

A Differential Approach to an Uncommon Case of Acute Anemia in a Child With Sickle Cell Disease

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Abstract

Introduction: Hyperhemolytic crisis is a rare and dangerous complication of sickle cell disease where the hemoglobin level drops rapidly. This can quickly lead to organ failure and death. In the literature, most cases of hyperhemolysis in sickle cell patients followed a red cell transfusion. **Case Summary:** In this article, we report a case of a 6-year-old African American boy with sickle cell disease who presented with fever, increased work of breathing, and consolidation in the left lower lobe of the lung on chest X-ray. He initially improved with oxygen, fluids, and antibiotics but his hemoglobin acutely dropped from 7.6 to 6 g/dL the next day of admission. He was not previously transfused, and his reticulocyte count remained high. Subsequent transfusion recovered his hemoglobin. **Conclusion:** This case demonstrates that in the background of the chronic hemolysis of sickle cell disease, an acute anemia should warrant exploration of aplastic crisis (parvovirus infection), immune hemolytic anemia, hepatic sequestration crisis, splenic sequestration crisis, and hyperhemolytic crisis as possible etiologies. Ongoing reticulocytosis and a source of infection may direct suspicion especially toward hyperhemolytic crisis even without preceding red cell transfusion. We propose that the optimum management should include full supportive care (including transfusions if necessary) and treatment of the underlying cause of hemolysis (such as infections or drug exposure).

Keywords

hyperhemolytic crisis, sickle cell anemia, acute chest syndrome, splenic sequestration, aplastic crisis

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Introduction

Sickle cell disease (SCD) is a commonly studied inherited hemoglobinopathy that carries a major public health burden.^{1,2} Central to the pathophysiology of SCD is obstruction of microvasculature by the impaired flexibility of polymerized sickle hemoglobin secondary to hypoxic environments.³ The major acute complications of SCD include severe anemia, infections, and a variety of vaso-occlusive phenomenon including, but not limited to, stroke, acute chest syndrome (ACS), and dactylitis. While SCD produces a chronic, compensated hemolytic anemia, an acute drop in hemoglobin can often be seen in patients admitted for complications of SCD. The major causes include aplastic crisis, immune hemolytic anemia, splenic or hepatic sequestration crisis, and hyperhemolytic crisis.⁴ We present an uncommon case of hyperhemolytic crisis in a pediatric patient with history of SCD and will then discuss the differential diagnosis for an acute anemia in this population that

attending physicians, residents, and medical students should consider.

Case Report

A 6-year-old African American male with HbSS SCD presented with fever and increased work of breathing of 1 day and 2 days of cough. At home, his mother recorded an oral temperature of 100.1°F. In the past, he had recurrent hospitalizations for acute pain crises and ACS. The mother and father both have sickle cell trait. His immunizations were up to date. His home medication was albuterol.

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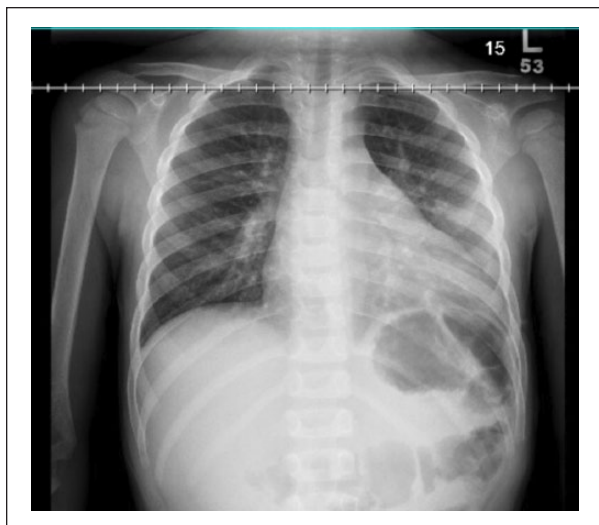


Figure 1. Streaky opacity in left lower lobe seen in our patient on admission.

On hospital admission, his temperature was 99.1°F. His blood pressure was 94/65 mm Hg, and his pulse was 118 beats per minute. His respiratory rate was 22 breaths per minute, and he had an oxygen saturation of 97% on room air. Physical examination revealed no hepatosplenomegaly and mild conjunctival pallor. A chest X-ray revealed a consolidation in the left lower lobe of the lung (Figure 1). He received intravenous fluid hydration, incentive-spirometry, and antibiotics (ceftriaxone and azithromycin) after blood culture was drawn.

His initial complete blood count revealed an elevated white blood cell count of 23 100 cells/mm³, a low hemoglobin of 7.6 g/dL, and a normal platelet count of 350 × 10⁹/L. A reticulocyte count was 21.3% on admission. An antibody screen was negative.

On the second day of admission, the patient's hemoglobin dropped 6 g/dL (20% drop) with no change in symptoms. Reticulocyte count remained high at 20%. Based on the indications for transfusion therapy in patients with ACS, he received a 15 cc/kg transfusion of packed red blood cells (RBCs). His hemoglobin levels recovered to 9.0 g/dL.

Final Diagnosis

Acute chest syndrome with severe anemia due to acute hemolysis and pneumonia.

Hospital Course

He remained afebrile. Subsequent blood cultures showed no growth, and he was discharged on an empiric course of cefdinir and azithromycin.

Discussion

An initial discussion of the more common causes (parvovirus-induced aplastic crisis and splenic or hepatic sequestration crisis) of a severe, acute anemia will then be followed by an explanation of the rarer phenomenon of transfusion-independent hyperhemolytic syndrome.

Aplastic crisis is characterized by an abrupt reduction in reticulocytes as well as red cell precursors in the bone marrow. Infection prompts this fall in hemoglobin and parvovirus B19 is often implicated.⁵⁻⁷ Patients often present with pallor and weakness. If aplastic crisis is too severe, the bone marrow cannot compensate and this can be life threatening. Recovery from a transient red cell aplasia is usually within 2 to 14 days. A higher reticulocyte count in this child would not be reflective of bone marrow suppression-related parvovirus infection. However, the literature suggests that the convalescent phase of an acute parvovirus infection can present with brisk reticulocytosis and pronounced anemia.⁸

Parvovirus B19 infection recognizably presents in 5 syndromes—erythema infectiosum (fifth disease), arthropathy (primarily in adults), transient aplastic crisis, nonimmune hydrops fetalis and intrauterine fetal demise, and pure RBC aplasia in immunocompromised individuals.^{8,9} Often occurring in school-aged children, erythema infectiosum is an illness that is characterized by prodromal symptoms of fever, coryza, and diarrhea followed by the classic “slapped cheek” rash 2 to 5 days later. Severe complications can develop from a parvovirus infection, including bone marrow necrosis leading to pancytopenia, stroke, glomerulonephritis, and even severe ACS.⁸

In an immunocompetent host without aplasia, a clinical diagnosis is sufficient if the classic malar rash and/or arthropathy following febrile illness are present. In a patient with an underlying hematologic disorder who presents with a low reticulocyte count and severe anemia, the diagnosis can be made by detecting parvovirus DNA through the nucleic acid amplification test.

A second etiology to consider would be splenic or hepatic sequestration. Sickled cells can block blood vessels exiting the spleen and cause it to enlarge rapidly, potentially leading to hypovolemic shock and death. Despite persistent reticulocytosis, the patient's hemoglobin will drop.¹⁰ Because splenic sequestration occurs in non-fibrotic spleens, infants are the most commonly affected population, along with children and adults with residual splenic activity. The diagnosis of acute splenic sequestration is based on (1) sudden enlargement of the spleen and (2) a >2 g/dL decline in hemoglobin from baseline with reticulocytosis.⁸ Management includes normal saline boluses for volume expansion and blood transfusions. Recurrence of splenic sequestration is

Table 1. Differential Diagnosis for Pure Red Cell Aplasia in Children.

Acquired	Congenital
Transient erythroblastopenia of childhood	Diamond Blackfan anemia
Infection associated—parvovirus B19	Aase syndrome
Acute: chronic hemolytic anemia (sickle cell disease)	Fanconi anemia
Drugs, toxins, and radiation	
Severe renal failure, nutritional deficiencies	

frequent but parental education of clinical signs of sequestration, use of transfusions, and judicious physical examination of the spleen have reduced mortality.⁸ In brief, hepatic sequestration crisis presents with hepatomegaly, right upper quadrant pain, and a falling hemoglobin and is managed similarly to splenic sequestration crisis.^{11,12} Our patient was an older child and exhibited no splenomegaly or hepatomegaly on physical examination, ruling out these causes.

The third etiology is hyperhemolytic crisis.¹³⁻¹⁸ It is defined as the presence of intravascular and extravascular hemolysis due to a mild oxygen deficiency that presents with acute, worsening anemia. There are proposed theories explaining the increased hemolysis including infections, drug exposure, occult splenic sequestration, and transfusion reactions. Hyperhemolytic crisis presents with a myriad of symptoms that can include fever and pain, evidence of hemolysis, development of severe anemia after transfusion, and a fall in absolute reticulocyte count that is followed by a rise in hemoglobin and reticulocyte count.^{13,14} In contrast, the reticulocyte count in our patient remained high (20% to 21%) with no transfusion preceding the acute anemia. Hyperhemolytic crisis status post transfusion is differentiated from a delayed hemolytic transfusion reaction because, in the former, there is destruction of both the patient's own and transfused RBCs.¹⁵ Though the presentation of an autoimmune hemolytic anemia can be difficult to distinguish from hyperhemolytic anemia, it is more commonly associated with a gradual drop in hemoglobin.¹⁹ Our patient also had a negative antibody screen.

We primarily attribute our patient's hemolysis to the vaso-occlusive nature of ACS as the sickling RBCs are prone to accelerated rates of hemolysis. Our case is unique as most cases of hyperhemolytic crisis in this population of sickle cell patients followed a red cell transfusion but a literature search revealed only one other case similar to ours.²⁰ A differential diagnosis for pure red cell aplasia in children is discussed in Table 1. The pathophysiology of ACS involves a variety of events that trigger deoxygenation of hemoglobin S, which cause sickling of RBCs, leading to vaso-occlusion, ischemia, and endothelial injury.¹ The diagnosis of

ACS is made when there is a new pulmonary infiltrate detected by chest radiograph involving at least one complete lung segment not due to atelectasis and one or more of the following: chest pain, temperature greater than 101.3°F, increased work of breathing, and hypoxemia relative to baseline. An absence of a true fever (as in our patient) does not rule out infection, so it is important to consider the entire clinical picture. Our patient had a left lower lobe infiltrate and the appearance of an increased work of breathing, which prompted a diagnosis of ACS.

Patients are managed with intravenous fluids, adequate analgesia to prevent hypoventilation and atelectasis, incentive spirometry, broad-spectrum antibiotic coverage (third generation cephalosporin and a macrolide), and transfusion therapy, which has been shown to improve oxygenation in ACS. There are conflicting views on the use of steroids. In children with mild to moderately severe ACS, dexamethasone therapy prevented clinical deterioration and reduced the need for blood transfusions.²¹ Other retrospective studies show that corticosteroid use in ACS may be linked to higher readmission rates.^{22,23} Patients should be encouraged to return to clinic following their hospitalization to reassess their hemoglobin levels.

Conclusion

In this report, we present a case of a 6-year-old male with sickle cell disease who developed an acute drop in hemoglobin after exhibiting signs of ACS. Hyperhemolytic crisis is diagnosed by decreased RBC counts, relative drop in hemoglobin, and high reticulocyte count. Approaching an acute anemia in young sickle cell disease patients involves consideration of autoimmune hemolytic anemia, parvovirus infection, sequestration crises, and hyperhemolytic crisis. While it is important to keep in mind that RBC transfusions have been known to precede hyperhemolytic crises, this is not always the case and the underlying cause of the hemolysis (in this case, ACS) should adequately be managed.

Author Contributions

Both authors contributed to the production and editing of the manuscript.

Declaration of Conflicting Interests

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Informed Consent

Written informed consent was obtained by the patient's parents for the publication of this case report.

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