Hyperhaemolysis in sickle cell disease — an unusual and potentially life-threatening complication

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As sickle cell disease is increasing in Australia, paediatricians and other health care providers need to be aware of the broad range of complications that can occur in this condition. Although the complications of splenic sequestration and chest crises are well recognised, the infrequent but equally dramatic complication of hyperhaemolysis is less well appreciated. Here, we report a case of hyperhaemolysis in a Victorian paediatric patient. (MJA 2010; 192: 281-282)

Clinical record

A 12-year-old boy with sickle cell disease (homozygous haemoglobin S) presented in July 2006 with abdominal pain and fever — symptoms of a vaso-occlusive crisis. His usual baseline haemoglobin level ranged from 65 g/L to 75 g/L. He was thriving, but had a history of numerous vaso-occlusive crises. His past management included repeated transfusions with Rhesus and Kell phenotypically matched, leukocyte-depleted (LD) red cells. During this admission, he was managed with intravenous (IV) fluids, IV analgesia, antibiotics and a transfusion of 1 unit of phenoytpically matched, crossmatch compatible, LD red cells. His pain gradually resolved and he was discharged home.

Twenty-four hours after discharge (7 days after the transfusion), he re-presented with marked lethargy, jaundice, tachycardia, and no increase in splenic size. His haemoglobin level was 45 g/L and reticulocyte count was increased, at 444×10^9/L (reference range, $20–200 \times 10^9$/L). He received a transfusion of a further 2 units of red cells (about 500 mL). However, he remained pale after the transfusion and his haemoglobin level had further decreased to 39 g/L. He also developed profuse haemoglobinuria.

Based on his estimated blood volume of 2350 mL, the total transfusion of 750 mL during the two admissions would equate to an increase in haemoglobin of 55 g/L, so the observed drop in haemoglobin level was consistent with haemolysis of both recipient and donor red cells. No red cell alloantibodies or autoantibodies were detected. A presumptive diagnosis of sickle cell hyperhaemolysis syndrome was made. Further transfusions were avoided, and the patient was treated with IV immunoglobulin (IVIG) (1 g/kg) and high-dose IV steroids (methylprednisolone, 20 mg/kg/day). IV mannitol and hyperhydration were commenced to avoid free haemoglobinaemia-associated renal damage. The patient recovered after 1 week and was discharged, with a haemoglobin level of 71 g/L.

Six months later, the patient experienced a further episode of marked haemolysis that occurred after a red cell transfusion for vaso-occlusive crisis. He presented to hospital 5 days after the transfusion with a 48-hour history of increasing pain, increased jaundice and discoloured urine. His bilirubin level was 129 μmol/L (reference range, < 10 μmol/L) (unconjugated, 125 μmol/L; conjugated, 4 μmol/L), which was greater than a previous measurement of 77 μmol/L. Again, no red cell alloantibodies or autoantibodies were detected, and his reticulocyte count was elevated, at 303×10^9/L. His haemoglobin level continued to fall after admission, reaching 24 g/L after 24 hours. He was managed with further IVIG and high-dose steroids. In view of his ongoing marked, symptomatic anaemia after 3 days of this treatment, he was transfused with 250 mL of phenotypically matched red cells, without complication, and was discharged 2 days later with a haemoglobin level of 71 g/L. He did not re-present with further haemolysis. Follow-up is ongoing, with management as clinically indicated.

This was a prolonged and dramatic event for the child and his family. Placing him on a regular transfusion program was discussed, but the risks of repeated transfusions and the possibility, although small, of another hyperhaemolysis event were considered to outweigh the benefits of maintaining a higher haemoglobin level in a child who was thriving. If a regular transfusion program were to be considered again in the future, it would be prudent to assess the risks and benefits of exchange transfusion. Treatment with erythropoietin was also considered but deemed unnecessary at this time. Pretransfusion steroid treatment was considered an appropriate addition to the future management of this patient.

Discussion

Sickle cell disease is increasing in incidence in Australia due to immigration patterns involving increasing numbers of people from regions where the disease is common, such as Africa.[1] Although hyperhaemolysis in sickle cell disease has been recognised for more than 20 years, this case highlights it as an uncommon but potentially life-threatening complication, involving destruction of both donor and recipient red cells after red cell transfusion.[2-5] Haemolysis can be rapid and profound. Onset is usually within 7 days after transfusion and is characterised by severe intravascular haemolysis, haemoglobinuria, and anaemia to levels of haemoglobin lower than pretransfusion levels. Reticulocytopenia may be present. Hyperhaemolysis has also been reported in patients with β thalassaemia and myelofibrosis.[6,7] Recurrent hyperhaemolysis is unusual in children, with few available data pertaining to this phenomenon in the paediatric population. The information provided by patients in whom recurrence occurs is particularly valuable. Human leukocyte antigen antibodies were not tested in the patient described here, nor were his haemoglobin S levels followed during these episodes. Measurement of these parameters in other affected patients would add to the body of data and knowledge on hyperhaemolysis.

The exact mechanisms responsible for hyperhaemolysis are not fully understood. High-performance liquid chromatography analysis of urine in a patient with haemoglobinuria after red cell tranfusion demonstrates both donor and recipient haemoglobin.[8] In typical haemolytic transfusion reactions, alloimmune mechanisms are responsible, with the development of red cell antibodies in the patient against antigens present on donor red cells. The antigens most commonly implicated are those of the Rhesus, Kell, Kidd, Duffy and MNSs blood group systems. Haemolytic reactions

due to alloimmunisation are associated with haemolysis of donor red cells only, and laboratory testing usually leads to identification of the causative red cell antibodies. Suggested mechanisms for hyperhaemolysis include cytokine-mediated haemolysis or uncontrolled macrophage activation.[9-11]

Recommended treatment of hyperhaemolysis includes avoidance of transfusion where possible and immune modulation with steroids and IVIG.[3,5,8] The mechanism of action of steroids and immunoglobulin has not been fully elucidated, but these treatments have been demonstrated to be effective in a number of patients. Repeated exposure to red cells after recovery may lead to recurrence of hyperhaemolysis, as seen in this case. Erythropoietin may be used in an attempt to reduce the need for further exposure to transfused red cells.[3] Prompt referral for expert management is essential.

Hyperhaemolysis is an uncommon but potentially fatal complication of sickle cell disease. Recognition of this unusual complication is important for medical staff who manage patients with sickle cell disease in Australia.

Competing interests

None identified.

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