Fatal Delayed Hemolytic Transfusion Reaction and Hyperhemolysis without Detectable Alloantibodies or Autoantibodies in a Patient with Sickle Cell Disease: A Case Report and Literature Review

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Abstract

Background: Sickle cell disease (SCD) is one of the most commonly inherited diseases worldwide and one of the most frequently occurring genetic disorders in France. Delayed hemolytic transfusion reaction (DHTR) is a classic complication in patients with SCD who undergo blood transfusions, and this condition may lead to hyperhemolysis syndrome (HS). DHTR is described as a transfusion complication and is often associated with anti-RBC antibodies.

Case report: We report the death of a 47-year-old man of Martinican origin, with sickle cell disease (SCD) and no history of alloimmunization, who was admitted to the Sens Medical Center in July 2015 due to a vaso-occlusive crisis (VOC). An antibody screening test based on the gel technique was conducted and no anti-RBC antibodies were detected. The patient was readmitted with a VOC two days after discharge and subsequently developed DHTR/HS after transfusion episodes. He succumbed to acute complications involving severe multiple organ failure after being transferred to Henri-Mondor University Hospital in Creteil. This case report was made available thanks to our Haemovigilance Network.

Conclusion: This case demonstrates the importance of DHTR prevention using national guidelines to carefully assess indications for RBC transfusion in patients with SCD. Early diagnosis is crucial to prevent this life-threatening complication. Special attention should be given to less well-known and less-well monitored patients who may be at high risk for DHTR. In any event, DHTR/HS without detectable anti-RBC antibodies presents a clinical and biological challenge to our understanding of this disorder.

Keywords: Delayed hemolytic reaction; Sickle cell; Red blood cells; Alloantibody; Transfusion; Hyperhemolysis

Introduction

Sickle cell disease is one of the most commonly inherited diseases worldwide and one of the most frequently occurring genetic disorders in France [1]. Blood transfusion plays an important role in the management of sickle cell disease (SCD). Nevertheless, transfusion is potentially hazardous in patients with SCD and some complications, including delayed hemolytic transfusion reaction (DHTR), are not easily prevented. DHTR typically occurs in patients 5-15 days after transfusion and is often associated with a vaso-occlusive crisis characterized by the following symptoms: anemia, dark (cola-colored) urine, elevated indirect bilirubin, and increased levels of lactate dehydrogenase (LDH) [2,3]. It remains unknown why some cases of

DHTR directly involve or lead to hyperhemolysis syndrome (HS), causing the destruction of both donor and recipient red blood cells, brisk intravascular hemolysis, and very low levels of total hemoglobin (Hb) (below pretransfusion levels) [4-6]. HS typically causes a fall in absolute reticulocyte count (a decrease from the baseline concentration) during hemolysis, and a rise in Hb and reticulocyte counts often accompanies recovery [2,5]. Delayed reactions typically result from a secondary immune response in a previously transfused or pregnant patient who has developed an alloantibody, and such reactions can be life-threatening [7,8]. The risk of developing DHTR is the most serious consequence of alloimmunization in SCD patients. Screening tests can be used to detect these antibodies so that red blood cells free of the antigen in question may be administered. In some cases, however, the alloantibody titer may be below detectable levels at the time of pre-transfusion testing, and thus the antibody remains undiscovered [9]. The incidence of alloimmunization to red blood cell

antigens in transfused patients with SCD is approximately 5-36%, which is greater than that in the non-sickle cell population [9]. Alloimmunization is also a risk factor for the production of red blood cell antibodies. Autoantibodies may exacerbate the hemolytic reaction, contributing to bystander hemolysis and, in some cases, explaining the destruction of both the donor's and patient's RBCs [10,11]. Autoantibody production occurs in approximately 6 to 10% patients who have sickle cell disease and undergo transfusion [11].

In this case report, we describe the occurrence of a fatal delayed hemolytic transfusion reaction/hyperhemolysis syndrome in a patient with SCD presenting a VOC, and we propose a management strategy for preventing and treating this transfusion complication using data from the associated literature.

Case Report

A 47-year-old male with SCD and no history of G6PD deficiency or alloimmunization was admitted to the Sens Medical Center in July 2015. The patient had been symptomatic since childhood and experienced frequent VOC episodes (2-4 episodes/year). He presented with particularly painful episodes, acute chest syndrome (ACS), and priapism. His basal Hb concentration was between 6.9 and 8 g/dL and was generally treated with hydroxyurea and folic acid.

The patient's blood type was O, phenotype D+C-, E-, c+, e+, K-, Jka +, Jkb-, Fya-, Fyb+, S-, s+, and his medical history included multiple previous transfusion episodes. These prior transfusions were not conducted at Sens Medical Center, and there was no evidence of any

previous transfusion reactions. The patient was admitted to the Sens Medical Center due to a VOC which included back pain, fever (T °38.7°C), abdominal pain, a cough with purulent sputum, and brown urine. A complete blood count was ordered and did not show signs of severe anemia, taking his baseline Hb into account (the patient's Hb was 7.1 g/dl). He was treated for dehydration and given pain medication, antibiotics, and oxygen. No atypical red blood cell alloantibodies were detected using the indirect antiglobulin technique (antibody screening using the Bio-rad gel card). And After testing, two ABO-compatible RBC units, Rh and Kell phenotype matched and cross-matched on day 2 were given by transfusion in accordance with national guidelines. The patient was discharged from the hospital on day 7, with an Hb concentration of 9.6 g/dl. Two days after the patient's discharge, he was readmitted to the same facility for another painful VOC. He was jaundiced and exhibited hemoglobinuria. At this time, his Hb level was 9.5 g/dl. On day 11, this level decreased to 8.9 g/dl, and one RBC unit was administered. Soon after this last transfusion, he abruptly developed severe whole body pain (day 12), and his Hb level dropped to 4.4 g/dl while his plasma lactate concentration rose to 21.5 mmol/l. The patient's laboratory results and Hb levels during his admission/readmission to Sens Medical Center are summarized in Table 1 and Figure 1 respectively. Additional serologic testing, including direct (DAT) and indirect (IAT) tests using Bio-Rad gel cards and the gel technique (Wadiana, Grifols S.A) was negative. The patient was again treated for dehydration and given oxygen as well as large doses of morphine to control his pain; he was anxious, irritable, and drowsy.

Parameters	Day 1	Day 3	Day 7	Day 10	Day 11	Day 12
	First admission: initial values	After receiving 2 RBC units	Discharge values	Readmission: initial values	After receiving 2 RBC units	DHTR event after receiving 1 RBC unit
Hb (g/dl)	7.1	9.2	9.3	9.5	8.9	4.4
Hct (%)	22	28	27	28	27	13
Reticulocytes (Giga/l)	NM*	NM	NM	NM	NM	NM
WBC count (Giga/l)	14.1	13.4	8.7	14.1	19.4	16.1
PLTs (Giga/l)	255	455	516	494	230	63
Total bilirubin (µmol/l))	NM	NM	NM	126.2	NM	NM
Direct bilirubin (µmol/l))	NM	NM	NM	117.3	NM	NM
LDH (IU/)	NM	NM	NM	834	NM	NM
AST (IU/l)	73	NM	NM	89	NM	NM
ALT (IU/l)	27	NM	NM	54	NM	NM
Serum creatinine (µmol/l)	60	54	63	58	51	320
BUN (µmol/l)	1.9	2.3	0	3.2	3.1	12.7
CRP (mg/l)	25	47.4	9	12.7	49.3	166.3
INR	1.2	NM	NM	1.1	NM	9
Fibrinogen (g/l)	NM	NM	NM	NM	NM	1.25

*NM: not measured

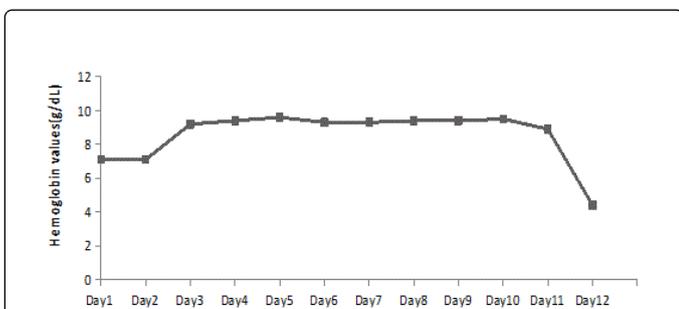**Table 1**: DHTR laboratory results by day: Sens Medical Center, Sens, France.

Figure 1: Delayed hemolytic transfusion reaction (DHTR) in a patient with sickle cell disease admitted into Sens Medical Center, France: Day 1: Sadmission; Day 2: Transfusion of two RBC units; Day 7: Discharge; Day 10: Readmission; Day 12: DHTR event with abrupt drop in Hb levels–transfusion of one RBC unit at 1:45 AM; two RBC units and three FFP (fresh frozen plasma) units at 1:00 PM.

On day 12, the patient received two RBC units in the intensive care unit before his same-day transfer to the Henri-Mondor University Hospital (located in Créteil, France) where he was to receive tertiary care. Upon admission, he had an Hb of 5.9 g/dl and elevated blood lactate concentrations (>15 mmol/l).

This resulted in multiple organ failure. The results of all biological testing, from admission into the Henri-Mondor University Hospital until the patient's time of death, are shown in Table 2.

Arterial blood gas measurements revealed a pH of 7.27, a PaCO2 of 38 mmhg, and PaO2 of 175 mmhg at a 100% inspired oxygen fraction. His vital signs revealed a temperature of 37.1°C, a heart rate of 118 beats per minute, a respiratory rate of 34 breaths per minute, and a blood pressure of 90/50 mmhg.

The physical exam revealed *conjunctival icterus*, tachycardia, and a voluminous spleen; hepatomegaly was not found. The patient received invasive monitoring and was treated with *noradrenaline* and aggressive fluid resuscitation to reverse hemodynamic shock; antibiotherapy with Tazocilline® (piperacillin/tazobactam) was continued.

Measurements	Day 1 Admission Values (transfusion: 6 FFP** units)	Day 2 Values (massive transfusion of 13 RBC units, 12 FFP units, and 2 platelet units)	Day 3 Values (Patient died after receiving 1 RBC unit and 3 FFP units).
Hb (g/dl)	5.9	6.6	9.5
Hct (%)	16	20	27
Reticulocytes (Giga/l)	44	NM	NM
WBC count (Giga/l)	11.6	NM	NM
PLTs (Giga/l)	21	69	79
Total bilirubin (µmol/l)	NM*	110	124
Direct bilirubin (µmol/l)	NM	83	111
LDH (IU/l)	NM	12,500	6,768
AST (IU/l)	NM	11,697	4,218
ALT (IU/l)	NM	3,273	1,133
Serum creatinine (µmol/l)	407	225	178
BUN (µmol/l)	13.6	5.8	3
INR	7.32	2.68	4.13
Fibrinogen (g/l)	0.8	1.4	2.1
FV (%)	6	31	NM

*NM:Not measured. **FFP:Fresh frozen plasma

Table 2: Laboratory results at the Henri-Mondor University Hospital, in Créteil, France.

It was only at this time that DHTR was diagnosed, and the decision was made to discontinue further transfusions. Given the patient's worsening hepatic function, he was scheduled for an emergency liver transplant. On day 13, he therefore underwent Molecular Adsorbent Recirculating System (MARS) [12] therapy, a form of artificial extracorporeal liver support that can be used to treat fulminant or chronic hepatic failure in patients who are waiting for a compatible donor. The patient's anemia continued to worsen, and he received a transfusion of several RBC and plasma units to maintain adequate circulation and hemostasis. Eculizumab (600 mg) was also administered on a *compassionate use* basis. Despite treatment, his clinical symptoms continued to worsen, and his liver transplant was cancelled. His death on day 14 was clearly transfusion-related, and this fatal adverse effect was reported to the French Haemovigilance Network.

Discussion

Here, we present a case involving a 47-year-old Martinican man with SCD who experienced a severe DHTR with no detectable pre- or post- transfusion anti-RBC antibodies. DHTR symptoms occurred on day 12 and were accompanied by hyperhemolysis. The patient had a history of multiple transfusions, but no known adverse reactions were ever reported. The fatal DHTR described here is a grade 4 adverse event attributable to transfusion and reported to our Haemovigilance Network. DHTR in sickle cell patients is a well-known complication of transfusion, entailing a significant drop in Hb (>25%) 5 to 15 days after transfusion. It is often caused by a secondary immune response to an antigen on the donor's erythrocytes and leads to the destruction of transfused erythrocytes [3,9,13]. This complication has a reported incidence of 3% to 7% in transfused SCD patients, and 4% to 12% of DHTRs may be fatal [14]. Other DHTR cases with no detectable anti-RBC antibodies were reported in the literature in approximately 30% of cases, but the pathophysiological mechanism mediating red cell destruction is still unclear [3,15]. Because cross-match and antibody screening involve inherent complications, specific antibodies cannot be systematically excluded in similar cases involving non-detectable antibodies. A negative antibody screen does not guarantee that the recipient's serum lacks clinically significant red cell antibodies. A negative antibody screen simply means that the recipient's serum does not contain antibodies that react with the method's screening cells. To illustrate this point, we provide the following example: a recipient may possess an antibody directed against a low-incidence antigen that is not present in the commercial screening cells. Furthermore, a compatible cross match does not guarantee the optimal survival of red blood cells. An antibody may not react due to the weak expression of an antigen on donor cells in a cross match, leading to a complex situation. A DHTR could occur if a preexisting, undetectable recipient antibody is activated and strengthened by a corresponding donor antigen, leading to the rapid destruction of donor cells.

Two prominent medical problems affected patient management in this case: first, the decision to administer early transfusion, during the patient's first admission with an Hb rate of 7.1 g/dl (baseline: 6.9-8 g/dl), was based on insufficient evidence. A referral institution or the hematology consultant should have been contacted and asked to provide transfusion advice. Second, the patient's DHTR was misdiagnosed in the Emergency Room when he was readmitted into the Sens Medical Center, even though the patient was exhibiting all of the clinical and biological signs of DHTR. Furthermore, we also noticed that neither the patient's reticulocyte count or HbA and HbS percentages were measured between his first admission and the onset of DHTR/HS on day 12, when the decision was made to refer the patient to the Henri-Mender University Hospital in Creteil. Indeed, this clinical case clearly illustrates the need to provide clinicians with streamlined information and guidelines for managing patients with SCD [16,17] especially guidelines pertaining to blood transfusion. Such recommendations must be strictly respected if we are to manage or prevent DHTR in patients with sickle cell disease. Clinicians should take these recommendations into consideration in order to optimize transfusion practice and avoid the risk of DHTR in less well-known and less-well monitored patients and in patients who do not undergo transfusions on a regular basis. Habibi et al. [3] reported that DHTR occurs in patients who receive relatively few transfusions (10 RBC units on average), and that, for more than half of these patients, the transfusion that triggered the episode was prescribed as a one-off preventive measure; these patients had rarely, if ever, been transfused. Whenever patients with SCD are admitted into the hospital, an investigation should be carefully carried out to learn about the individual's transfusion history and any episode involving prior antibodies. Thus, close communication between clinicians and the blood transfusion center is crucial. If a transfusion is necessary, national recommendations concerning patients with SCD must be followed. The use of Rh-Kell matched RBC units has reduced alloimmunization and hemolytic transfusion reactions [18]. The incidence of alloimmunization to RBC antigens in transfused patients with SCD is approximately 20-25%, which is greater than that of the general population [2,19]. Following alloimmunization, a rapid reduction in alloantibody titer may make the antibody undetectable by routine screening, hence the need for accurate records. A centralized database, accessible across health-care systems, that includes patient red cell antibody histories should be created to inform the transfusing facility of previously identified antibodies (even if they are no longer detectable) and thereby ensure the selection of compatible RBC units for transfusion.

Although no standard treatment exists, managing patients with DHTR necessitates the avoidance of further transfusions because they can cause hemolysis to worsen. However, if the patient presents with rapid hemolysis and severe anemia, then a transfusion may be necessary. In such cases, intravenous immunoglobulin (IVIG) and Erythropoietin (EPO) should be administered concurrently [7]. For severe cases, EPO-Eculizumab should be considered [3-20]. In cases where additional transfusions are necessary, EPO-Rituximab may prove successful [3].

Conclusion

DHTR is a serious and potentially life-threatening complication of RBC transfusion. All clinicians managing patients with SCD must be aware of the risk of DHTR to ensure prompt recognition and management. Indications for transfusion according to national recommendations should be followed. To minimize adverse events or transfusion-related reactions, close liaison with the blood bank is necessary. Such cooperation will provide the help needed to investigate any current or historical antibodies in less well-known and less-well monitored patients who may be at high risk for developing DHTR. DHTR should be appropriately investigated and reported to the National Haemovigilance Network.

Acknowledgments

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