Delayed haemolytic transfusion reactions in patients with sickle cell disease

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Summary: We describe two cases which illustrate the difficult diagnostic and therapeutic problems posed by delayed haemolytic transfusion reactions in patients with sickle-cell disease. The cases emphasize the need for meticulous phenotypic and serological assessment of sickle-cell patients prior to transfusion therapy.

Introduction

Blood tranfusion remains a major prophylactic and therapeutic measure for patients with sickle-cell disease (SCD).¹ Red cell allo-immunization is a frequent complication of this therapy,^{2,3} occurring in up to 36% of multitransfused cases.⁴ There are, however, few published reports of delayed haemolytic transfusion reactions (DHTR) in SCD patients,⁵⁻⁷ possibly because they are often mistaken for vaso-occlusive sickling crises. We describe two cases which illustrate some of the problems posed by DHTRs in patients with SCD.

Case reports

Case 1

An 18 year old woman with homozygous sickle-cell anaemia presented with a febrile illness after arriving in England from Nigeria. She had previously been transfused at 9 years of age.

No cause was found for her fever, which resolved with antibiotics. However, over 6 days her haemoglobin (Hb) fell to 5.5 g/dl (Figure 1) and 2 units of B, Rh (D) positive red cells were infused. Prior to transfusion her red cells were B, Rh (D) positive, a direct antiglobulin test (DAT) was negative, and no atypical red cell antibodies were detected in serum with a 2-donor cell panel by two-stage papain (TSP) or indirect antiglobulin techniques (IAT).

She was referred to Central Middlesex Hospital 10 days after discharge. Her haemoglobin was 6.9 g/dl and repeat DAT was negative. However, anti-E and -C^w allo-antibodies were detected in serum (using TSP).

Figure 1 Delayed haemolytic transfusion reaction in Patient 1. DAT = direct antiglobulin test, MF = mixed-field reaction. The columns at the top of the figure indicate the red-cell antibodies detected at various stages of illness. The arrows indicate the units transfused.

Four days later (14 days post-transfusion) she was admitted as an emergency with a 1-day history of right hypochondrial pain. She was pyrexial (39.2°C), jaundiced, and her liver extended 14 cm below the right costal margin. Her haemoglobin was 3.0 g/dl (87% HbS, 10% HbA, 3% HbA₂), reticulocytes were 18% and DAT was negative. Serum bilirubin was 200 µmol/l, hydroxybutyric dehydrogenase 1205 IU/l and aspartate transaminase (AST) 67 IU/l. Hepatic sequestration was diagnosed⁸ and 3 units of C-, C^w-, E- and K-negative

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blood were crossmatched and infused uneventfully. However, the on-call laboratory staff were not informed of her recent transfusion, and used 4-day-old serum for the crossmatch. Twelve hours after transfusion she developed chest pain and a fever of 39.9°C. A blood film showed spherocytes + + +, DAT was positive (IgG; mixed-field) and, besides anti-E and -C^W antibodies, anti-C, -K and -Jk^b antibodies were demonstrable in serum.

Over 7 days her haemoglobin fell from 7.7 to 4.6 g/dl, serial HbS and HbA concentrations indicating haemolysis of transfused cells (Figure 1). She was discharged, afebrile, 14 days after admission.

Ten days later her liver was barely palpable and her haemoglobin was 5.4 g/dl. The DAT, however, was still positive (+; IgG only), but the pattern of agglutination was no longer of mixed-field type, suggesting presence of an auto-antibody. Indeed, iso-electric focusing of peripheral blood haemolysate showed absence of HbA.

Two weeks later her haemoglobin had risen to 6.1 g/dl, reticulocytes were 53%, DAT was strongly positive (+ + +; IgG only) and serum bilirubin was 106 µmol/l. By selective adsorptions with phenotyped cells, serum and a red cell eluate were shown to contain a broad-reactive IgG (IgG_i) auto-antibody, reactive against all cells of a 10-donor panel (using TSP).

Soon afterwards, the patient returned to Africa.

Case 2

A 25 year old Nigerian woman was admitted with an incomplete abortion. She had previously had 3 blood transfusions in Africa. Her haemoglobin was 5.4 g/dl, she was Group O, Rh (D) positive and DAT was negative. Two units of Group O, Rh (D) positive red cells were crossmatched urgently (by IAT) and infused uneventfully; her uterus was then surgically evacuated. A subsequent antibody screen with pre-transfusion serum was positive against both red cells of a 2-donor panel (using TSP and IAT techniques); anti-s antibodies were later identified with a 10-donor panel by IAT (Figure 2).

Seven days after transfusion she was readmitted with vomiting and abdominal pain. She was febrile (38.2°C) and jaundiced. Her haemoglobin was 4.4 g/dl, reticulocytes 10%, bilirubin 135 µmol/l, AST 236 IU/l and alanine aminotransferase 127 IU/l. Initially, she was thought to have a vaso-occlusive sickling crisis. However, a blood film showed spherocytosis, DAT was positive (IgG and C3d; mixed-field) and, besides anti-s antibodies, her serum contained anti-C and -E allo-antibodies (TSP and IAT) and a broad-reactive red-cell auto-antibody (TSP). The next day her haemoglobin was 2.6 g/dl. Four units of Group O, rr (cde/cde), K- and s-negative blood were cross-matched (by IAT and TSP) and infused, and she

Figure 2 Delayed haemolytic transfusion reaction in Patient 2. DAT = direct antiglobulin test, MF = mixed-field reaction. The columns at the top of the figure indicate the red-cell antibodies detected at various stages of illness. The arrows indicate the units transfused.

was discharged 2 days later, afebrile, with a haemoglobin of 8.6 g/dl.

Ten days after this transfusion she was readmitted with headache and dizziness. She was jaundiced, pyrexial (38.2°C), and her haemoglobin was 4.0 g/dl. DAT was positive (mixed field; IgG and C3d) but no new antibodies were detected. One unit of Group O, rr, K- and s-negative blood was given. After this she developed severe arthralgia and flitting pains in her limbs and back, distinct from the pains usually associated with her vaso-occlusive crises. Her condition then improved, the haemoglobin stabilizing at 4.6 g/dl. Follow-up serum contained anti-Fy^a allo-antibodies in addition to those previously identified.

Discussion

These cases illustrate the following features of DHTRs in SCD patients: (1) the difficulties encountered in their diagnosis and assessment; (2) the propensity for multiple antibody production; and (3) the problems associated with their prevention and management.

Clinically, DHTRs in SCD patients may be difficult to separate from sickle crises.⁷ The presentation of Patient 1 with jaundice, hepatic enlargement and a rapidly falling haemoglobin suggested an hepatic sequestration crisis;⁸ in retrospect, these events were probably due to trapping of red cells in

hepatic reticulo-endothelial tissue rather than blockage of hepatic venous sinusoids. (Functional asplenia⁹ may have resulted in predominantly hepatic red-cell destruction.) The fever and flitting joint pains of Patient 2 simulated acute serum sickness; these symptoms may have been due to defective complement activation, a feature of SCD⁹ which may alter the presentation of haemolysis induced by complement-fixing antibodies.⁷ In both patients, a positive DAT (with mixed-field pattern of agglutination) and spherocytosis were the most useful diagnostic indicators of DHTR. Laboratory tests in steady-state sickle-cell patients such as haematocrit, reticulocyte count and serum bilirubin are generally outside normal ranges^{7,9} and of limited diagnostic value. However, in conjunction with serial measurement of HbS and HbA levels, they may help in monitoring the haemolysis.

Red cell allo-immunization occurs in up to 36% of multi-transfused SCD patients.²⁻⁴ Factors that may contribute to this incidence of antibody formation include the large volumes of blood received during exchange procedures and the red-cell antigen mismatch associated with inter-racial

transfusion. Even allowing for these factors, however, SCD patients appear to be immunological 'hyper-responders';⁷ the reasons for this are not clear. Certainly, both of our patients developed multiple red cell allo-antibodies and an auto-antibody over a relatively short time. We now therefore adopt a more conservative policy towards transfusion therapy. Our current practice² is to perform extended red cell phenotyping on all SCD patients prior to initiating any transfusion programme. This includes typing for ABO, Rhesus, Kell, MNSs, Jk, Lewis, Js^a and Js^b antigens, and U typing for all S- and s-negative individuals. C- and E-negative (rr or R₀) blood is given to all R₀ (cDe/cDe) subjects since, as with both patients described, Rh (D) positive blood untyped for C and E antigens may stimulate production of anti-C and -E allo-antibodies. In view of the strong immunogenicity of the Kell antigen we routinely give K-negative blood to K-negative SCD patients. It may be significant that, since adopting this policy, we have not seen a DHTR associated with multiple red-cell antibody development.

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