaction may be acute or delayed (chronic). *Acute transfusion* those temporarily associated with transfusion of blood products and takes place within 24 hours of transfusion while *Delayed transfusion* occur 3–10 days after the transfusion of RBC products that appear to be serologically compatible. These reactions occur in patients who have been alloimmunized to minor RBC antigens during previous transfusions. Acute hemolytic transfusion reaction is a potentially fatal transfusion reaction and can be either due to immune and nonimmune mechanisms. Immune mediated acute hemolytic transfusion reactions result from infusion of red blood cells that are incompatible with the patient's anti-A, anti-B, or other red blood cell antibodies and Typically causes intravascular hemolysis presenting with sudden onset fever or chills, so it is important to monitor patient during transfusion and stop the transfusion immediately if there is any change in vital signs or unexpected signs. In severe reactions cardiovascular, renal and respiratory support. Non-immune acute hemolytic transfusion occur when red blood cells are destructed by factors other than antibodies. Patient at risk for delayed hemolytic or serological transfusion reaction include those with a history of red blood cell antibodies, Delayed hemolytic transfusion reaction is usually due to anmnestic immune response to a foreign antigen on donor RBCs (most commonly Rh or other minor blood group antigens) previously encountered by recipient Typically causes extravascular hemolysis and The most prominent clinical features include dark urine or jaundice followed by fever chest or abdominal pain and hypertension. Most patient do not require treatment other than additional transfusion to maintain desired hemoglobin.

Introduction

Blood transfusion is a form of transplantation in which whole blood or blood cells from one individual are transferred intravenously into the circulation of a host. Blood transfusion are most often performed to replace blood lost by hemorrhage or to correct defect caused by inadequate production of blood cells. The major barrier to successful blood transfusion is the immune response to cell surface molecules that is different between individuals. The most important alloantigen system in blood transfusion is the ABO system. ABO antigens is represented by virtually all cells including red blood cells. Individuals lacking particular blood group antigen produce natural IgM antibodies against the antigen. If the individual are given blood cells expressing the target antigen, the preexisting antibodies binds to the transfused cells activate complements and cause transfusion reactions. Blood transfusion is one of the most procedures used in hospitalized patients. Patient may result in serious side effects by different types of transfusion reaction including hemolytic transfusion reaction, which account for 5% of these serious adverse reactions. Hemolytic transfusion is a type II hypersensitivity reaction, It Could be immune mediated or on non-immune mediated, serious side effects are seen if not treated and may lead to death. The aim of this study is to explain the pathophysiology of hemolytic transfusion reactions and to elucidate the possible causes that is associated with hemolytic transfusion reaction. [1]

Method

This paper is a case study collected by Warren G. Magnuson Clinical Center National Institutes of Health Clinical Center Bethesda, on a patient who had incompatible hemolytic transfusion reaction and the patient complained that the vein in his right arm became quite painful during the procedure the procedure was repeated 2 days later; a larger transfusion was given. Following the transfusion, the patient complained of pain in the arm vein, he vomited, and he had a severe nosebleed, pain over the kidney, and an “oppressive sensation in the chest.” The next day, he had of urine test, which was black however, the patient manifestations are closely related to the immunological events whether it is acute or chronic and how this issue is managed. [2]

Results

Acute hemolytic transfusion reaction was suspected because The patient experienced hypotension, pain, reddish urine, dyspnea, sense of "impending doom," oliguria within minutes post transfusion more ancillary tests were done and the results are positive direct anti-globulin (DAT), hemoglobinemia, hemoglobinuria, low haptoglobin, high LDH, elevated bilirubin . Non-immune causes were ruled out because culture was negative and drug induced hemolysis are ruled out.

Discussion

The most common cause of clinically significant hemolytic transfusion reactions is Immunologic incompatibility between donor and recipient cell types. It could be acute reactions those occurring within 24 hours after transfusion develop in response to red cells transfused in patients with preexisting antibodies. Naturally occurring antibody reactions against ABO-incompatible transfusions have been implicated in most fatal cases. Incompatible A and B blood-group antigens interact with preexisting IgM antibodies and less commonly with hemolytic IgG antibodies, both of which fix and activate complement. Leading to the Formation of excessive terminal membrane attack complexes (MAC) consisting of components C5 through C9 creates multiple pores in the transfused red cell membranes, initiating intravascular hemolysis. The resulting excess free hemoglobin overwhelms the binding capacity of plasma albumin can be measured with assays of hemoglobinuria. Free heme may induces renal vasoconstriction through nitric oxide scavenging. Causing acute tubular necrosis and renal failure.

Incomplete complement activation generates the anaphylatoxins C3a and C5a activating mast cells, releasing histamine and serotonin. Along with the products of hemolysis, including residual red-cell stromal components, activated monocytes and leukocytes, enzymes, and anaphylatoxins, mediate the release of pro-inflammatory cytokines and chemokines especially tumor necrosis factor α and interleukin-8. Furthermore, activation of the bradykinin and kallikrein systems and coagulation pathways results in a systemic inflammatory response syndrome of increased capillary permeability, vasodilatation, hypotension, and fever. In extreme cases, the syndrome progresses to shock, with multiple end-organ failure and death. Incomplete complement activation also

destroys red cells through C3b opsonization inducing erythrophagocytosis in the liver and spleen. Complement coated red cells are phagocytosed in many stages, with gradual removal of red-cell membrane and surface area resulting in spherocytes and microspherocytes. [3]

Delayed hemolytic transfusion reactions are caused by secondary (anamnestic) immune responses in patients immunized by previous transfusions, allogeneic stem-cell transplants, or pregnancy. These reactions rarely constitute a medical emergency. In many instances, alloantibodies appear on routine testing in the blood bank and are not associated with clinical events. Clinical manifestations, if they occur, include anemia and jaundice due to extravascular red-cell destruction, followed by hemoglobin degradation and liberation of bilirubin into the plasma. Fever, hemoglobinuria, and hemoglobinemia are even less frequent. Occasionally, severe hemolytic reactions in patients receiving long-term transfusions for hematologic conditions such as sickle cell disease, thalassemia, or malaria can precipitate by stander hemolysis. Incompatibility between the donor's plasma and the recipient's red cells, termed minor ABO incompatibility, with subsequent red blood cell destruction in the recipient, is the most common cause of clinically significant hemolysis in such cases. [2]

Life-threatening hemolysis due to passenger lymphocyte syndrome has been reported to develop 5 to 14 days after heart–lung, liver, kidney, and intestinal transplantations, as well as after hematopoietic stem-cell infusions. Reduced-intensity conditioning regimens and cyclosporine as prophylaxis against graft-versus-host disease (GVHD) or rejection have been associated with an increased risk of passenger lymphocyte syndrome. With the addition to preparative regimens (e.g., fludarabine), newer immunosuppressive agents, and modified combinations for GVHD prophylaxis (methotrexate- containing regimens) has significantly reduced the incidence of passenger lymphocyte syndrome. [4]

Hematopoietic transplantation may also result in acute hemolysis due to incompatible red-cell destruction in the graft by recipient antibodies (Major ABO incompatibility). Prolonged destruction of graft red cell precursors in the recipient's bone marrow may result in pure red-cell aplasia for up to 1 year after transplantation. .

Nonimmune mechanisms of hemolysis include transfusion of blood concurrently with hyperosmolar solutions, transfusion of overheated blood, and transfusion of accidentally frozen

blood. Blood transfusion under pressure through small bore needles or with the use of leukoreduction filters during processing may result in mechanical lysis of red cells.

Autoimmune hemolytic anemias and drug-induced hemolytic anemias may be exacerbated by transfusion and can therefore mimic hemolytic transfusion reactions. Transfusion of blood contaminated with hemolytic bacteria and transfusion in patients with sepsis may mimic immune-mediated hemolysis, as can transfusion of donor red cells with intrinsic defects for example glucose-6-phosphate dehydrogenase Deficiency or transfusion in recipients with these red-cell defects. [2]

Diagnostic consideration

An acute hemolytic transfusion reaction is considered to be a medical emergency. Although fever, flank pain, and reddish urine represent the classic triad of an acute hemolytic transfusion reaction, this type of reaction may also be suspected if one or more of the following signs or symptoms appears within minutes to 24 hours after a transfusion: a temperature increase of 1°C or more, chills, rigors, respiratory distress, anxiety, pain at the infusion site, flank or back pain, hypotension, or oliguria. One fascinating early symptom, a "sense of impending doom," has been reported by numerous patients; it should not be ignored. The severity of acute hemolytic transfusion reactions may be related to the titer strength of anti-A antibodies, anti-B antibodies, or both in the recipient's plasma, as well as the volume of incompatible blood transfused and the rate of transfusion. Most deaths have been associated with infusions of 200 ml or more of incompatible blood, although volumes as small as 25 ml have been fatal, particularly in children. Laboratory testing does not predict the severity of the reaction. When an acute hemolytic transfusion reaction is suspected, the transfusion should be stopped immediately, and the blood being transfused should be saved for analysis. Laboratory testing should include repeat ABO and Rh compatibility testing, along with additional antibody testing for non-ABO incompatibility. Visual inspection of urine and plasma, as well as testing for urine and plasma free hemoglobin, is standard. Timing is critical, since free hemoglobin is cleared rapidly from the circulation. alternative causes, including infectious agents, must be ruled out by means of Gram's staining and cultures of the remaining transfused component. A newly identified positive direct antiglobulin test (direct Coombs test), which detects IgG or complement bound to the red-cell membrane, is pathognomonic of immune-mediated hemolysis and the indirect antiglobulin test (Indirect Coombs test) detects the presence of

antibodies in the patient's serum. Although severe hemolytic episodes produce strong reactions to the direct antiglobulin test, the strength of the reactions does not correlate with the degree of hemolysis. The test result may occasionally be negative in a patient with acute severe immune mediated hemolysis if the antigen–antibody complexes are cleared from the circulation before the test sample is obtained. Delayed hemolysis, occurring days to a month after transfusion, is less evident than an acute hemolytic transfusion reaction, since the temporal relationship to transfusion is often overlooked. New-onset anemia, jaundice, elevated lactate dehydrogenase and bilirubin levels.[2]

Management

Management must occur in an intensive care unit, along with a renal consultation, since dialysis may be required. Hydration with isotonic saline to maintain urine output is recommended to minimize the effects of free heme mediated renal and vascular injury. Supplemental diuretics (a 40-mg intravenous bolus of furosemide, followed by a continuous infusion at a dose of 10 to 40 mg per hour in the absence of hypotension) are helpful in such cases. Forced alkaline diuresis may be helpful. Sodium bicarbonate (130 mmol per liter in 5% dextrose or water) is administered through a separate intravenous line at a starting rate of 200 ml per hour to achieve a urinary pH of more than 6.5. The infusion is discontinued if either the arterial pH exceeds 7.5 or the urinary pH fails to increase after 2 to 3 hours. Electrolyte abnormalities such as hyperkalemia are common and warrant swift correction. In patients with disseminated intravascular coagulation and severe bleeding, platelets, fresh-frozen plasma, and cryoprecipitate infusions may be required to maintain a platelet count, and the fibrinogen level. No evidence supports the routine use of therapeutic high-dose glucocorticoids, intravenous immune globulin, or plasma exchange. However, when transfusion of incompatible units is necessary, prophylaxis with glucocorticoids (hydrocortisone at a dose of 100 mg, administered just before transfusion and repeated 24 hours later) and intravenous immune globulin (1.2 to 2.0 g per kilogram, administered over a period of 2 to 3 days, with the first dose given just before the Incompatible transfusion) has been used. Acute hemolytic reactions to transfusion of incompatible units, although frightening and potentially lethal, are self-limited in most instances. Delayed hemolytic transfusion reactions are often clinically silent and are revealed by a positive antibody screen alone on routine laboratory testing. These episodes do not require intervention but must always be reported to the transfusion facility in order to reduce the risk of reactions to future transfusions. For patients receiving multiple transfusions who are at

risk for more serious delayed hemolytic transfusion reactions (especially patients with hemoglobinopathies), phenotypically matched red-cell transfusions or units that are negative for antigens known to be immunogenic and clinically significant, such as those in the Rh system.

For patients with sickle cell disease who have hyperhemolysis, directed treatment strategies have included immune modulators such as glucocorticoids, intravenous immune globulin, and rituximab, as well as erythropoiesis stimulating agents, since the endogenous erythropoietin response may be inadequate or delayed. [2]

Conclusion

Hemolytic transfusion reactions are recognized as an important cause of transfusion associated reactions and may be subclinical, mild, or lethal**.** Acute, immune-incompatible reactions to ABO mismatched transfusions have declined dramatically with the introduction of electronic verification systems. Other reactions, including delayed hemolytic transfusion reactions, hyperhemolysis, and passenger lymphocyte syndrome in transplant recipients, pose diagnostic and therapeutic challenges. Preventive strategies have been effective in reducing hemolysis-associated morbidity and mortality in all categories of hemolytic transfusion reactions. Established systematic protocols for quickly identifying and responding to suspected reactions, as well as reporting them, remain the cornerstone of timely management of hemolytic transfusion reactions.

Reference

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