Hyperhemolysis syndrome in a case of sickle cell disease

Sir,

Hyperhemolysis is a potentially fatal hemolytic transfusion reaction, with hemoglobin (Hb) and hematocrit levels falling dramatically when compared to the values before the transfusion. This condition is usually seen in patients with sickle cell disease (SCD) and beta-thalassemia.[1]

SCD is a hereditary condition characterized by homozygous Hb S, hemolytic anemia, and painful crisis. Patients with SCD typically require red blood cell (RBC) transfusions to manage the complications and reduce morbidity. Alloimmunization is a complication of numerous transfusions that develops when antibodies produced by the recipient identify foreign surface antigens on transfused RBC (alloantibodies). A delayed hemolytic transfusion reaction/hyperhemolysis syndrome can occur as a result of this condition.[2]

The development of severe anemia with posttransfusion Hb levels that are lower than pretransfusion levels is known as hyperhemolysis syndrome (HS). HS has been found in individuals with thalassemia, myelofibrosis, anemia of chronic diseases, and lymphoma, in addition to an elevated prevalence in hemoglobinopathies such as SCD. This unusual disorder has the potential to be fatal. Fever, jaundice, and malaise are commonly seen in the clinical presentation of HS. The results of the laboratory tests show higher bilirubin and lactate dehydrogenase (LDH) levels, as well as a drop in absolute reticulocyte count. In many cases, the direct antiglobulin test is negative, and new alloantibodies may or may not be detected.[3]

We present a case of a young male with SCD who presented with vaso-occlusive crisis and developed hyperhemolysis syndrome (HS) as evidenced by posttransfusion fall in Hb and hematocrit values with jaundice and dark red-colored urine. He was managed supportively and discharged in a clinically stable state on the 16th day of hospitalization.

An 18-year-old male was admitted to our hospital with complaints of intermittent high-grade fever with chills for 3 days, watery loose stools 2–3 episodes/day, severe generalized pain, and nausea. He was a known case of SCD on tablet folic acid 5 mg OD. He was treated as a case of vaso-occlusive crisis with analgesics, intravenous fluids, antibiotics in view of raised total leukocyte count, and 2 units of packed red cell transfusion in view of low Hb percentage. Three days after the last packed red cell transfusion, the patient complained of sudden onset breathlessness and dark red-colored urine. On examination, the patient's pulse rate was 112 bpm, respiratory rate was 28/min, with a saturation of 95% on room air, blood pressure – 110/70 mmHg, and icterus and pallor were present. Systemic examination revealed no abnormalities.

Laboratory investigations revealed a further fall in Hb – 6.8 mg/dl, hematocrit 20.2 along with raised liver enzymes, serum glutamic-pyruvic transaminase – 196 mg/dl, serum glutamic-oxaloacetic transaminase – 577 mg/dl, serum LDH – 4743 mg/dl, and total bilirubin levels – 6.9 mg/dl (indirect bilirubin – 4.9 mg/dl). Direct Coomb's test was done to rule out autoimmune hemolysis of RBC's which was negative and total creatine kinase was normal. Urine dipstick analysis was done which was positive for blood, to differentiate hemoglobinuria from hematuria and myoglobinuria, centrifugation was done and the color of supernatant was not clear which confirmed hemoglobinuria. Urine microscopic examination revealed no RBC's in urine. Computed tomography urography was normal. A diagnosis of HS was, hence, made after ruling out other possible conditions. The patient was treated with supportive care by withdrawing further transfusions, careful administration of intravenous fluids, input–output monitoring, and other supportive care. He was started on tablet prednisolone 1 mg/kg/day and was given in tapering dose. The patient was planned for the administration of intravenous immunoglobulins (IVIG) but was withheld as the patient's general condition and laboratory parameters were improving. The patient was discharged in a clinically stable state after complete resolution of his symptoms and rising Hb and hematocrit values.

HS is differentiated into acute and delayed types based on the interval between the time of transfusion and the development of clinical signs, as well as the possibility of alloantibodies formation. Acute HS develops within 7 days of transfusion without alloantibody formation, whereas delayed HS develops after 7 days, and alloantibody formation is common.[4] The pathophysiology of HS has yet to be fully understood. Hemolysis by activated macrophages, increased RBC

Figure 1: Dark red coloured urine due to hemoglobinuria

phosphatidylserine exposure, and suppression of erythropoiesis have all been proposed as mechanisms. When both native and donor RBCs are hemolyzed, bystander hemolysis occurs, possibly as a result of complement activation. Hb levels in HS may be lower as a result of active macrophages breaking more RBCs. When phosphatidylserine is expressed on the surface of RBCs, it causes enhanced clearance from circulation.[5]

Exclusion of alternative causes and management with steroids and immunoglobulins are the cornerstones of DHRT/HS treatment. Mild cases can be treated with prednisolone (1–2 mg/kg/day) while Hb levels are closely monitored. Avoiding additional blood or component transfusions is vital to avoid symptoms worsening, but in certain situations, Hb drops to dangerously low levels, necessitating RBC transfusions.[6] Additional immunoglobulin G treatment may be required in extreme situations, with the knowledge that it involves the risk of renal damage and thromboembolic events. Because of the rapid recovery of reticulocyte count, rituximab can become an effective treatment. Erythropoietin has been explored as a potential treatment to overcome erythropoiesis inhibition; however, further research is needed to prove efficacy. Similarly, the C5 convertase inhibitor eculizumab has been used to treat hyperhemolysis in SCD patients.[7,8]

This case highlights the need for clinicians to be aware of the risk of hyperhemolysis in patients who experience transfusion complications. Earlier detection may allow for more abrupt withdrawal of further transfusions and delivery of steroids, IVIG, and immunomodulators whenever required resulting in a faster resolution.

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There are no conflicts of interest.

Sameera Dronamraju, V. S. Irshad, Sourya Acharya, Samarth Shukla[1], Sunil Kumar

Departments of Medicine and [1]Pathology, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences (Deemed to be University), Sawangi (Meghe), Wardha, Maharashtra, India

Address for correspondence:
Dr. Sameera Dronamraju,
Department of Medicine, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences (Deemed to be University), Sawangi (Meghe), Wardha, Maharashtra, India.
E-mail: sameeradronamraju1993@gmail.com

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