CASE REPORT

When a transfusion in an emergency service is not really urgent: hyperhaemolysis syndrome in a child with sickle cell disease

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SUMMARY

A 13-month-old boy with sickle cell disease (SCD) from Equatorial Guinea, who had recently arrived in Spain, presented with fever. He had suffered from malaria and had received a blood transfusion. Following physical examination and complementary tests, intravenous antibiotics and a red blood cell (RBC) transfusion were administered. Soon after a second transfusion 5 days later, the haemoglobin level fell below pretransfusion levels, together with reticulocytopenia, and haematuria—the so-called hyperhaemolysis syndrome—requiring intensive care and treatment with intravenous immunoglobulins and corticosteroids, with resolution of the complication. We want to emphasise the importance of suspecting this rare, though severe complication that can appear after any RBC transfusion especially in patients with SCD, as the clinical syndrome can simulate other more common complications of these patients and a further transfusion is contraindicated. There is no standardised treatment, but intravenous immunoglobulin and corticosteroids are usually effective.

BACKGROUND

The hyperhaemolysis syndrome (HS) is a rare post-transfusional reaction of unknown aetiology characterised by a brisk intravascular haemolytic crisis with the total haemoglobin (Hb) level dropping below pretransfusion levels, reticulocytopenia, haemoglobinuria and abnormally high lactate dehydrogenase (LDH).^{1 2} It can appear acutely (before 7 days) or delayed (after 7 days) after a red blood cell (RBC) transfusion. It can be mistaken for a delayed haemolytic transfusion reaction (DHTR) although direct antiglobulin test (DAT) is negative, or when positive it does not explain the haemolytic crisis.¹ Most patients suffered from haemoglobinopathies, but this syndrome has also been described in other pathologies.^{1 3} It can be accompanied by fever, bone pain, chest pain and so on, mimicking other complications. This interferes in the diagnostic process and misdiagnosis can lead to the patient being transfused, precipitating or increasing the HS and even requiring intensive care. Although not standardised, treatment with intravenous

immunoglobulins (IVIG) and corticosteroids may be effective, as it was in our case.

CASE PRESENTATION

A 13-month-old black boy presented with fever (maximum 38°C) and vomiting in the last 12 hours. He had no other symptoms. He lived in Malabo (Equatorial Guinea) and had arrived in Spain 24 hours before.

His medical history revealed a normal pregnancy, delivery and neonatal period in Equatorial Guinea. He had been breast fed until 2 months of age, had no allergies or intolerances and was well vaccinated according to Guinea's calendar (no pneumococcal vaccine). The patient had three previous admissions: at 6 months due to malaria, at 8 months due to pneumonia and at 12 months due to pneumonia and a Gram-positive bacteraemia requiring two RBC transfusions (minimum Hb level 5.6 g/dL), when the diagnosis of sickle cell disease (SCD) was made. Family history was unremarkable.

Physical examination revealed mucocutaneous pallor, ejection systolic murmur II/VI, splenomegaly, 4 cm below the left costal margin, an oxygen saturation (by pulse oximetry) of 93% and a temperature of 38°C. The rest of the examination was normal.

The initial blood count showed the following: Hb 7 g/dL, white cell count $20.7 \times 10^9/L$ (segmented 37, bands 0, lymphocytes 53, monocytes 8, eosinophils 2, basophils 0%; erythroblasts 62/100 leucocytes), platelets $158.0 \times 10^9/L$ and reticulocytes 15%. C reactive protein (CRP) 27 mg/L; urea, creatinine and electrolytes; coagulation tests, blood gas were normal. Chest X-ray showed an atelectasis in the lingulae.

The mother referred that the child baseline Hb level was around 9–10 g/dL, although no medical report stating this was provided. The only medical report provided from the last admission a month before showed a pretransfusion Hb level of 5.6 g/dL, but no blood test post-transfusion. Due to the findings on physical examination (mucocutaneous pallor, systolic murmur, apparently new splenomegaly) and laboratory tests (baseline Hb level drop >2 g/dL and reticulocytosis), a splenic sequestration associated with infection was suspected, and so a transfusion of packed RBCs was administered. In addition, intravenous fluids and antibiotic therapy with cefotaxime, and oxygen therapy were

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Table 1 Laboratory tests through the admission

Days of admission	1	2	5	6	7	8	14	18
Leucocytes ($\times 10^9/L$)	20.7	7.68	12.96	11.80			16.32	
Haemoglobin (g/dL)	7 $\rightarrow$ 10.1	9.8	6 $\rightarrow$ 8.4	7.1	6	5	6.9	7.2
Reticulocytes (%)	15.4			4.4			25.13	
Reticulocytes ($\times 10^9/L$)	414.6			110.8			630.8	
Platelets ($\times 10^3/\mu L$)	158	61	56	83		106	167	139
CRP (mg/L), normal <3 mg/L	22	98	65	77			5	
LDH (IU/L), normal 135–235 IU/L			1856					354
Ferritin (ng/mL)			2574					
Bilirubin (mg/dL)	1.29		1.6					1.2
Urine	Normal	Urinalysis: 50 RBC/ μL Microscopy: 2–4 WCC/hpf; frequent urinary casts	Normal	Urinalysis: 100 WCC/ μL , 250 RBC/ μL , proteins 500 mg/dL, ketonuria 5 mg/dL, bilirubin 1 mg/dL Microscopy: 10–15 WCC/hpf, 4–6 RBC/hpf, bacteriuria, frequent urinary casts				Normal
Blood cultures	(–)							
DAT			(–)	(–)				
G6PDH				Normal				
<i>Plasmodium</i> blood smear	(–)		(–)					
<i>Plasmodium</i> PCR				(–)				

CRP, C reactive protein; DAT, direct antiglobulin test; G6PD, Glucose-6-phosphate dehydrogenase; hpf, high power field; LDH, lactate dehydrogenase; RBC, red blood cell; WCC, white cell count.

instituted. On the second day of admission, intravenous vancomycin was added due to persistence of fever, remaining febrile. On the fifth day of admission, a new blood test revealed a Hb level of 6 g/dL, 4% reticulocytes, platelet count of $56.0 \times 10^9/L$ and CRP of 44.7 mg/L/mg/dL. Then, a second RBC transfusion was provided. A thick blood smear did not show malarial parasites but as patients with SCD may have clinical malaria with very low parasitaemias that may be even undetectable on a thick smear^{4 5} and fever persisted, intravenous artesunate was added. On the next day, the patient started having dark red urine—secondary to haemoglobinuria—with a drop in Hb level, with normal urine output and renal function (table 1). He remained stable with good mucous/skin colour, blood pressure 87/52, heart rate 122 beats/min, temperature 37.2°C, O₂ saturation 97% and no signs of respiratory distress. He had systolic murmur I/VI, good bilateral ventilation and a hepatomegaly and splenomegaly of 3 cm.

INVESTIGATIONS

The investigations that were carried out are shown in table 1

DIFFERENTIAL DIAGNOSIS

Various diseases can mimic a HS.

Malaria usually presents with anaemia, thrombocytopenia and occasionally haemoglobinuria. Malarial anaemia can be acute or chronic, and it is multifactorial: haemolysis, shortened erythrocyte survival and spleen sequestration. It was discarded when PCR for *Plasmodium* was negative.

Sepsis features commonly with fever, progressive anaemia, leucocytosis, thrombocytopenia, hypotension, tachycardia and hyperbilirubinaemia. Haematuria—but not haemoglobinuria—can be present in the setting of consumption coagulopathy. Our

patient did not present a clinical worsening, did not have haemodynamic instability, coagulopathy nor organ failure. He was treated with empiric antibiotics (cefotaxime and vancomycin) according to our protocols, and no growth was reported in the cultures.

Anaemia and thrombocytopenia can also occur due to a microangiopathic disease which causes an intravascular haemolysis with negative DAT, hyperbilirubinaemia and a highly elevated serum ferritin⁶ and LDH. However, our patient had a normal renal function and did not show schistocytes on the peripheral blood smear.

The haematophagocytic lymphohistiocytosis syndrome has also similar symptoms. Patients suffer fever, splenomegaly, jaundice, bicytopenia or pancytopenia and a highly elevated serum ferritin.⁷ Haematuria can be secondary to coagulopathy which was not present in our patient. There was no lymphadenopathy, hypofibrinogenaemia or hypertriglyceridaemia either.

Considering the previous transfusion, an acute haemolytic transfusion reaction (AHTR) or DHTR had to be kept in mind. Although an AHTR can show similar symptoms (fever, rash, flank pain, shortness of breath, choloria, haemoglobinuria and hypotension), it is not plausible, as typically symptoms begin within the first minutes of the infusion. Besides, the possibility of an erroneous transfusion was ruled out. In the DHTR, the haemolysis is milder, mostly extravascular, with positive DAT and high reticulocyte count. Presenting symptoms are mainly silent, occasionally with anaemia, fever, abdominal pain, jaundice and dyspnoea, and without haemoglobinuria (see table 2).

Intravenous artesunate is related with delayed-onset haemolytic anaemia, but this occurs after 2–3 weeks administering the drug and mostly in those patients with high parasitaemias. The mechanism is

Table 2 Differences between a delayed haemolytic transfusion reaction (DHTR) and the hyperhaemolytic syndrome

	DHTR	Hyperhaemolytic syndrome
Symptoms of painful crisis	May or may not be present	Generally present
Time of onset	>7 days	Acute: <7 days Delayed: 7–15 days
Haemolysis	Extravascular	Intravascular
Hb	≥Pretransfusion Hb	<Pretransfusion Hb
Reticulocytes	↑	↓
Immunohaematological study	DAT + detection of responsible ALoAb	DAT±, but ALoAb does not explain symptoms
Transfusion	<ul style="list-style-type: none"> ▶ No haemolysis when transfusing blood without ALoAg ▶ Anaemia improves 	<ul style="list-style-type: none"> ▶ Haemolysis even if ALoAg is avoided ▶ Anaemia worsens
Treatment	Transfusion if necessary Avoiding ALoAg in following transfusions	Avoiding transfusion IVIg+CT

ALoAb, alloantibody; ALoAg, alloantigen; CT, corticosteroids; DAT, direct antiglobulin test; Hb, haemoglobin; IVIg, intravenous immunoglobulin.

unclear. Evidence suggests that this happens secondary to a reduced lifespan of these once-infected RBCs, whose parasitic structures had been previously removed by the spleen without destroying the erythrocyte itself (pitted erythrocytes).^{8–10}

Even if ceftriaxone has been associated with intravascular haemolytic anaemia by immune complex formation,^{11 12} cefotaxime is a very unusual cause of haemolysis.^{13 14}

Finally, HS is a rare but severe complication that may occur after transfusions. It has mainly been reported in patients with SCD. Symptoms include fever, pain (difficult to distinguish from ‘sickle pain’), intravascular haemolysis, anaemia (typically with Hb level lower than pretransfusion values) and reticulocytopenia. DAT is frequently negative. If positive, it does not explain the haemolytic crises.¹

TREATMENT

Artesunate treatment was suspended, an intravenous dose of 1g/kg of IVIg was given and the patient was transferred to the paediatric intensive care unit (PICU) of a tertiary hospital due to the possibility of worsening and poor peripheral venous access.

At the PICU, he received a second dose of IVIg and intravenous methylprednisolone 30 mg/kg/day for 5 days (figure 1).

OUTCOME AND FOLLOW-UP

Clinical and analytical parameters improved (table 1 and figure 1). Antibiotic therapy was suspended on the 8th day of admission and on the 14th day he returned to our hospital where he continued to evolve favourably until he was discharged on the 18th day of admission. Basal Hb level after the episode has ranged between 8.5 and 9.9 g/dL and splenomegaly remains. He has not received any other transfusions since.

DISCUSSION

The clinic of HS consists of bone pain, chest pain, fever and so on and therefore it can be confused with other medical conditions, or in patients with SCD, with complications of the disease. Therefore, patients may mistakenly be transfused, precipitating or increasing the haemolytic process with haemoglobinuria and requiring intensive care. The analytical

Figure 1 Progress during admission. Hb, haemoglobin; IVIg, intravenous immunoglobulin; MP, methylprednisolone; Retics, reticulocytes; Bt, blood transfusion.

parameters that can be found are: a drop in Hb level below pretransfusion levels, reticulocytopenia, negative DAT in acute forms, abnormally high LDH and ferritin level,⁶ aggravated by subsequent transfusions. In urine, both Hb S and A can be detected by electrophoresis, although Hb A predominates.¹⁵ The main differential diagnosis is with a DTHR (see table 2).

The aetiology of HS is unknown. Four hypotheses have been exposed¹: (1) 'bystander haemolysis', with a higher risk of formation of C5-9 membrane attack complex in patients with SCD; (2) macrophage activation because reticulocytes and mature sickle RBCs adhere more avidly to macrophages than normal RBC. The rise in macrophage activity could cause reticulocytopenia via peripheral consumption, and is consistent with the increased erythroid activity shown in bone marrow aspirates. (3) Role of Rh genotype: there are discrepancies between genotype and phenotype (differences in amino acid sequences not shown in serological assays but detected as foreign by the host immune system) especially in the black population. This makes advisable to perform a PCR-based DNA typing in these patients; (4) role of human leucocyte antigen (HLA) antibodies: as there is a lack of identifiable post-transfusion RBC alloantibodies to justify the syndrome, something else must activate the complement (HLA, proteins, etc) and produce lysis of red cells. Multireactive HLA antigens have been detected in a case of acute post-transfusion haemolytic reaction.¹⁶ Some HLA antigens only present in immature RBC may persist on mature red cells (Bennet-Goodspeed antigens) and have been described as a cause of post-transfusion intravascular haemolysis in rare cases.¹

The first case was described in 1980 in a patient with SCD¹⁷ and subsequently in people with thalassaemias. It has been described both in patients with and without haemoglobinopathies.^{1 3} Its actual incidence is unknown due to lack of knowledge and underdiagnosis. In the study at Guys and St. Thomas' Hospital,¹ only nine cases were recorded for 4 years in a population of 1000 patients with SCD, 100 of whom were on a transfusion programme. Of the 79 reported patients (77 reported by Danae¹ and 2 more recent cases^{18 19}), 29 (39.7%) appeared in the paediatric age with a median of 7.8 years, with no gender difference; 22 children (75.8%) had SCD, 4 (13.8%) had β -thalassaemia major and 3 (10.3%) thalassaemia intermedia. Nine children (31%) had antibodies before transfusion and 11 (37.9%) developed them later. Four of the cases (5%) resulted in death.

The hyperhaemolytic reaction can be acute with negative DAT or delayed, starting after 7 days of the transfusion, usually with positive DAT, although the detected alloantibodies are not responsible for the reaction. The delayed reaction is the most frequent form of presentation of this rare post-transfusion complication and it may be more easily confused with the classic DTHR (although our patient presented the acute form). For this reason, a high index of suspicion must be maintained. Severe complications can follow the reaction, and acute respiratory distress syndrome, pancreatitis, congestive heart failure, acute renal failure, splenic sequestration and subarachnoid haemorrhage have been described.^{1 20 21}

There is no agreement in the treatment for HS, but most patients have responded to IVIG and steroids. Transfusions must be avoided as they only produce a more intense RBC lysis. It is therefore advisable in patients where the transfusion may be vital and cannot be avoided to administer both treatments before.

Rituximab may play a role as a preventive treatment.¹ Other treatments such as erythropoietin,^{1 6 15 18–20 22} rituximab^{1 2 18 19 23} and eculizumab^{1 6} have been tried in the event, but with limited success.

Given the low incidence of HS, the lack of knowledge about its pathophysiology, its clinical presentation and that there is no standardised treatment, it would be ideal to have a hemovigilance system that would provide a basis of evidence to know and detect this syndrome early, as well as to identify markers that could predict the risk of recurrence, to make a better blood selection for a lower alloimmunisation, and to establish correct management and alert systems.^{1 24}

In our case, probably the most prudent initial attitude would have been not to transfuse. If we consider that most children with SCD at these ages already have a lower baseline haemoglobin (7–8 g/dL), that splenic sequestration usually produces a more severe anaemia, that there were no signs of haemodynamic compromise and that splenomegaly remained the same hours later, it might have been better to wait and see the evolution in those early hours and he would not have developed this severe complication.

Learning points

- Hyperhaemolysis syndrome is a serious post-transfusion reaction that occurs after one or more transfusions, especially in patients with sickle cell disease, although it can occur even without baseline haemoglobinopathies.
- Its main clinic is fever and pain crisis, so the problem is often aggravated when treated with repeated transfusions. They usually present haemoglobinuria, reticulocytopenia and haemoglobin level fall below pretransfusion levels.
- Given the low incidence and lack of studies and a hemovigilance system, its incidence, aetiopathophysiology and treatment are not standardised. For this reason, it is necessary to have a high index of suspicion.

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