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A Case Report on Hyperhaemolysis Syndrome in a Patient with Sickle cell Anaemia

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Authors' contributions

This work was carried out in collaboration among all authors. Author OCN wrote the protocol, managed the literature searches and final draft. Author OCI collected and managed analysis of samples. Author NCG wrote the first draft of the manuscript, and managed the initial design. Author JED managed the literature search and final draft. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Aims: Increase awareness to the diagnosis of Hyperhaemolysis syndrome and prevent critical anaemia.
Presentation of Case: A 40 year old woman with sickle cell anaemia (SCA) was readmitted with symptoms suggestive of sepsis. In the previous admissions she was received 5 units of cross-matched compatible red blood cells (RBCs), and was discharged on last admission with a PCV of 24%. On readmission, she had a PCV of 13%, and was transfused 4 units of cross-matched

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compatible RBCs. Her PCV marginally improved to 16% but dropped to 12% the next day, with deteriorating clinical condition. 2 units of cross-matched compatible RBCs transfusions was requested with a haematologist review. A diagnosis of hyperhaemolytic syndrome was made, supported by laboratory findings of; haemoglobinuria and hyperbilirubinemia on urine analysis: negative direct antiglobulin test (DAT); negative Indirect antiglobulin test (IDAT); poor reticulocyte response with reticulocyte count of 8.3% (0.5%–2.5%), and reticulocyte production index at 1.66; Peripheral blood smear showed nucleated RBCs and spherocytes, Albumin- 32g/dl (35- 50g/dl), increased total bilirubin- 55.4mmol/L (17- 22.3 mmol/L). Further blood transfusions was suspended, and steroids commenced for 5 days. Patient's clinical condition subsequently improved. She was discharged on the 5th day of steroid therapy with a PCV of 20%, followed by tapering doses of prednisolone for 4 weeks. One year of follow-up showed no new red blood cell antibody in her serum, no need further transfusions, and a steady state PCV of 25%.

Conclusion: Hyperhaemolysis syndrome is a potentially life threatening complication of blood transfusion. High index of suspicion and early recognition is important especially when managing patients with SCA who present with worsening anaemia after RBC transfusions.

Keywords: Blood transfusion; hyper haemolysis syndrome; severe haemolysis; steroid.

1. INTRODUCTION

Sickle Cell Anaemia is an inherited disorder of haemoglobin characterised by chronic haemolysis punctuated by acute crisis. Management of acute and or chronic complications often include blood transfusions which could be top-up and or exchange transfusions. Nonetheless, transfusion is not without risks, including the more obvious acute haemolytic transfusion reactions to the less dramatic and often missed Hyperhaemolysis Syndrome (HHS). Hyperhaemolysis syndrome is characterised by worsening haemolysis on further transfusions, and subsequently potential life-threatening anaemia [1-7]. Early recognition and proper management is lifesaving.

2. CASE PRESENTATION

We present a 40 year old woman who was diagnosed with sickle cell anaemia (SCA) in childhood. She presented with generalised body weakness and pain, loss of appetite, and vomiting of 2 days duration. She was admitted after evaluation, and initially managed for sepsis. She had been admitted twice in the past 4 weeks prior to the present admission, where she was managed for vaso-occlusive crisis and hyperhaemolytic crisis respectively. Management during the previous admissions included, the transfusion of 5 units of cross-matched compatible red blood cells (RBCs). One week prior to this readmission, she was discharged from the hospital with a PCV of 24% after being managed for hyperhaemolytic crisis.

On readmission, she had a packed cell volume (PCV) of 13%, and was transfused 4 units of cross-matched compatible red blood cells. Her PCV marginally improved to 16% by the 4th day on admission, but reduced to 12% on the 5th day, with the her clinical condition deteriorating. 2 units of cross-matched compatible RBCs transfusions was requested urgently, and the haematologist was invited to review the patient. At the time of review, the patient was already on the second unit of blood. She was passing dark coloured urine with evidence of haemoglobinuria and hyperbilirubinemia on urine analysis. Working with a diagnosis of hyperhaemolytic syndrome, further blood transfusions was suspended. Steroids (Hydrocortisone) was commenced for 5 days. Further laboratory work-up revealed a negative direct antiglobulin test (DAT); negative Indirect antiglobulin test (IDAT); poor reticulocyte response was found with reticulocyte count of 8.3% (normal range, 0.5%–2.5%), and reticulocyte production index at 1.66; Coagulation studies were normal. Peripheral blood smear showed nucleated RBCs and spherocytes. Albumin- 32g/dl (normal 35-50g/dl), total bilirubin- 55.4mmol/L (normal 17-22.3 mmol/L); Blood culture revealed no growth after 7 days; HIV I and II tests were non-reactive; HBsAg was non-reactive; anti-HCV was non - reactive. Abdominal Ultrasound revealed she lacked a spleen. Patient's condition improved daily. She was discharged home on the 5th day of therapy with a PCV of 20% followed by tapering doses of prednisolone for 4 weeks. One year of follow-up showed no new red blood cell antibody in her serum nor had she required further blood transfusion. Her PCV had maintained steady state of 25%.

3. DISCUSSION

Hyperhaemolysis syndrome (HHS) is characterised by paradoxical worsening anaemia after transfusion of cross matched compatible RBCs, with post-transfusion haemoglobin concentration being less than pre-transfusion haemoglobin [8,9]. In addition to an increased prevalence in hemoglobinopathies, such as SCA, HHS has also been reported in patients with other haematoloical conditions, such as thalassaemia, myelofibrosis, anaemia of chronic disorders, lymphoma, and non haemtological conditions [9-14].

The concept of HHS being a syndrome, was coined by Petz et al [3], who described 5 unusual features of haemolysis that has now become the diagnostic criteria for HHS. These features included; 1) acute or delayed Haemolytic Transfusion Reactions (HTR) depending on the length of time from transfusion to the development of symptoms, and the formation or non formation of alloantibodies: 2) A more severe anaemia after transfusion, suggesting that not only the transfused red cells were haemolysed, but destruction of patient's own RBC may play a role resulting in significant decrease in Haemoglobin concentration levels: 3) A marked reticulocytopaenia (a significant decrease from the patient's usual absolute reticulocyte level) and recovery manifested by reticulocytosis and gradual improvement in Haemoglobin concentration level: 4) Additional transfusion may further exacerbate haemolysis, and may become life-threatening and even cause death: 5) After a recovery period, similar symptoms may recur following subsequent transfusion in some patients [3,4,15].

The clinical presentation is non specific and includes fever, jaundice, and severe pain [6,8]. Important laboratory values expected include elevated lactate dehydrogenase, elevated bilirubin, decreased reticulocyte count, and increased nucleated red blood cells on peripheral blood film [6,8]. Our patient exhibited some of these clinical features and laboratory values. Part of the diagnostic challenge of identifying HHS in SCA is that symptoms are largely similar to those of vaso-occlusive crises that patients with SCA commonly experience [16]. The symptoms of pain, fever, jaundice, and passage of dark coloured urine seen in our patient did not differ greatly from her presenting symptoms for previous hospitalizations. These symptoms are not uncommon for a patient with an underlying disease of chronic haemolysis [16].

In the acute form, clinical symptoms are seen within seven days of the transfusion. Alloantibodies are usually not formed within this time frame, and thus DAT is usually negative [4,5,6,8]. In the delayed form, clinical symptoms are seen beyond seven days after transfusion, and alloantibodies are more likely to have formed. A direct antiglobulin test in this case would likely be positive [4,5,6,8]. The patient in the case report possibly had an acute form as symptoms developed within seven days of transfusion, and DAT was negative.

A definitive prevalence for hyperhaemolysis syndrome in sickle cell disease, both in adult and paediatric patients, has yet to be established. Mwesigwa et al, reported a prevalence of 5% in SCD patients [17].

The pathogenesis of HHS is still a subject of debate, but the most cited hypotheses are: i) bone marrow suppression, [1] ii) bystander mechanisms, and iii) macrophage activation [1,3,4,5].

The treatment of hyperhaemolysis syndrome often starts with holding further transfusions to prevent further haemolysis. The mainstay of treatment is glucocorticoids and intravenous immunoglobulin (IVIG). This is often instituted alone or blood transfusion with cross matched Least incompatible RBCs may be given along side [1,4,5,14,18].

Recurrence of HHS, and HHS refractory to a combination of IVIG/steroids treatment have been documented. Monoclonal antibodies like eculizumab, tocilizumab, and rituximab have shown limited effectiveness in treatment especially in refractory cases [4,5,10,19,20].

Mortality is rare and often results from misdiagnosis, and the resultant rapid haemolysis following further blood transfusions to correct anaemia [1,4,10,21].

4. CONCLUSION

Hyperhaemolysis syndrome is a potentially life-threatening complication of seemingly innocuous transfusion treatment especially when unidentified. It is well documented in sickle cell anaemia, but often missed because the presentation is similar to other complications commonly seen in patients with SCA. This case report is aimed to increase awareness of providers to this diagnosis and prevent critical anaemia.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT

Authors declare that written informed consent was obtained from the patient for publication of this case report.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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