Case Report

An acute hemolytic transfusion reaction due to the "anti-c" rhesus antibody: A case report emphasizing the role of transfusion medicine

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Abstract:

Rhesus (Rh) mediated hemolytic transfusion reactions (HTR) are usually immunoglobulin G mediated and delayed onset. Rh antibodies being the cause of acute HTR (AHTR) and intravascular hemolysis are still under debate. We report here a case of a 53-year-old male who developed AHTR due to "anti-c" antibodies within 3 h of blood transfusion, precipitating fatal acute liver failure in a patient with hepatitis C related chronic liver disease. This case emphasizes the need of inclusion of antibody screening in routine pretransfusion testing as well as a critical role of transfusion medicine specialists for early diagnosis and minimizing transfusion-related morbidity and mortality.

Key words:

Antibody, hemolytic, rhesus, transfusion, transfusion reaction

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Introduction

Rhesus (Rh) system is the second most important blood group system after ABO with highly immunogenic antigens. Rh mediated hemolytic transfusion reactions (HTR) are immunoglobulin G (IgG) mediated and usually results in extravascular hemolysis and delayed HTR (DHTR). The most commonly reported non-ABO acute HTRs (AHTR) are due to Kidd, Diego, and P antigens, etc [Table 1].[1-8] Anti-c Rh antibody although has been reported to cause hemolytic disease of newborn and DHTR, AHTR has not been much reported. Furthermore, possibility of Rh antibodies being the cause of intravascular hemolysis is still under debate.[7] We report an unusual case of AHTR due to anti-c causing intravascular hemolysis and mortality due to acute exacerbation of a chronic liver disease.

Case Report

A 53-year-old male was referred to our center as acute on chronic liver failure with complaints of jaundice, abdominal distension, generalized weakness, and dehydration.

He was a known case of Hepatitis C related chronic liver disease since 2008. He probably acquired this infection due to the blood transfusions given during knee surgery in 1996. He also received multiple transfusions owing to variceal bleed 2-3 times a year in the past 4 years.

At the time of admission, the patient was pale, deeply icteric, and hypotensive (BP 90/60 mm Hg); he had bilateral pedal edema and ascites. Laboratory investigations were as follows: Hemoglobin 6.9 g/dl, hematocrit 24%, platelet count 81,000 cells/cu mm, total serum bilirubin 28.8 mg/dl, serum alanine transaminase 160 U/L, serum aspartate transaminase 53 U/L, serum alkaline phosphatase 131 U/L. Patient was on supportive treatment, and a request was received for two units of packed red cells.

The blood sample was screened for irregular antibodies as per our standard protocol using a commercial ID-Diacell I-II-III antibody screening Panel (Diamed, Switzerland) and ID-cards "LISS/Coombs" (Diamed , Switzerland).

The test was positive with Panel II (4+) and Panel III (4+) with negative autocontrol. Antibody was confirmed as anti-c Rh antibody using ID DiaPanel, antibody identification panel (Diamed , Switzerland). The titration was performed by conventional tube method using double dilution method and was found to be 512 in anti-human globulin phase.

The direct antiglobulin test (DAT) was performed using "LISS/Coombs" (Diamed, Switzerland) and DC-Screening I (Diamed, Switzerland) ID-Cards. Polyspecific DAT was 4+ positive, and Monospecific DAT showed the presence of IgG antibodies only (4+). Anti-c was identified in the elute obtained from patient's red blood cells (RBCs) by Diacidel acid elution Reagents (Diamed, Switzerland). The

Table 1: Review of literature for antibodies associated with acute hemolytic transfusion reaction

References	Antibody	Postreaction DAT	Past history of antibodies	Pretransfusion cross matching	Clinical outcome
Mun *et al.* 2012[1]	Anti-Di(a)	Positive	Nil	Compatible	Mild IHTR[a]
Xu *et al.* 2012[2]	Anti-AnWj	Positive with anti C3d only	Nil	Incompatible (1+IAT)	Severe IHTR, mortality after 6 months
Baughn *et al.* 2011[3]	Anti-Ge3	Negative	Known anti-Ge3	Incompatible	Mild acute HTR[b]
Baumgarten *et al.* 2006[4]	Anti-Do[a]	—	Anti-E, anti-Fy[b], anti-S	Compatible	Recovered
Kwon *et al.* 2004[5]	Anti-Jra	Case 1: Positive anti-IgG only	Case 1: Evidence of anti-Jra and Anti-K	Incompatible	Case 1: Recovered
		Case 2: Positive with IgG + C3d	Case 2: Known anti-Jra	Incompatible	Case 2: Mild HTR
Park *et al.* 2002[6]	Anti-E, anti-c, anti-JKb	Negative	Nil	Compatible	Severe IHTR
Pradhan and Chaudhary 1999[7]	Anti-c	—	Nil	Compatible	Severe IHTR
Molthan *et al.* 1984[8]	Anti-C	Negative	-	-	Acute IHTR
Present study, 2014	Anti-c	Positive with IgG only	NA[c]	NA	Acute IHTR, mortality after 4 weeks

[a]IHTR = Intravascular hemolytic transfusion reaction, [b]HTR = Hemolytic transfusion reaction, [c]NA = Not applicable, DAT = Direct antiglobulin test

Rh phenotype and most probable genotype of the patient was R_1R_1 (DCe/DCe).

The positive antiglobulin tests (DAT and indirect antiglobulin test) and the presence of "anti-c" Rh antibody in eluate raised the suspicion of HTR. On reevaluation, the history revealed that on January 22, 2013, the patient received two units of whole blood transfusion in a local hospital on out-patient basis during which he felt uneasy. He further developed high-grade fever, chills, and severe abdominal pain 3 h after the transfusion. By the next morning, he noticed yellow discoloration of the skin and was passing red colored urine (Investigations not available). There was no rise in hemoglobin level after transfusion (Baseline Hb 6.7 g/dl). The serum bilirubin rose from baseline 1 mg/dl to 9 mg/dl by next day. The patient condition deteriorated during the next 7 days. Patient was referred to our hospital at this point of time on February, 2013.

A diagnosis of AHTR (i.e., within 24 h of transfusion) precipitating acute liver failure in a patient with hepatitis C virus-related chronic liver disease was made. Crossmatch compatible "c" antigen negative packed RBCs, and plasma components were issued and transfused.

Despite supportive care, the general condition of the patient deteriorated following an episode of variceal bleed leading to hepatorenal syndrome and patient succumbed to his illness on 18.2.2013.

Discussion

This is an unusual case of AHTR due to anti-c Rh antibody. Though Rh antibodies are IgG and do not activate complement, this patient had red colored urine suggestive of hemoglobinuria (intravascular hemolysis) 3 h after transfusion suggestive of intravascular hemolysis. Very few such cases of Rh antibodies causing intravascular hemolysis and acute presentation have been reported.[7,8]

Hemolytic transfusion reaction may be acute (within 24 h) or delayed (from 1 to 16 days), and both may be associated with intra or extravascular hemolysis.[9] If the RBC antibodies are capable of complement binding, the interaction of antibody with antigen on the red cell membrane can initiate a sequence of complement activation, which leads to the development of the membrane attack complex, causing lysis of RBCs, that is, intravascular hemolysis. Acute renal failure, shock, and/or disseminated intravascular coagulation (DIC) are the potential fatal complications which are cytokine-mediated leading to defects in coagulation and production of other elements of a systemic inflammatory response. If the antibodies do not fix complement, then the red cells undergo extravascular hemolysis in the spleen or liver.

Severe acute forms of HTRs usually occur when transfused RBCs interact with preformed antibodies in the recipient. The non-ABO IgG alloantibodies often arise after sensitization to foreign RBC antigens during pregnancy or following blood transfusion or less commonly during transplantation. Our patient had received multiple transfusions in the past and was alloimmunized to "c" antigen which was probably missed during pretransfusion testing. In India, routine pretransfusion testing in many of the peripheral centers does not include antiglobulin phase of cross matching which is essential to detect clinically significant antibodies such as Rh, Kell, Kidd, Duffy, etc. Limited centers have the facility for antibody screening and identification and to provide antigen negative blood to alloimmunized recipients and automation is yet to be adapted.

Non-ABO mediated AHTRs are not much common compared to delayed HTRs. The Table 1 shows few such reported cases of AHTRs. Rh mediated AHTRs and intravascular hemolysis has been debated in many case reports. Molthan *et al.* reported four cases of anti-C mediated transfusion reactions with intravascular hemolysis and hemoglobinuria.[8] Park *et al.*, reported AHTR due to multiple alloantibodies (anti-E, anti-c, anti-Jk[b]) which caused intravascular hemolysis.[6] Our case adds one more example that Rh antibodies can fix complement and cause intravascular hemolysis.

Anti-c, mostly IgG, is clinically the most common Rh antibody after anti-D and is reported to cause hemolytic disease of newborn and DHTR as a single or with anti-E antibody.[10] According to the north Indian study, the incidence of RBC alloimmunization in transfused patients is reported to be 3.4% (18/531), with anti-c being the most common (specificity 38.8%).[11]

As a consequence of AHTR, this patient had a marked rise in S. Bilirubin from 1 mg/dl to 9 mg/dl 48 h after transfusion which was misinterpreted as acute liver failure and was not treated in line with management guidelines of HTR. It is essential to timely recognize, diagnose, and manage the transfusion reaction to prevent HTR-related morbidity and mortality.

Typical clinical presentation with 24 h after blood transfusion includes, fever, chills, hemoglobinuria, back pain, flank pain, hypotension, renal failure, and/or DIC (oozing at IV site, diffuse bleeding at surgical site, abnormal DIC test results) or a state of shock. In anesthetized patients, the initial manifestations of an AHTR may be hemoglobinuria, hypotension or diffuse bleeding at the surgical site.

Hemolytic transfusion reaction can be confirmed by the laboratory features of hemolysis including free plasma hemoglobin (hemoglobinemia), urine hemoglobin (hemoglobinuria), unconjugated hyperbilirubinemia, reduced serum haptoglobin, and increased serum lactic dehydrogenase. The blood bank should also rule out any clerical or identification and cross matching errors. The presence and nature of the antibody can be identified with Coombs' tests and using red cell panels. It is inevitable to look for features of renal failure (urea, creatinine) and DIC (coagulation profile, platelet count, fibrin degradation products, d-Dimer) to prevent progressive damage to the organs.

A variety of cases has been reported since decades emphasizing the possibility of the presence of alloantibodies in transfusion recipients time and again. Despite this, the inclusion of antibody screening in routine pretransfusion testing is being ignored in many peripheral centers. It is high time the blood banks review their policy of testing to ensure multiple checks at various levels to prevent these mishaps especially in patients requiring multiple transfusion and pregnant women.

Prevention strategies for HTR in a known alloimmunized patient include informing the patient his antibody profile and handing him a blood bank identity card, and most importantly minimizing unnecessary blood transfusion. The blood bank should maintain hospital records of every patient requiring multiple blood transfusions.

This case emphasizes the critical role of blood bank for early diagnosis and treatment of AHTR, especially due to antibodies in individuals with multiple transfusions. Awareness of this entity will ensure safe blood transfusion, taking special care to screen for antibodies and thereby minimizing the morbidity and preventing potential mortality. Transfusion Medicine specialists need to be promptly consulted by the treating physician when the latter encounter patients with an acute fall in hemoglobin level following recent transfusion(s).

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