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Some Critical Presentations of Sickle Cell Disease (SCD) Crisis Among the Pediatric Population from India: A Rare Case Series

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ABSTRACT

Sickle Cell Disease(SCD) is a group of inherited RBC disorders caused by abnormal hemoglobin polymerization leading to erythrocyte rigidity and vaso occlusion. Acute painful episodes and dactylitis (vaso-occlusive crises), acute chest syndrome, sepsis, hemolytic episodes, splenic sequestration, aplastic crisis, stroke and priapism are some of its complications. In this case series, we have reported 3 children from rural setups in India, presenting with various crises like an aplastic crisis, vaso-occlusive crisis and hyper hemolytic crisis. The first case was a case of scrub typhus with parvovirus B19-induced aplastic crisis in preexisting sickle cell disease, who had a triad of SCD, fever and reticulocytopenia. The second case was a classical vaso-occlusive crisis leading to acute chest syndrome with a chest X-ray revealing a consolidation and small pleural effusion in the left lower lobe. 3rd case was diagnosed as hyper hemolytic syndrome after blood transfusion in SCD and treated with high-dose intravenous methylprednisolone and IVIG along with other supportive measures. Prompt recognition of symptoms, a high index of suspicion and aggressive management can prevent adverse outcomes in these critical cases of SCD.

INTRODUCTION

Sickle cell disease is a group of inherited RBC disorders caused by abnormal hemoglobin resulting in acute pain episodes and dactylitis (vaso-occlusive crises), acute chest syndrome, sepsis, hemolytic episodes, splenic sequestration, aplastic crisis, stroke and priapism and chronic complications namely poor growth, nephropathy, retinopathy, osteonecrosis, functional asplenia, cholelithiasis, learning and cognitive difficulties, silent cerebral infarcts, c pulmonary hypertension and congestive cardiac failure[1]. A point mutation in the beta globin chain, changes amino acid glutamic acid to valine at position 6, resulting in the formation of hemoglobin S. Hemoglobin S polymerizes forming sickle-shaped hemoglobin which causes hemolysis, vaso-occlusion and alters the blood viscosity resulting in, endothelial dysfunction and inflammation[2].

Case Summary: In this series, we have reported 3 children hailing from a rural setup in India, presenting with non-specific constitutional and hematological clinical crises on the pretext of the presence of sickle cell disease. Serial hematological investigations aided in clinching this rare yet treatable clinical diagnosis.

Case 1: A 4-year-old female, second born to a non-consanguineous couple, presented with fever for 10 days which was initially low grade, intermittent and later became high grade, accompanied with chills and rigor. Furthermore, the patient complained of easy fatigue, which has persisted even in day-to-day activities for the last 2 days. No history of pain in the abdomen, joint pain, chest pain, or breathlessness was elicited. She is immunized up to date with normal developmental milestones and belongs to a lower middle-class socio-economic group. On general examination, pallor was found with appreciable tachycardia. No icterus, clubbing, or lymphadenopathy was recorded. Systemic examination highlighted isolated hepatosplenomegaly. The patient was given paracetamol and injection ceftriaxone and routine blood investigations for infectious etiology (malaria, dengue, enteric fever, scrub typhus) sent. A complete hemogram revealed isolated low hemoglobin and reticulocyte count with elevated ESR. Peripheral blood smear showed microcytic, hypochromic cells with anisopoikilocytosis. Alongside, scrub typhus IgM turned out positive. 1 unit of packed RBC was transfused and oral doxycycline was started in a dose of 4mg/kg/day. Bone marrow aspiration studies revealed reduced erythropoietin. HPLC reports revealed increased HbS and HbA2 indicating a double heterozygosity for HbS and beta thalassemia traits. Suspecting the aplastic crisis, we sent a sample for parvo virus B19, which turned out to be positive. The final diagnosis was a case of scrub typhus with parvo virus B19-induced aplastic crisis in a preexisting sickle cell disease. So the message is, that any child with SCD, fever and reticulocytopenia should be suspected to have parvo virus B19 infection until proven otherwise.

Fig. 1: Case 1

Fig. 2: Parvo Virus B19 Report of Case 1

Case 2: A 10-year-old female child, 1st born to a non-consanguineous couple, hailing from a low socio-economic status, presented with high-grade fever and severe lassitude for the last 2 days and excruciating chest pain, localized over the left 3rd and 4th intercostal spaces, not radiating, exaggerating with exertion and subsiding on rest for last 3 days. No history of chills, rigors, gastrointestinal upset, convulsions, or rash was elicited. On general examination, tachypnoea, tachycardia with pallor and pyrexia were recorded, while systemic examination yielded hepatosplenomegaly and reduced air entry in bilateral lung fields. The child was started on injection ceftriaxone, oral paracetamol and azithromycin. Blood investigation revealed isolated anemia accompanied by raised acute inflammatory markers, with normal iron studies and a negative infectious disease profile. Chest roentgenogram revealed a consolidation and small pleural effusion in the left lower lobe. 2 units of packed RBC were transfused over 2 consecutive days. HPLC report revealed sickle cell disease and it was nothing but the classical vaso-occlusive crisis precipitated by the sickled RBC leading to the causation of the acute

chest syndrome. Optimizing pain alleviation and fluid management prevents the transition of this painful episode into the life-threatening crisis of acute chest syndrome. The exact etiology of pain is unknown, but the pathogenesis may be initiated when blood flow is disrupted in the micro vasculature by sickled RBC and other cellular elements resulting in tissue ischemia.

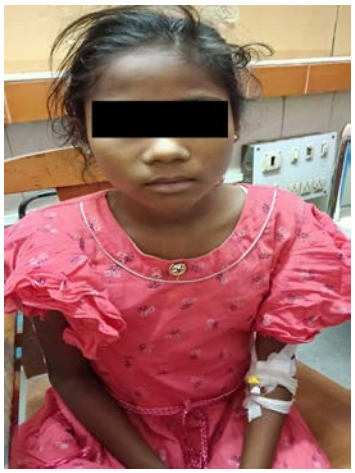


Fig. 3: Case 2

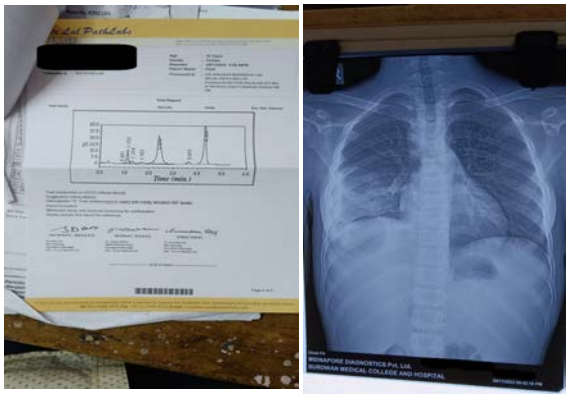


Fig. 4: HPLC Report and Chest X-Ray of Case 2

Case 3: A 5-year-old, first-born male child to a consanguineous couple from middle socio-economic status with sickle cell disease was admitted with an acute lower respiratory infection and treated with IV fluids, analgesics and antibiotics and was transfused one unit of packed RBC. At the time of discharge, laboratory parameters revealed hemoglobin 9g/dl, Hct 30.8%, LDH 643 u/l and a bilirubin level of 4.29 mg/dl. Two days after discharge (seven days after the RBC transfusion), he was re-admitted with yellowish discoloration of skin and sclera, passage of reddish urine, pain and parenthesis in both lower limbs, lethargy and shortness of breath for the last one day. Hematological investigations revealed-Hb 4.72g/dl, Hct 14.7%, WBC count-3.78 $\times 10^9$/litre, LDH 3,910 u/l, bilirubin-13.65 mg/dl, HbA-4% and HbS-86% in HPLC. Excluding infection and other SCD complications, we considered a diagnosis of hyper hemolytic syndrome and started high-dose intravenous methylprednisolone (1.5 g/day). A day after, his Hb levels dropped even further, reaching 3.0 mg/dl and her LDH levels increased to 6,680 u/l, accompanied by altered sensorium. Considering the severity of his clinical state, 1 unit packed RBC was transfused, 1 gm/kg IVIG was administered, along with erythropoietin (4,000 u) and folic acid. Her hemodynamic parameters improved and she was discharged after two weeks with Hb of 7.96 mg/dl, Hct of 24.5%, LDH-1,694 u/l and bilirubin level -5.69mg/di. Serial immune hematological studies performed after this crisis also showed negative DAT and HLA antibodies. Hyper hemolytic syndrome is an uncommon but severe complication of aluminization that occurs in patients after RBC transfusions, especially those with SCD who are submitted to multiple transfusions throughout their lives. The symptoms of hyper hemolytic syndrome can easily be mistaken for other sickle cell disease complications, including infections and vaso-occlusive crises. It usually begins seven days after RBC transfusion. It is mainly caused by the destruction of both donor and recipient RBCs, though the exact etiopathogenesis is yet unknown. One possible explanation for autologous RBC destruction is bystander hemolysis, whereby sickled RBCs are destroyed by antibodies without expressing the specific antigen against which this antibody is directed. The appropriate management of hyper hemolytic syndrome is by avoiding further transfusions and administering steroids and immunoglobulins which can drastically modify the course of the disease and yield favourable outcomes.

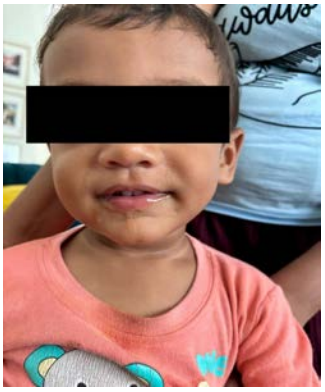
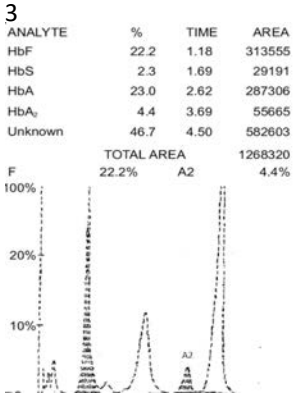


Fig. 5: Case 3



ANALYTE	%	TIME	AREA
HbF	22.2	1.18	313555
HbS	2.3	1.69	29191
HbA	23.0	2.62	287306
HbA_2	4.4	3.69	55665
Unknown	46.7	4.50	582603
	TOTAL AREA		1268320

Fig. 6: HPLC Report in Case 3

RESULTS AND DISCUSSIONS

SCD is a multi-system disorder resulting from the complex interplay of hemolysis, chronic inflammation, and systemic vascular damage. Its complications include acute chest syndrome, hepatic sequestration, stroke, acute painful crises, nephrotic syndrome and splenic sequestration crisis. In the maiden case, human parvovirus B19 is implicated as an etiological factor for complications escorting transient red cell aplasia in patients with sickle cell disease. Smith-Whitley K *et al* and Saad AA also described such cases of human parvo virus B19-induced aplastic crisis in children with SCD[3,4]. In the 2nd case, it was witnessed that the presenting features of acute chest syndrome frequently overlap with lower respiratory tract infection and bronchial asthma. Chest x-ray should therefore be performed in all children with sickle cell disease presenting with more than one of the following signs and symptoms of temperature >38.5 degrees Celsius, chest pain, tachypnoea, wheezing, cough, increased work of breathing relative to baseline. Various literature including Ahmed B *et al* described cases with acute chest syndrome and revealed rational antimicrobial usage namely macrolides, similar to syrup azithromycin and oseltamivir, along with blood transfusion, oxygen therapy and respiratory support forms the crux of the first line of treatment[5-8]. Inhaled nitrogen oxide and arginine supplementation alongside corticosteroid administration has an integral role in reducing the complications manifold. Proceeding towards the ultimate case scenario, we have a gross comprehension of the fact that sickle cell disease patients are at risk of developing multiple complications from transfusion, including aluminization to RBC Ag's, delayed hemolytic transfusion reactions and hyper hemolysis syndrome. The hemolytic syndrome is a serious complication of trandfusion, characterized by the destruction of both transfused and autologous RBC resulting in severe anemia and post-transfusion hemoglobin less than pre-transfusion levels. We have reported a case of 5 year old male child, a known case of sickle cell disease, who developed severe anemia following blood transfusion. This case aims to highlight the importance of early recognition of hemolytic syndrome as quoted by Sweidan A *et al* and others to avoid irrational management with excessive blood transfusion[9,10]. The transfusion-free approach, comprising steroids and immunoglobulins paves the way for clinical recovery.

CONCLUSION

SCD is a debilitating genetic disease that can present with various crises like aplastic crisis, vaso-occlusive crisis and hyper hemolytic crisis. Prompt recognition of symptoms, a high index of suspicion and aggressive management can prevent adverse outcomes.

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