CASE REPORT

Fatal Delayed Haemolytic Transfusion Reaction and Hyperhaemolysis Syndrome in a Pregnant Woman with Sick Cell Anaemia

Asral Wirda Ahmad Asnawi · Jameela Sathar ·
Rashidah Mohamed · Rohayu Deraman · Sri Kumaran ·
Shahada Sobah Abd Hamid · Muhd Zanapiah Zakaria

Received: 13 June 2014 / Accepted: 23 December 2014 / Published online: 1 January 2015
© Indian Society of Haematology & Transfusion Medicine 2014

Abstract Clinical manifestations of sickle cell disease (SCD) arise from the tendency of the sickle haemoglobin to polymerize and deform red blood cells into the characteristic sickle shape. Sickle cell crisis is a devastating complication that may occur in patients with SCD. If not managed properly permanent organ damage and even death may be the final outcome. A case of a 32-year-old Nigerian lady, Gravida 1 Para 0 in her first trimester, with SCD who developed signs and symptoms of delayed haemolytic transfusion reaction after receiving packed red cell transfusion is demonstrated. Multiple red cell alloantibodies were detected in the patient's plasma; anti-Fy a, anti-Jk b and anti-E. The patient miscarried and

succumbed to complications of hyperhaemolysis with delayed haemolytic transfusion reaction, acute chest syndrome and renal failure. There is an urgent need for mandatory red cell antibody screen and identification especially in high-risk cases. Prevention of alloimmunization by supplying phenotype-specific red cells is also required.

Keywords Sickle cell disease · Sickling · Hyperhaemolysis · Delayed haemolysis · Transfusion reaction

Introduction

Sickle cell disease (SCD) is a severe form of inherited haemolytic anaemia due to an A > T point mutation in codon 6 of the β globin gene. The resulting haemoglobin S (HbS) ($\alpha 2\beta 2\text{Glu} \rightarrow \text{Val}$) has reduced solubility and is prone to polymerize under low oxygen tension [1]. Sickle cell anaemia is not common in Malaysia. The few reported cases of SCD and sickle cell trait involved mainly Malaysian Indians, although there were some Malays affected [2]. However, it is much more common in Africans, whereby an estimated 1 in every 12 births are affected. SCD usually requires red blood cell transfusions to manage complications including anaemia, acute chest syndrome, stroke and splenic sequestration. Alloimmunization is a serious complication after exposure to donor or foreign red cells and incidence is reported as high as 5 to 36 % in SCD patients [3, 4]. Clinical manifestations of delayed haemolytic transfusion reactions (DHTR) can be different from those described in other patients. We report a case of fatal post-transfusion hyperhaemolysis in an adult patient with SCD in pregnancy.

A. W. A. Asnawi (✉)
Faculty of Medicine and Health Sciences, Universiti Sains Islam
Malaysia, Level 13 Menara B, Persiaran MPAJ, Jalan Pandan
Utama, 55100 Kuala Lumpur, Malaysia
e-mail: wirda@usim.edu.my

J. Sathar · S. Kumaran · S. S. A. Hamid · M. Z. Zakaria
Department of Haematology, Hospital Ampang, Jalan Mewah
Utara, Pandan Mewah, 68000 Ampang, Selangor, Malaysia
e-mail: jsathar@hotmail.com

S. Kumaran
e-mail: sri_boys36@hotmail.com

S. S. A. Hamid
e-mail: shaiszam@gmail.com

M. Z. Zakaria
e-mail: zpeah98@gmail.com

R. Mohamed · R. Deraman
Department of Pathology, Hospital Ampang, Jalan Mewah
Utara, Pandan Mewah, 68000 Ampang, Selangor, Malaysia
e-mail: drashidah@gmail.com

R. Deraman
e-mail: shuji_ayu@yahoo.com

Case Presentation

A 32-year-old Nigerian lady with homozygous SCD, a primigravida at 15 weeks was admitted with sudden shortness of breath, lower abdominal pain and vaginal bleeding. Last sickling crisis was 20 years ago where she received donor red cell transfusion. She had been in Malaysia for more than 10 years and had never required hospitalization or blood transfusion. Usual haemoglobin (Hb) level was around 7–10 g/dL and minor joint pains were treated conservatively with analgesics obtained from a local general practitioner.

Upon confirmation of her pregnancy she received antenatal care from a private hospital but was not under any follow-up with a haematologist. Routine antenatal check-up showed haemoglobin was 6 g/dL and two units of packed red cells were transfused. No record of antibody screen for unexpected antibodies was found. She presented 8 days later to her obstetrician with severe bilateral upper limb joint pain. (Pain score at that time was 9/10). Initial treatment was analgesics and antibiotics. However, symptoms quickly progressed to acute shortness of breath with signs of miscarriage. She was immediately transferred to the National Haematology referral center.

Investigations

Serial Hb level showed a rapid fall from 5 to 3 g/dL in 2 days. Total bilirubin was markedly elevated at 160.2 $\mu\text{mol/L}$ (0–17 $\mu\text{mol/L}$), with an indirect component of 62.2 $\mu\text{mol/L}$ and direct of 98 $\mu\text{mol/L}$. Unanalysis showed cola-coloured urine, suggestive of haemoglobinuria. Urea was 9.2 mmol/L (1.7–8.3 mmol/L) and creatinine was 212 $\mu\text{mol/L}$ (44–80 $\mu\text{mol/L}$) with severe metabolic acidosis. Chest radiograph showed pulmonary infiltrates in the lower zones.

The patient was grouped as O Rh(D) positive. Direct antiglobulin test (DAT) performed on red cells from EDTA-anticoagulated samples using polyspecific anti-human globulin (AHG) was negative. Three-cell screening panel (ID DiaCell I-II-III) for indirect antiglobulin test was positive. For the detection of red cell antibodies, gel card (LISS/Coombs) and tube method were positive. Multiple red cell panel was used; ID-DiaPanel (0.8 %) 11-cell panel and CSL Phenocell (3 %) 10-cell panel respectively. Heterologous allogeneic adsorption studies were used to separate the overlapping antibody reactions. This was performed using selected group O donor red cells of R1R1 (CDe), R2R2 (cDE) and rr (cde) phenotype. One of these cells was phenotyped for Jk a negative and Jk b negative. The red cells that carry the antigen corresponding to a specific antibody adsorbed the antibody, while leaving

other antibodies behind [5]. A potentiating agent, RAM-PEG, which consists of low ionic strength solution (LISS) and polyethylene glycol, was added to enhance the reaction. The patient's plasma was incubated with these different donor cells at 37 °C for 15 min. The mixture was then centrifuged to separate supernatant from the red cell sediment. An antibody identification panel performed on the remaining supernatant showed presence of multiple alloantibodies; anti-Fy a, anti-Jk b and anti-E. Red cell phenotype was performed using DiaClon antisera with direct agglutination and indirect antiglobulin test performed as instructed was cDe (most likely R₀R₀), kk, Fy(a – b+) and Jk(a + b–).

Outcome and Follow Up

Upon arrival she was distressed and anxious, jaundiced and severely tachypnoeic and tachycardic. Blood pressure was 135/89 mmHg and temperature was 38 °C. SPO₂ was only 91 % on high flow mask. A complete miscarriage ensued without excessive blood loss. Compatible red cells were unable to be obtained readily due to the presence of multiple alloantibodies detected. Two of her immediate family members were tested and found to be compatible. Red cell exchange was administered with 2 units of compatible red cells. Haemodialysis was considered, however because the renal deterioration was due to sickling crisis and concomitant haemolysis, all attempts were made to correct them with adequate blood and exchange transfusion. On the second day of admission to our hospital, she succumbed to complications of shock, acute renal failure with severe metabolic acidosis. Autopsy was not performed.

Discussion

We described a patient with SCD in whom fatal haemolysis developed following a top-up transfusion for low Hb. The initial clinical manifestation of haemolysis were similar to those seen in painful vaso-occlusive crisis of SCD, but was followed by the rapid onset of severe intravascular and extravascular haemolysis with continued drop of the Hb level well below the initial pretransfusion level. The rapid drop in Hb level may be contributed by hyperhaemolysis syndrome. It is regarded as a separate clinical manifestation that can only follow a DHTR [6]. The exact mechanism of hyperhaemolysis syndrome is not well understood. However, it may be explained by the 'bystander haemolysis', where the patient's red cells are destroyed following a defective regulation of the complement system. It is typically characterized by the simultaneous destruction of both donor red cells and the patient's own cells. The

haemolysis may occur even in the absence of detectable alloantibodies. A subsequent transfusion, even one which is phenotype-matched and compatible, may exacerbate the haemolysis [7]. Some authorities believe that hyperhaemolysis can be explained by the haemolysis of the donor red blood cells coupled with the suppression of erythropoiesis [8]. Treatment of hyperhaemolysis syndrome usually involves administration of intravenous immunoglobulin (IVIG) and steroids. Further transfusions are avoided as best as possible. Similar observations were documented by Talano J-AM and colleagues in their report of hyperhaemolysis in SCD children [3].

Unfortunately, there is no single test to diagnose either DHTR, in which the workup is laborious and time-consuming or hyperhaemolysis syndrome. The DAT test is often negative. We conclusively demonstrated that multiple alloantibodies caused the red cell destruction; anti-E, anti-Fy a and anti-Jk b, which are all regarded as clinically significant. Intravascular haemolysis was demonstrable by evidence of fall of Hb level and haemoglobinuria within 10 days of red cell transfusion. Supplying phenotype-matched red cells was a hindrance in this case partly because of the rarity of the Fy a negative phenotype in Malaysia (1 % but slightly more prevalent in Malaysian Indians) and also due to the combination of specific phenotype that was required for compatibility in this patient. The RH haplotype Dce (R_o) is most prevalent in Africans (44 %). Ambruso et al. have demonstrated that prevention of alloimmunization by supplying of phenotype-specific red cell is an approach, which is cost effective and leads to a tenfold decrease in alloantibody formation [9, 10].

An antibody screen for unexpected red cell antibodies as well as an extended red cell phenotype had not been done for the initial red cell transfusion our patient received. She unfortunately succumbed to complication of sickle cell crises including acute chest syndrome, which caused hypoxaemia with hyperviscosity due to sickling, severe acidosis and profound hypertension. This case demonstrates the urgent need for prompt identification of at-risk patients for red cell alloimmunization [11]. The transfusion needs for patients with SCD should be tailored to each individual with clear clinical indications. A centralized database of immunized patients requiring special transfusion needs is absent as well as the lack of immediate access to suitable blood for transfusion. All patients with SCD must be screened and donor phenotype-specific red cells supplied to

prevent alloimmunization. Clinicians must be aware of the life-threatening complications associated with red cell transfusions. A database for blood donors of African decent may prove useful for future cases and especially in emergency situations as the unique red cell phenotype may be obtained more readily.

Acknowledgment We would like to thank the Director General, Ministry of Health Malaysia for granting permission to publish this case.

Conflict of interest The authors have no financial disclosures or conflicts of interest relevant to this manuscript.

Financial support None of the authors have a financial interest in any of the products, devices or drugs mentioned in this manuscript.

References

1. Vulliamy T, Vaeda J (2006) Molecular and cytogenetic analysis. In: Lewis SM, Bain BJ, Bates I (eds) *Dacie and Lewis practical haematology*, 10th edn. Churchill Livingstone, Philadelphia, p 555–594
2. Hafiza A, Noor Hamidah H, Noor Farisa AR, Azlin I, Ainoon O (2010) A family study of HbS in a Malay family by molecular analysis. *Malays J Pathol* 32(2):137–141
3. Talano J-AM, Hillery CA, Gotschall JL et al (2003) Delayed haemolytic transfusion reaction/hyperhaemolysis syndrome in children with sickle cell disease. *Pediatrics* 111:E661–E665
4. Vinchinsky EP, Earles A, Johnson RA et al (1990) Alloimmunization in sickle cell anaemia and transfusion of racially unmatched blood. *New Engl J Med* 322(23):1617–1621
5. Judd WJ (1994) *Methods in immunohaematology*, 2nd edn. Montgomery Scientific Publications, Durham
6. Cullis JO, Win N, Dudley JM, Kaye T (1995) Post-transfusion hyperhaemolysis in a patient with sickle cell disease: use of steroids and intravenous immunoglobulins to prevent further red cell destruction. *Vox Sanguis* 69:355–357
7. Win N, Doughty H, Telfer P, Wild BJ, Pearson TC (2001) Hyperhemolytic transfusion reaction in sickle cell disease. *Transfusion* 41:323–328
8. Petz LD, Calhoun L, Shulman IA, Johnson C, Herron RM (1997) The sickle cell hemolytic transfusion reaction syndrome. *Transfusion* 37:382–392
9. Ambruso DR, Githens JH, Alcorn R, Dixon DJ, Brown LJ, Vaughn WM, Hays T (1987) Experience with donor matched for minor blood group antigens in patients with sickle cell anaemia who are receiving chronic transfusion therapy. *Transfusion* 27(1):94–98
10. Rosse W, Gallagher D, Kinney T et al (1990) Transfusion and alloimmunization in sickle cell disease. *Blood* 76:1431–1437
11. Higgins JM, Sloan SR (2008) Stochastic modeling of human RBC alloimmunization: evidence for a distinct population of immunologic responders. *Blood* 112:2546–2553