Case Report

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Hyperhemolysis with hemoglobin H disease

Abstract

Hyperhemolysis syndrome is one of serious and potentially life-threatening complications of red blood cell transfusion, and is well described in sickle cell disease as well as in thalassaemias and other anaemias. It also is a great diagnostic and management challenge to laboratory scientists and attending physician taking care of patients with such kinds of diseases. A Myanmar patient with hemoglobin H disease presenting with acute hyperhemolysis syndrome was diagnosed timely and successfully treated with intravenous immunoglobulin (IV Ig) and methylprednisolone. A high index of suspicion allowing early diagnosis and prompt management can save lives of patients with hyperhemolysis syndrome.

Keywords: thalassaemia, hemoglobin H, hyperhemolysis, dyspnea, electrophoresis

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Abbreviations: IV Ig, intravenous immunoglobulin; YGH, yangon general hospital; JVP, jugular venous pulse; Hb, hemoglobin; MCV, mean red cell volume; MCHC, mean cell hemoglobin concentration; G6PD, glucose 6 phosphate dehydrogenase; DAT, direct antiglobulin test; HS, hyperhemolysis syndrome; HPLC, high performance liquid chromatogram

Introduction

Thalassaemia is common among Asian countries including Myanmar. The clinical presentations of thalassaemia patients vary. One of the rare but serious and life-threatening presentations is acute hyperhemolysis syndrome.

Case presentation

A thirty two year-old lady, a known patient with hemoglobin H disease was admitted to the Department of Clinical Haematology, Yangon General Hospital (YGH) for severe dyspnoea especially on exertion as well as at rest and on lying flat in March, 2017. She is a single daughter of unrelated parents of Chinese-Bamar origin. She was first diagnosed to have thalassaemia at the age of eight years during clinical and laboratory work-up for her childhood symptoms of poor exercise tolerance, frequent febrile illness, pallor and poor growth. She received two units of whole blood transfusion at the age of eight years but she was transfusion-free till the age of sixteen years. As her hemoglobin was persistently low during her high school years,

she was transfused a total of 20units of blood in two years between age 16 and 18 at a district hospital. Menarche started late at the age of eighteen years.

Due to frequent transfusion requirements, she was first referred to the Department of Clinical Haematology, (Yangon General Hospital) at the age of eighteen. At that time she was diagnosed to have hemoglobin H disease based on hemoglobin electrophoresis (which showed hemoglobin A and H) and presence of H inclusion bodies on supravital stain of peripheral blood. From age eighteen years to thirty two years, she received less frequent transfusions. A total of 30units were transfused in this 14year period. On reviewing the records, her pre-transfusion hemoglobin level was around 5 and 6g/dl. Anti-E anti rhesus antibody was detected in her serum in 2011 as a result of red cell alloimmunization. During the week before hospitalization she started to have progressive dyspnoea on exertion and she had dyspnoea at rest at the time of admission to the hospital. She looked very pale, slightly icteric, slightly orthopnoeic with raised jugular venous pulse (JVP). Extremities were cold. She had tachycardia (heart rate 110 beats/min). At the time of admission hemoglobin (Hb) was 2.2g/dl with red cell count $0.99 \times 10^6/\mu l$. Haematocrit (Hct) was 8.4% with mean red cell volume (MCV) 84.8fL, mean cell hemoglobin (MCH) 22.2pg and mean cell hemoglobin concentration (MCHC) 26.2g/dl. Reticulocyte count was $0.0804 \times 10^6/\mu l (8.12\%)$. White cell count was $6.84 \times 10^3/\mu l$ with neutrophil count $3.72 \times 10^3/\mu l$ and lymphocyte count $2.26 \times 10^3/\mu l$. Platelet count was normal at $262 \times 10^3/\mu l$ (Table 1).

Table 1 Haematological and biochemical parameters in a patient with hemoglobin H disease having acute hyperhemolysis syndrome

	2/3/17	5/3/17*	6/3/17**	8/3/17 Day 2	9/3/17 Day 3	11/3/17 Day 5	13/3/17 Day 7	19/3/17 Day 13	1/4/17 Day 26
Hb (g/dl)	2.2	2.4	2.8	3.2	3.6	5.2	6	5.9	6.6
Hct (%)	8.4	9.6	11	11	12.7	21	23.6	23.4	25.6
RBC (x10⁶/µl)	0.99	1.08	1.27	1.36	1.55	2.32	2.65	2.69	3.05
Retic (%)	8.12	21	24.54	13.51	14.01		16.83	5.18	9.18
ARC (x10⁶/µl)	0.0804	0.2268	0.3117	0.1837	0.2172		0.446	0.1393	0.28
MCV (fL)	84.8	88.9	86.6	80.9	81.9	90.5	89.1	87	83.9
WBC (x10³/µl)	6.84	10.74	7.55	3.21	4.49	9	7.71	5.4	5.24
Neu (x10³/µl)	3.72	5.91	4.75	2.46	3.44	5.2	4.57	3.52	3.36

Table Continued....

	2/3/17	5/3/17*	6/3/17**	8/3/17	9/3/17	11/3/17	13/3/17	19/3/17	1/4/17
				Day 2	**Day 3**	**Day 5**	**Day 7**	**Day 13**	**Day 26**
Lym (x10³/µl)	2.26	2.65	1.54	0.48	0.78	3.1	1.82	1.29	1.61
Plt (x10³/µl)	262	125	120	59	83	147	166	141	246
LDH (U/L)			1230	1048.2	713.9	649	582.2	440	
SB (µmol/l)			55	48		28.9	38	34	47.6

Hb, hemoglobin; Hct, haematocrit; RBC, red blood cell count; Rectic, reticulocyte count; ARC, absolute retic count; MCV, meal cell volume; WBC, white blood cell count; Neu, neutrophil; Lym, lymphocyte; Plt, platelet; LDH, lactate dehydrogenase; SB, serum bilirubin

*After getting four packed red cell units

**After getting seven packed red cell units

Day=Day after receiving intravenous normal human immunoglobulin and methyl prednisolone

Her blood group types as O; rhesus antigen CcDee (R1r) and Mi antigen were positive. Glucose 6 phosphate dehydrogenase (G6PD) enzyme level was normal. Screening tests for paroxysmal nocturnal hemoglobinuria (sugar water test and heat resistance test) were all negative. Pre-transfusion screening showed that the direct antiglobulin test (DAT) was negative, and apart from anti-E alloantibody, there was no other additional red cell alloantibodies detected. Four units of rhesus antigen E negative cross-matched compatible packed red cells were given. She noticed that her urine colour turned black after getting transfusion. Recheck hemoglobin after getting transfusion of four units of packed red cells was 2.4g/dl with red cell count 1.08x10⁶/µl (Table 1). Another three units of rhesus antigen E negative cross-matched compatible packed red cells were given but there was no increment in hemoglobin level. Hemoglobin was still low at 2.8g/dl with red cell count 1.27x10⁶/l. Lactate dehydrogenase LDH was 1230U/L and serum bilirubin was 55µmol/L. Urine hemosiderin was detected (Table 1). So the diagnosis of acute hyperhemolysis syndrome was made.

Treatment and response

Treatment with intravenous human normal immunoglobulin (IV Ig) 40G (1G/Kg) and intravenous methylprednisolone 500mg were given for two days. One dose of Subcutaneous Erythropoietin 4000 iu was also given. Patient's dyspnoea was significantly improved since day 1 of IV Ig and methylprednisolone. Urine darkness was progressively improved day by day (Figure 1 & 2). Hemoglobin progressively increased to 3.2g/dl, 3.6g/dl, 5.2g/dl and 6g/dl respectively on day 2, day 3, day 5 and day 7 after receiving IV Ig and steroid. Progressive rise in reticulocytes was also observed: 13.51%, 14.1% and 16.83% on day 2, day 3 and day 7 respectively. LDH progressively fell to 1048.2unit/l, 713.9unit/l, 649unit/l, 582.2unit/l respectively on day 2, day 3, day 5 and day 7 after receiving IV Ig and steroid. Serum bilirubin level fell to 38µmol/l from 55µmol/l after receiving IV Ig and steroid (Table 1).

Outcome and follow-up

The patient was discharged from hospital on day 9 and followed at out-patient department on day 13. She was totally asymptomatic. Only a slight jaundice with 2cm splenomegaly was noticed on physical examination. Hb was maintained at 5.9g/dl with red cell count 2.69x10⁶/µl. Hct was 23.4% with (MCV) 87fL, mean cell hemoglobin 21.9pg and (MCHC) 25.2g/dl. White cell count was 5.4 x 10³/µl with neutrophil count 3.52x10³/µl and lymphocyte count 1.29x10³/µl. Platelet count was 141x10³/µl. Absolute reticulocyte count was 0.1393x10⁶/µl(5.18%). Serum LDH was 440unit/l and serum bilirubin was 34µmol/L (Table 1). Next follow up on day 26 showed asymptomatic patient with Hb was maintained at 6.5g/dl with red cell count 3.05x10⁶/µl. Platelet count was 246x10³/µl. Absolute reticulocyte count was 0.2800x10⁶/µl (9.18%) (Table 1).

Figure 1 High colored urine (extreme right).

Figure 2 After treatment with IV Ig and steroid became progressively normal colour (to progressive left in Figure 1 & 2).

Discussion

Hyperhemolysis syndrome (HS) is a serious and potentially life-threatening complication of red blood cell transfusion.[1] A case of fatal HS has been reported in a child with sickle cell disease in 1993 by Friedman et al.[2] Since then, this syndrome has also been reported in several thalassaemia patients as well as in subjects with other types of anaemia like myelofibrosis, chronic lymphocytic leukemia and anaemia of chronic disorder.[3–8] As far as we are aware there is only one case report of Hb H disease presented with Hyperhemolysis in the literature.[8] The term HS is applied when:

i. The post-transfusion hemoglobin (Hb) levels are lower than pre-transfusion values

ii. There is severe intravascular hemolysis and

iii. There is a fall in the absolute reticulocyte count from baseline levels.[9]

Presenting features of HS include fever, sickle pain, development of severe anaemia after transfusion, post-transfusion Hb level lower than the pre-transfusion value, evidence of hemolysis (hemoglobinuria, hyperbilirubinemia, raised LDH), a fall in absolute reticulocyte count (decrease from patient's usual base level), recovery manifested by a rise in Hb and reticulocyte count, and additional transfusion exacerbating ongoing hemolysis (may lead to protracted course or even death).[1] HS can be further classified into acute and delayed forms.[10] The acute form usually occurs less than seven days after receiving the blood transfusion. The DAT is usually negative and no red cell alloantibodies are identified in the patient's serum. In cases with preformed alloantibodies, transfusion of antigen-negative crossmatch-compatible blood may not prevent the occurrence of HS. In the acute form of HS, serological investigations of post-transfusion and follow-up samples may not reveal the formation of new/additional red cell alloantibodies. The delayed form usually occurs more than seven days post-transfusion. The DAT is positive and new alloantibodies are often identified in the patient's serum sample post-transfusion.[1]

The pathogenesis of HS remains unclear but appears to be complex. The possible mechanisms include bystander hemolysis, suppression of erythropoiesis and red blood cells being destroyed by the activated macrophages.[1,10] Recognition of this complication of transfusion is crucial because additional transfusion in such patients may exacerbate the hemolysis and resultant anaemia.[2] The acute form of HS poses a diagnostic challenge because identification of a new red cell antibody is often absent. A high index of suspicion is important. The DAT, antibody screen, close attention to reticulocyte count, serum bilirubin, LDH, serial measurement of Hb electrophoresis and high performance liquid chromatogram (HPLC) analysis of the urine may allow early recognition.[9,10] Awareness and recognition of HS is important. Further transfusion may exacerbate the ongoing hemolysis, worsen the degree of anaemia and lead to a protracted course or

even death.[1,2,9] It is recommended that transfusions are avoided and therapy is initiated with IV Ig and methylprednisolone.[3] Intravenous immunoglobulin 0.4g/kg/day for 5days or 1g/kg/day for 2days and intravenous methylprednisolone 0.5g/day (adult) and 4mg/kg (pediatric patients) for 2days can correct the severe anaemia in HS.[10,11]

Conclusion

HS is a serious and potentially life-threatening complication of red cell transfusion. Although well described in patient with SCD, there is very few case reports of HS in association with HbH disorder. In our case, a high index of suspicion allows us an early diagnosis and with prompt management, the patient responded well to IV Ig and steroids therapy".

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None.

Conflict of Interest

The author declares no conflict of interest.

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