


# Delayed Hemolytic Transfusion Reaction in a Patient with Sickle Cell Disease: Case Report

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**Background:** Blood transfusion is a key treatment of sickle cell disease (SCD) complications. Delayed hemolytic transfusion reaction (DHTR) is a delayed reaction, that occurs days to weeks following a transfusion, characterized by mild anemia and/or hyperbilirubinemia and is one of the serious complications of blood transfusion. The symptoms of DHTR resemble those of vaso-occlusive crisis secondary to SCD leading to difficulty or delaying in diagnosis of DHTR. DHTR may lead to multiple organ failure and death.

**Case Report:** A 31-year-old female patient with a known case of SCD presented to our ER in King Fahad hospital Hofuf in the Kingdom of Saudi Arabia, with a history of generalized body ache, exertional dyspnoea, headache and easy fatigability for a few days on a background history of episodic hospital admissions for SCD, but she was admitted 3 times over the previous 6 months and received 6 units of packed red blood cells (PRBCs). The last blood transfusion was 18 days earlier. She was sick and her Hb level was 4.5 g/dL with positive Coombs test and positive alloantibodies, diagnosed as DHTR. We treated her with prednisolone tablets 1 mg/kg daily, intravenous immunoglobulins, 0.4 gm/kg daily for 5 days, and rituximab 500 mg IV every week for 4 weeks. Her Hb level raised up to 8.2 g/dL and she was discharged in good condition.

**Conclusion:** Identifying risk factors for DHTR by history and presentation is urgently needed in order to risk stratify the transfusion regimen. It is important to avoid additional transfusions in these patients if possible because these may exacerbate the hemolysis and worsen the degree of anemia.

**Keywords:** sickle cell disease, delayed hemolytic transfusion reaction

## Introduction

Red blood cells (RBCs) transfusion is crucial in the treatment of acute and chronic complications in SCD; however, it is complicated by RBC alloimmunization, iron overload, transfusion reactions and infection.<sup>1</sup> Transfusion with RBCs matched for Rh (D, C, E, c, e) and K antigens for patients with SCD can be life-saving and is the standard care in many centers but development of antibodies against transfused RBCs may occur leading to DHTR. These alloantibodies are detected by a positive direct antiglobulin test (DAT) and are not always detected in many cases. In DHTR both transfused and autologous RBCs hyperhemolysis occurs and may be accompanied by reticulocytopenia, leading to worsening of the anemia.<sup>2</sup> SCD patients develop RBCs alloantibodies much more frequently than non-SCD transfused patients, in addition to having a significantly higher risk of suffering from DHTR.<sup>3</sup> The incidence of alloimmunization in patients with SCD is 5–36%. One complication of alloimmunization is DHTR/H syndrome, with an incidence of 11%.

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In patients with SCD, clinical findings in DHTR occur about 1 week after the RBCs transfusion and include the onset of increased hemolysis associated with pain and severe anemia.<sup>4</sup> In some studies, the appearance of clinical signs has a median of 9.4 days after the blood transfusion. As a complication of severe intravascular hemolysis, acute chest syndrome, pulmonary hypertension and (multi)organ failure may occur and the overall mortality of DHTR was 6% in a retrospective study of 99 DHTRs occurring in 69 referral center patients over 12 years.<sup>5</sup> DHTR can be complicated by hyperhemolysis.<sup>6</sup>

Patients with DHTR often have mixtures of both allo and autoantibodies; rhesus (RH) antibodies and those considered as irregular natural antibodies are frequent. A third of SCD patients will not develop an antibody after a DHTR.<sup>7</sup> No antibodies are detected in 30% of patients with DHTR. Prevention is based on the prevention of alloimmunization via the use of matched RBCs for highly immunogenic blood groups, taking into consideration previous transfusion history of the patient especially in patients undergoing occasional transfusion, which is associated with a higher risk of DHTR development than chronic transfusion, in addition to this, use of immunotherapy should be considered.<sup>8</sup> DHTR represents 4.2% of all causes of death in SCD, this percentage could be underestimated because DHTR is frequently misdiagnosed as simple vaso-occlusive episodes. Occurrence of DHTR as well as its clinical progression from mild to severe is unpredictable and its prevention in SCD is challenging because only little is known about its mechanism since in some cases of DHTR no antibodies are detected.<sup>9</sup> Detectable antibodies in SCD DHTR are frequently alloantibodies against antigens such as Rh, K, Fy, Jk, and Ss but antibodies against many other RBC antigens as well as autoantibodies and nonspecific antibodies can be found.<sup>9</sup> Risk factors for DHTR include: history of immunization, previous history of DHTR, and transfusion for an acute complication in addition to lower cumulative number of transfused units ( $\leq 12$  units).<sup>9</sup> Diagnosis of DHTR in patients with SCD who recently received blood transfusion depends on clinical and laboratory criteria like pain, anemia, urine color, elevated lactate dehydrogenase (LDH) and immune-hematological analysis which may or may not reveal the presence of new antibodies and change in HbA level.<sup>9</sup> Patients with SCD need close monitoring for detection of DHTR because it could be severe and life threatening so besides supportive measures, specific therapy according to severity criteria should be followed. Severity criteria include: acute chest syndrome,

acute pulmonary hypertension, stroke and organ failure (liver or kidney). Intravenous immunoglobulins (IVIg) therapy (0.4 g/kg/day for 3–5 days), is often used for prevention of antibody-mediated immune destruction and its mechanism of action remains incompletely understood. Side effects of IVIg include: hyperviscosity, hypercoagulability, renal toxicity, and hemolysis in non-blood group O. With low Hb level in DHTR, the risk of hyperviscosity in SCD patients is low. IVIg is recommended as the first-line therapy for patients with DHTR, even in patients with undetectable antibodies because antibodies may develop later. Steroids in high dose is used for immune system modulation and as a first line therapy for severe DHTR with or without IVIg, synergistic action between them has been reported in suppressing macrophage activity. There are no guidelines at present for the use of steroids or IVIg as a first line therapy and no evidence-based studies to support the use of one over the other. Treatment with eculizumab, an inhibitor of the C5-convertase is used early in cases of severe DHTR, with hyperhemolysis to prevent irreversible multi-organ organ failure. Meningococcal vaccine is mandatory with eculizumab treatment. Plasma exchange can also be used in severe cases of hyperhemolysis, it was reported that it can detoxify heme in patients with multi-organ failure without DHTR. In addition to the above therapies blood transfusion may be indicated in the presence of profound anemia and organ hypoxia but rituximab prophylaxis should be given. Use of haptoglobin or hemopexin to detoxify plasma free Hb and free heme, respectively are promising options which may be explored in the future as therapy for DHTR.<sup>9</sup> We are presenting DHTR in a 31-year-old female who is known to have SCD with infrequent hospital admissions.

## Ethical Considerations

Approval for the case report was obtained from Hass/King Fahad Hospital research committee and informed written consent was obtained from the patient that the case details could be published.

## Case Presentation

A 31-year-old Saudi female patient with a known case of SCD presented to our ER in King Fahad Hospital, Hofuf in the Kingdom of Saudi Arabia, with a history of generalized body ache, exertional dyspnoea, headache, easy fatigability and dark urine for a few days on a background history of infrequent (episodic) admissions for vaso-occlusive crisis but she was admitted 3 times to hospital

over the previous 6 months because of anemia and thrombocytopenia (secondary to splenomegaly) and she received 6 units of packed red blood cells (PRBCs). Last blood transfusion was 18 days and her hemoglobin (Hb) level before transfusion was 6.5 g/dL. No history of previous antibodies against RBCs was detected. Prior transfusions blood were matched for ABO and D antigens only. On examination she was pale and sick. Chest and cardiovascular examination were not remarkable and abdominal examination showed splenomegaly (which was present since last admission). Investigations showed: her Hb level was 4.5 g/dL, WBCs: 9.86/L, platelets: 84,000, reticulocytes count 6%, BUN: 3.6 mmol/L, creatinine: 69 mmol/L, AST: 84 U/L, ALT: 20 U/L, LDH: 664 IU/L, total bilirubin: 40.2 mmol/L, direct bilirubin: 14.8 mmol/L, albumin: 40 g/L, PT: 13, PTT: 30.8, INR: 1, with positive direct Coombs test and positive alloantibodies and there was no compatible blood for her for blood transfusion. Hemoglobin electrophoresis: HbS: 84%, HbA2: 4%, HbF: 12%, HbA: 0%, G6PD test: normal. HBs Ag, Anti HCV Ab and HIV serology were all negative. The patient was diagnosed to have DHTR and so we treated her with prednisolone tablets 1 mg/kg daily, intravenous immunoglobulins, 0.4 gm/kg daily for 5 days, and rituximab 500 mg IV every week for 4 weeks in addition to folic acid 5 mg once per day. The patient did not receive and was not on hydroxycarbamide. Her response to treatment was good and after 1 week of treatment complete blood count (CBC) showed: WBC: 5.63, and Hb: 6.9 g/dL, platelet: 100,000. The patient was discharged after the second dose of rituximab, in good condition and was re-admitted after 1 week for the third dose of rituximab infusion. CBC after the 3rd dose of rituximab was as follows: WBC: 6.31/L, Hb: 8.2 g/dL, platelets: 132,000. There was improvement in hemoglobin level in this patient with prednisolone, IVIG and rituximab and without being given a blood transfusion.

## Discussion

Patients with SCD often need RBCs transfusion to save their lives, DHTR is a serious complication of RBC transfusion due to alloimmunization leading to hyperhemolysis and DHTR.<sup>10</sup> DHTR typically occurs days or weeks following blood transfusion of seemingly compatible RBCs. The delay of onset of DHTR could reflect the recrudescence of alloantibody not detected at the time of the RBC compatibility testing prior to transfusion. Following another blood transfusion, exposure to the implicated

alloantigens, the immunological memory generated during the prior transfusion will facilitate an amnestic immune response that results in production of alloantibodies against the transfused units of blood which leads to destruction of the transfused RBC.<sup>11</sup> According to the guidelines for blood transfusion for patients with SCD, all patients with SCD should receive serologically cross-matched-compatible leukodepleted RBCs and should be monitored with care by doing an antibody screening test including a direct antiglobulin test (DAT).<sup>9</sup> This is what happened to our patient in this case report where she developed features of DHTR after 18 days of RBC transfusion. Her presentation was with symptoms similar to vaso-occlusive crisis with dropped Hb and a positive direct Coombs test, positive alloantibodies and her hemoglobin electrophoresis showed zero level of Hb A only 18 days after a transfusion and this is very specific for DHTR vs other causes of anemia in SCD. The above findings were similar to the study carried out by Habibi et al<sup>5</sup> about delayed hemolytic transfusion reaction in adult sickle-cell disease: presentations, outcomes, and treatments of 99 referral center episodes, where they found that the most common clinical manifestations of DHTR were as follows: dark urine/hemoglobinuria in 94%, painful vaso-occlusive crisis in 89%, and 50% had a secondary acute chest syndrome. The median Hb concentration was 5.5 g/dL and LDH peak was 1,335 (798–2,086). A total of 61% of patients had previous antibodies and 28% had previous DHTRs.<sup>5</sup> In our patient, her Hb level was 4.5 g/dL and LDH was 664 IU/L. In another retrospective study done by Aygun et al<sup>12</sup> about the clinical significance of alloimmunization to RBC antigens in sickle cell patients both pediatric and adult sickle cell patients who were followed over a 10-year period, they found that the alloimmunization rate was 29% in pediatric and 47% in adult sickle cell patients when partial or extended RBC antigen match was not performed and DHTR occurred, however it did not result in a severe clinical outcome in most instances. The incidence of alloimmunization in general is high in patients with SCD because of higher prevalence of C, E, Fy<sup>a</sup>, Jk<sup>b</sup>, and S polymorphic blood group antigens in donors. Another cause of alloimmunization in SCD may be due to the inflammatory nature of this condition. Additional factors for alloimmunization could be genetic.<sup>9</sup> The patient in this case report had infrequent hospital admissions for SCD crisis and had occasional transfusions and this put her as a high risk case for the development of DHTR, since, as reported in the literature, patients who had an

episodic blood transfusion are more prone to develop DHTR than chronic transfusion. A recent prospective study of adults showed that DHTR was exclusively occurring in patients receiving episodic transfusions.<sup>9</sup> Occasional transfusions are associated with a higher risk of DHTR than chronic transfusion.<sup>8</sup> Management of DHTR if made early will give the chance for implementation of specific treatments such as steroids, immunoglobulins, erythropoietin and eculizumab with good outcomes.<sup>2</sup> In one study, supportive care alone was used in 53%, or within 74% including erythropoietin and sometimes rituximab and/or an immunosuppressant. Additional blood transfusion was either ineffective or worsened hemolysis.<sup>5</sup> In a case reported by Vlachaki et al<sup>13</sup> they had good outcome adjunctive therapy with the use of eculizumab in a patient with sickle cell disease who presented with DHTR with hyperhemolysis. Our patient in this case report received steroids, IVIg, and rituximab infusion and her Hb level raised without blood transfusion. Prevention of DHTR is based on the attenuation of alloimmunization via extended-matched RBCs or the use of rituximab.<sup>2</sup> Follow up with antibody screening at regular intervals will help in detection of any possible post-transfusion antibodies which, once known, will help selection of future units for transfusion and thus re-stimulation can be avoided.<sup>9</sup>

## Conclusion

Since DHTR is unpredictable and could be fatal, patient history and clinical presentation is needed to identify risk factors for DHTR. Early diagnosis of DHTR is essential so as to implement specific therapy early and to avoid additional blood transfusions which may exacerbate hemolysis and cause further drops in Hb levels.

## Recommendations

Improvement of our knowledge regarding presentation and risk factors of DHTR will help in proper management of this life-threatening condition.

Transfusion protocols should be available with strategies to minimize alloimmunization and risk stratification with restricted indications for transfusion for patients with alloimmunization or previous DHTR.

Decision for blood transfusion for SCD patients should be re-evaluated especially for DHTR high risk patients.

Further studies are needed for DHTR patients to highlight optimum ways of management of this life-threatening condition.

## Disclosure

The authors report no conflicts of interest in this work.

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