



## Revista Brasileira de Hematologia e Hemoterapia Brazilian Journal of Hematology and Hemotherapy

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### Case Report

# Hyperhemolysis syndrome in a patient with sickle cell anemia: case report



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### ARTICLE INFO

#### Article history:

Received 10 August 2014

Accepted 27 November 2014

Available online 11 April 2015

### Introduction

Sickle cell anemia (SCA) is a genetic disorder characterized by homozygous hemoglobin S (Hb S), chronic hemolytic anemia and painful episodes.<sup>1</sup> Patients with SCA usually require red blood cell (RBC) transfusions to manage complications and to reduce morbidity during surgical procedures.<sup>1</sup> One possible complication of multiple transfusions is alloimmunization, which occurs due to the recognition of foreign surface antigens on transfused RBC by antibodies produced by the recipient (alloantibodies).<sup>2,3</sup> This phenomenon can lead to a delayed hemolytic transfusion reaction/hyperhemolysis syndrome (DHTR/HS).<sup>1</sup> However, patients who present this syndrome generally do not show any new alloantibodies, and a direct antiglobulin test (DAT) is usually negative.<sup>4,5</sup> As no new antibodies are detected and the symptoms can be confused with other SCA complications, this syndrome represents an important diagnostic challenge. The recognition of this syndrome is important for the management of the symptoms and to prevent future onsets. As it is triggered by blood

transfusions, it is important to recognize it and avoid further transfusions.

This paper aims to highlight the importance of recognizing HS, because wrong management of a crisis with an extra RBC transfusion can increase the hemolysis and cause life-threatening anemia. We report a case of a young girl with SCA that developed an episode of hyperhemolysis seven days after a blood transfusion.

### Case report

An 18-year-old girl with SCA was admitted with acute chest syndrome and was treated with intravenous fluid, analgesia and antibiotics. Her blood tests showed an hemoglobin (Hb) level of 6.10 g/dL, hematocrit (Ht) of 19.2%, lactate dehydrogenase (LDH) of 743 U/L, and bilirubin level of 5.95 mg/dL (unconjugated: 3.69 mg/dL). She received one unit of phenotypically matched packed RBCs, with no complications during the procedure. Laboratorial exams at discharge showed Hb level of 9.32 g/dL, Ht of 30.8%, LDH of 643 U/L and bilirubin level of 4.29 mg/dL.

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<http://dx.doi.org/10.1016/j.bjhh.2015.03.005>

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Two days after discharge (seven days after the RBC transfusion) she was re-admitted with jaundice, hemoglobinuria, pain crisis, paresthesia of feet, lethargy, dyspnea and pulmonary rales in lower third of both lungs. Her Hb level was 4.71 g/dL, Ht 14.7%, white blood cell count (WBC)  $37.8 \times 10^9$  cells/L, LDH 3910 U/L and bilirubin 13.65 mg/dL (unconjugated 9.55 mg/dL). No RBC antibodies were detected using the gel method (Serascan Diana 2/Serascan Diana 2P – Grifols, S.A.) and confirmed with the ID-System (BIO RAD®). HLA antibodies were also not detected by a LABScreen® MULTI (One Lambda Inc.) assay. Her Hb A level was 4% and Hb S was 86%. Excluding infection and other SCD complications, we considered the hypothesis of DHTR/HS and started high-dose intravenous methylprednisolone (1.5 g/day). One day after, her Hb levels dropped even further, reaching 3.0 mg/dL and her LDH levels increased to 6680 U/L, accompanied by a decreased level of consciousness. Given the severity of the case we decided to give her one unit of packed RBCs. We also started the administration of 1 g/kg intravenous immunoglobulin (IVIG), erythropoietin (4000 U) and folic acid. She improved and was discharged after two weeks with Hb of 7.96 mg/dL, Ht of 24.5%, LDH of 1694 U/L and bilirubin level of 5.69 mg/dL. Serial immunohematological studies performed after this crisis also showed negative DAT and HLA antibodies.

## Discussion

A young SCA patient was diagnosed with DHTR/HS seven days after a RBC transfusion. She presented with severe anemia, Hb levels lower than before the transfusion, signs of hemolysis and pain crisis. Faced with this situation and excluding other causes, the hypothesis of DHTR/HS was established. DHTR/HS is an uncommon but severe complication of alloimmunization that occurs in patients submitted to RBC transfusions, especially those with SCD, who are submitted to multiple transfusions during their lives.<sup>4</sup> The rate of alloimmunization in SCD patients is around 5–36%,<sup>1,6</sup> and the incidence of DHTR/HS in SCD patients is around 1–19%.<sup>1,7</sup>

When we evaluated her medical chart, we observed that she had a similar condition three years previously. Two days before a hip surgery she underwent a partial exchange transfusion and received phenotypically matched RBCs. Before transfusion her Hb level was 7.2 mg/dL, Ht was 21.9% and WBC was  $17.3 \times 10^9$  cells/L. The surgery went well, and she did not need any other transfusions during or after the procedure. However, five days after the surgery (seven days after the transfusion) she was admitted as an emergency presenting with fatigue, jaundice, pallor and tachycardia. She did not exhibit fever or pain. Her laboratory tests showed Hb of 4.08 mg/dL, Ht of 12.7%, WBC of  $41.5 \times 10^9$  cells/L, LDH of 3346 U/L and bilirubin level at 12.09 mg/dL. Concerned about the risk of infection, intravenous fluid and oxacillin were administered. Blood cultures were negative. She was also managed with the transfusion of one unit of packed RBCs. Her symptoms improved and two days after she was discharged on oral antibiotics. On that occasion she was diagnosed with infection, despite the fact that she did not present with fever or signs of bacterial infection. The symptoms of DHTR/HS can easily be mistaken for other sickle cell disease

complications, including infections and vaso-occlusive crises.<sup>7</sup> The most important issue is to recognize the temporal appearance of the symptoms and its correlation with transfusions of RBCs. DHTR/HS usually begins seven days after a RBC transfusion (range: 4–11 days).<sup>1</sup> It is also important to measure the Hb levels. Thus, the diagnosis of DHTR/HS is made by clinical features, time between RBC transfusion and clinical onset, laboratory tests and exclusion of differential diagnoses.<sup>6</sup>

Before the first supposed episode, when she was 15 years old, our patient had received over 16 RBC transfusions. Thus, she had a high risk of developing alloantibodies, even receiving phenotypically matched RBCs. Over time, some alloantibodies decrease to levels not detected by serological tests.<sup>1</sup> Once those antibodies are not detected, cells seem to be phenotypically compatible and are released for transfusion. However, subsequent re-exposure to the antigens that triggered the antibody production stimulates an anamnestic response leading to hemolysis.<sup>1,6</sup>

HS is mainly caused by destruction of both donor and recipient RBCs, but the exact mechanism is still not well understood.<sup>4,5</sup> One possible explanation for autologous RBC destruction is “bystander hemolysis” whereby sickled RBCs are destroyed by antibodies without expressing the specific antigen against which this antibody is directed.<sup>5</sup> Another explanation for the patient's RBC reduction is the activation of macrophages leading to peripheral destruction. Sickled RBCs expose some antigens (e.g. phosphatidylserine) and high levels of IgG on their outer surface, allowing recognition by hyperactivated macrophages.<sup>6</sup> Our patient did not exhibit any alloantibodies or HLA antibodies after the hemolysis crisis, so it is believed that the patient's and donor's RBCs were destroyed by the hyperactivated macrophages.

HS is characterized by severe anemia, with Hb lower than pre-transfusional levels, pain, fever and signs of hemolysis (jaundice, increased LDH, hyperbilirubinemia and hemoglobinuria).<sup>1,5</sup> Reticulocytopenia may be present<sup>5</sup>; HS can be classified into acute or delayed.<sup>4</sup> In the first situation, symptoms appear within seven days of receiving RBCs, and a DAT is generally negative. The delayed form usually appears seven days after a transfusion.<sup>4</sup> DAT results are usually positive and new alloantibodies can be detected in the patient's serum.<sup>5</sup> DHTR/HS can also be associated to some complications such as acute chest syndrome, congestive heart failure, pancreatitis, acute renal failure, subarachnoid hemorrhage, acute respiratory distress syndrome, pneumonia, and splenic sequestration.<sup>1,3</sup> There is no specific test to diagnose DHTR/HS, and in many cases no alloantibodies are detected. Win<sup>5</sup> proposes that laboratory investigations when DHTR/HS is suspected should contemplate reticulocyte count, serum bilirubin level, LDH, DAT, screening for antibodies, serial measurement of RBCs, Hb electrophoresis, and high-performance liquid chromatography (HPLC) analysis of the urine.

The treatment of DHTR/HS is based on the exclusion of other causes and management of steroids and immunoglobulins.<sup>4,5,8</sup> Mild cases can receive prednisolone (1–2 mg/kg/day) with close monitoring of Hb levels.<sup>5</sup> Avoiding new RBC transfusions is an important issue to prevent worsening of symptoms, but in some cases the Hb decreases to levels so low that RBC transfusions become necessary. Our patient

reached a very low Hb level with a decreased level of consciousness. We compared risks and benefits and decided to give her one unit of RBCs, aware that subsequent transfusions could exacerbate hemolysis and become life threatening.<sup>4</sup> We initiated IGIV at the same time to avoid exacerbation of the hemolysis.<sup>5</sup> We also treated her with methylprednisolone, erythropoietin and folic acid. Steroids and IVIG may have a synergistic effect in suppressing macrophages,<sup>4,5</sup> and new evidence suggests that they can shorten the course of hemolysis.<sup>5</sup> The role of erythropoietin is not well established, but its serum levels are low for this level of anemia.<sup>5</sup> Win suggests that erythropoietin may correct anemia in DHTR/HS by directly stimulating erythroid precursors and preventing the destruction of young RBC.<sup>5</sup>

Other studies have reported a similar scenario, successfully treating patients with life-threatening HS with RBC transfusions, steroids and immunoglobulin.<sup>4,6,9</sup> One study<sup>5</sup> recommends the use of low-dose IVIG (0.4 g/kg/day) for five days and intravenous methylprednisolone (0.5 g/day for adults and 4.0 mg/kg/day for children) for two days. Some studies also suggest the use of Rituximab and cyclophosphamide in severe cases.<sup>10</sup>

HS is a severe disease and few recurrent cases have been described in the literature. In some cases it can be life threatening. This condition can be misdiagnosed with other SCD complications, so it is very important to think about DHTR/HS when faced with a hemolysis crisis in a SCD patient, especially after a RBC transfusion. The correct management of HS by avoiding further transfusions and giving steroids and immunoglobulin can change the course of the disease.

### Conflicts of interest

The authors declare no conflicts of interest.

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