Hyperhaemolysis syndrome in haemoglobin E / beta thalassaemia responding to cyclophosphamide therapy

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Introduction

Hyperhaemolysis syndrome (HS) is a rare condition where blood transfusions are followed by destruction of both donor and recipient red cells, in the absence of significant detectable red cell antibodies. This phenomenon is reported only in a few children and is extremely rare in thalassaemia syndromes [1, 2, 3, 4]. We report a case of HS in a child with low G6PD enzyme levels and Hb E beta thalassaemia, in whom intravenous immunoglobulin (IVIG), oral methylprednisolone and splenectomy failed but cyclophosphamide therapy resulted in a successful outcome.

Case report

A 5-year old boy born to non-consanguineous parents, from a remote village in the North Central Province of Sri Lanka was found to have severe anaemia and hepatosplenomegaly at 3 ½ years of age. Haemoglobin electrophoresis showed Hb F (11%) and Hb E in the child, Hb E in the mother and elevated Hb A (6.8%) in the father.

He received four transfusions of ABO and Rh compatible non-washed red cells in the local hospital and post-transfusion Hb levels were maintained at 10-11 g/dl for ten months. Following the fourth transfusion he became jaundiced (serum bilirubin 94.5 µmol/l, indirect 75.6 µmol/l), passed dark urine (urobilinogen ++ haemosiderin +), and haemoglobin dropped to 3 g/dl. No trigger for acute haemolysis from G6PD deficiency was identifiable. He was admitted to Lady Ridgeway Childrens' Hospital, Colombo where repeated blood transfusions with extended phenotypically matched leucocyte depleted red blood cells resulted in further haemolysis and reduction of haemoglobin to below pre-transfusion levels. Extensive

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haematological and serological investigations were done to detect a cause for the accelerated haemolysis. His blood group was confirmed as O R1R1 with a phenotype kk, JK a+, JK b-, Fy a+, Fy b+, Ss. Antibody screening with Selectogen test was negative for S_1 and S_2 repeatedly. Direct antiglobulin test (DAT) was negative for IgG but positive for C_3d. Consecutive assay during haemolysis found low levels of G6PD enzyme. Ham's test was negative. A diagnosis of hyperhaemolysis syndrome was made in this child with Hb E beta thalassaemia and G6PD enzyme deficiency.

Immune modulation with intravenous immunoglobulin (IVIG) at 1 mg/kg and oral methylprednisolone 2 mg/kg/d over 2 weeks [5] failed to achieve a sustained response. Over the next year blood transfusions were required at 2 weekly intervals but his anaemia was uncorrected. His growth remained static. Annual red cell consumption was 650 ml/kg and congestive heart failure, iron overload (serum ferritin >2000 ng/ml) and hypersplenism were observed.

A second course of immune modulation and methylprednisolone was tried without success. Splenectomy (spleen 18 x 12 x 5 cm, weight 650 g) also did not correct the HS. A trial of oral cyclophosphamide at 50 mg/kg/d was prescribed for 4 days. A remarkable response took place and post-transfusion haemoglobin of 10 g/dl was sustained for 4 weeks. Hair loss was the only side-effect of cyclophosphamide therapy. He has remained free of HS with transfusion requirement at 10 to 14 week intervals.

Discussion

This child had haemolytic anaemia of multiple aetiologies ie. HbE/beta thalassaemia and concomitant G6PD deficiency. Management of anaemia became very difficult when he developed haemolysis following compatible transfusions. Extensive haematological investigations did not reveal any allo- or auto-antibodies. In the absence of antibodies and C_3d positivity on the DAT the diagnosis of HS was made.

It is important to recognise this condition in which transfusions worsen the haemolysis. The mechanism of red cell destruction in this syndrome is not certain. A complement mediated haemolysis due to defective regulation of complement pathway is supported by C_3d positivity [3]. The explanations for absence of antibodies are cell mediated antibody independent lysis, lysis within the spleen due to tissue bound antibody and antibody dependent cell associated cytotoxicity.

Immune modulation is recommended but the child did not respond to IVIG and methyl prednisolone therapy [5]. A short course of high dose cyclophosphamide corrected HS. This therapeutic response with cyclophosphamide which interferes with cell replication may support the possibility of hyperactive macrophages causing the haemolysis. The child did not develop transfusion reactions in the ensuing two years. Further studies on the place of cyclophosphamide in HS are warranted.

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