CASE REPORT

Fatal delayed haemolytic transfusion reaction in a patient without previous transfusions but with an obstetric history of 13 pregnancies

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SUMMARY

Delayed haemolytic transfusion reaction is a rare, life-threatening complication of blood transfusion that has been typically described among patients with sickle cell disease (SCD) due to alloimmunisation induced by their exposure to red blood cell antigens through recurrent transfusions. We report the case of a patient who suffered from fatal delayed haemolytic transfusion reaction (DHTR) occurring 1 week after blood transfusion. Indirect antiglobulin testing confirmed the presence of anti-Kell antibodies that were absent in the pretransfusion sample. The patient did not receive blood transfusions in the past, but her obstetric history was remarkable for 13 pregnancies. Although DHTR occurs more commonly among patients with SCD, this type of reaction can occur in any patient who is able to mount an immune response. We would like to draw the attention of physicians to this rare and potentially lethal complication of blood transfusion, especially in grand multiparous women.

BACKGROUND

The incidence of delayed haemolytic transfusion reaction (DHTR) has been estimated to occur in one per 2500 transfusions (~0.04%), but reaches 7%–10% in patients with sickle cell disease (SCD).^{1,2} DHTR is presumed to occur after previous exposure to red blood cell (RBC) antigens, most commonly through previous transfusions or pregnancy and less commonly through haematopoietic cell or solid organ transplantation.³ Eventually, with time, the titre of antibodies against specific RBC antigens decreases to levels that are undetectable by routine laboratory testing. DHTR occurs due to anamnestic immune response on the recipient's re-exposure to the same RBC antigen during transfusion. The antibodies commonly associated with DHTR are directed to the Rh, Kell, Duffy, Kidd, MNS and Diego blood group systems.⁴ Most of these reactions are mild and unrecognised because they occur a long time after the causative transfusion, beginning after 24 hours and usually within 1–2 weeks. Fatal DHTR is a rare event that has been typically reported among patients with SCD who received multiple transfusions throughout their lives.⁵ Fatal DHTR in patients without SCD is extremely rare where sensitisation usually occurred after previous transfusions.^{6–9} The occurrence of fatal DHTR in patients without history of previous

blood transfusion has been reported only once.¹⁰ We have recently cared for a patient who suffered from fatal DHTR without any history of previous transfusions. The most remarkable feature in our case, similarly to the single other case,¹⁰ was the high number of pregnancies reported. Erythrocyte sensitisation most likely resulted from the patient's 13 previous pregnancies.

CASE PRESENTATION

An 83-year-old female patient presented to the emergency department with progressive weakness and black stools (melaena). Her medical history was remarkable for diabetes mellitus, hypertension, chronic kidney disease, atrial fibrillation and permanent pacemaker for complete atrioventricular block. Her chronic medications included metformin, bisoprolol, simvastatin and warfarin. A presumptive diagnosis of upper gastrointestinal bleeding was made; her vital signs showed mild tachycardia of 108 beats per minute and a blood pressure of 115/70 mm Hg. Laboratory tests showed haemoglobin 5.8 g/dL, leucocytes 14 000 cells/mm³, reticulocyte count 5.3% (reticulocyte index=0.74), international normalised ratio (INR) 4.7, blood urea nitrogen (BUN) 101 mg/dL and a serum creatinine of 1.52 mg/dL. Studies done before transfusion showed O, Rh-positive blood, a negative direct antiglobulin test and a negative antibody screen. The patient was treated with two units of fresh frozen plasma and three units of crossmatch compatible, O, Rh positive, packed RBC transfusions. An upper gastrointestinal endoscopy failed to show an apparent source of her blood loss. She was discharged home after 4 days; her predischarge haemoglobin and INR levels were 9.5 g/dL and 1.45, respectively. One week after discharge, the patient was referred back to the emergency department due to progressive weakness. She denied passage of black stools. On physical examination, she was weak and icteric; her vital signs were normal except for tachycardia of 115 beats per minute, and a digital rectal examination showed faeces with normal colour and consistency. Chest X-ray showed clear lungs without any infiltrates. Her laboratory results showed the following: haemoglobin 4.8 g/dL, leucocytes $18.8 \times 10^9/L$, reticulocyte count 1.3% (reticulocyte index=0.18), INR 2.1, BUN 59.7 mg/dL, serum creatinine 1.92 mg/dL, total bilirubin 10.5 mg/dL.

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(mainly indirect) and low haptoglobin ($<10\text{ mg/dL}$). A peripheral blood smear showed schistocytes. The direct antiglobulin test was positive for IgG (2+) and C3 (1+). Antibody screen revealed the presence of anti-Kell antibody (negative at immediate spin and positive at 37°C and antihuman globulin phases).

INVESTIGATIONS

A transfusion reaction investigation revealed no clerical errors or incompatibility. Her initial pretransfusion blood sample was re-examined showing the same findings as mentioned above. Phenotyping of the transfused RBCs showed that one of the units was positive for the Kell antigen. Elution study did not reveal any novel antibody that was missing in the serum. The patient did not receive blood transfusion in the past, but her obstetric history was remarkable for 13 pregnancies, the last being in 1972. There were no available data concerning previous antibody screen from her last delivery.

OUTCOME AND FOLLOW-UP

A presumptive diagnosis of DHTR was made and methylprednisolone was started. As sepsis could not be ruled out conclusively, broad-spectrum antibiotics with piperacillin–tazobactam and vancomycin were also started. Her condition rapidly worsened with severe metabolic acidosis, severe intravascular haemolysis, rapidly progressive renal failure, respiratory failure with severe hypotension and eventually succumbed to death within 16 hours of admission to the hospital. Blood and urine cultures obtained prior to antibacterial therapy were negative.

DISCUSSION

To date, the very few reported cases of fatal DHTR in patients without SCD occurred in patients who received transfusions at some stage during their lives.^{7–9} Our case is unique in that the patient did not receive any transfusions in the past. Her only exposure to foreign RBC antigens was during her numerous pregnancies. In this case, DHTR was caused by an anamnestic response of anti-Kell antibodies, undetected in the pretransfusion blood specimen by routine screening procedures. The temporal relation between the transfusions and the detection of significant quantities of antibody suggests that transfusion of Kell antigen-positive cells evoked an anamnestic immune response. Most cases of DHTR are mild leading only to destruction of the transfused RBC carrying the implicated antigen. However, the extremely low haemoglobin levels, lower than the pretransfusion levels, indicated that extensive haemolysis including both donor and recipient cells had occurred. This subset of DHTR has been described by some as hyperhaemolytic transfusion reaction and ‘hyperhaemolysis’ syndrome.¹¹ Furthermore, while reticulocytosis is normally a hallmark of haemolytic reactions, reticulocytopenia, as seen in this case, has been a well-documented manifestation of hyperhaemolysis.^{12–13} The exact mechanisms responsible for this extensive haemolysis have not been entirely elucidated. One potential reason for the autologous RBC destruction in these patients is the formation of a non-specific antibody that binds complement and destroys both donor and recipient red cells, known as bystander haemolysis.¹¹ Another possible explanation is a hyperactive phagocytic activity of macrophages where a sudden high titre of antibodies leads to destruction of donor cells leading to cytokine release and reactive oxygen radicals that may damage autologous cells.¹³ Other possible mechanisms that have been suggested to play a role include human leucocyte antigen antibody formation, suppression of erythropoiesis and excessive eryptosis.¹¹ In addition, it is

likely that the patient’s pre-existing renal dysfunction may have played a role in this catastrophic outcome, as the patient’s renal function worsened very rapidly with severe metabolic acidosis.

Current management of DHTR in patients with SCD and without SCD is empirical and includes supportive care, optimisation of erythropoiesis (using erythropoiesis-stimulating agents and intravenous iron), immunosuppression (steroids, intravenous immunoglobulins and rituximab) and minimising further RBC transfusions.¹¹

Until now, only one similar case report has been published,¹⁰ in that case, similarly to current case, it was a 48-year-old female patient who had nine pregnancies. Because crossmatched RBC are not matched for the minor blood group antigens (Kell, Kidd, Duffy, etc), RBC transfusions can give rise to antibodies which are directed at these antigens. However, the immunological changes that occur during pregnancy markedly increase the risk of alloimmunisation against RBCs, platelets and leucocytes. It seems that fetal–maternal bleeding during pregnancy or delivery is a major antigenic stimulus for immunisation against RBCs.¹⁴ We believe that the repetitive antigenic stimuli that occurred during the patient’s 13 pregnancies played a crucial role in her outcome. Indeed, historic reports have suggested that DHTRs and delayed serological transfusion reactions occur more frequently in females presumably due to the risk of previous alloimmunisation through pregnancy. However, an old study that evaluated the frequency and clinical significance of alloimmunisation post-transfusion did not show any differences in the frequency of alloimmunisation by gender.¹⁵ Failure to observe a higher frequency of alloimmunisation in females could have occurred if the males received more transfusions resulting in more challenges.¹⁵ In addition, as some aetiologies of DHTR remain unexplained since there are cases in which there is an absence of detectable alloantibodies,¹⁶ it is possible that some genetic factors may have facilitated the process of alloimmunisation among some patients.¹⁷

Our intention is to increase the awareness of physicians to this rare and potentially lethal complication of transfusion and to emphasise the importance of obtaining a detailed history of previous transfusion and number of pregnancies due to the

Learning points

- ▶ Delayed haemolytic transfusion reaction (DHTR) is a rare complication of blood transfusion and is typically described among patients with sickle cell disease due to alloimmunisation induced by recurrent transfusions.
- ▶ Fatal DHTR without previous transfusion is extremely rare. The patient described suffered from fatal DHTR without previous transfusions but had a very remarkable obstetric history of 13 pregnancies.
- ▶ The exact mechanisms responsible for this catastrophic haemolysis (hyperhaemolysis) have not been entirely elucidated.
- ▶ Management of DHTR is empirical and includes supportive care, immunosuppression (steroids, intravenous immunoglobulins and rituximab) and minimising further red blood cell (RBC) transfusions.
- ▶ Special emphasis should be given to previous exposure to RBC antigens by obtaining a detailed history of previous transfusion and number of pregnancies. This information may help identify those recipients of blood transfusions who are at increased risk for DHTR.

potential role of alloimmunisation. In addition, establishing a nationwide network for blood banks will enable an effective recording and management of blood donor and blood recipient data, including previous antibody screen. This information may help identify those recipients of blood transfusions who are at increased risk for DHTR.

Contributors EC wrote the initial draft, gathered blood bank data and contributed to the discussion of the findings. NB gathered data, described findings reported in the study, wrote the discussion and the final version.

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