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Severe Hemolytic Anemia With Concurrent Methemoglobinemia and Acute Kidney Injury in a Patient With G6PD Deficiency

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Abstract

Glucose-6-phosphate dehydrogenase (G6PD) deficiency can cause severe hemolysis following oxidative stress. Methemoglobinemia may occur concurrently, further complicating oxygen delivery. We report the case of a 44-year-old man who presented with dyspnea, jaundice, cola-colored urine, and severe anemia following a recent respiratory illness. Laboratory investigations revealed a hemoglobin concentration of 5.5 g/dL, lactate dehydrogenase of 3,409 U/L, and undetectable G6PD activity (0.0 IU/g hemoglobin). The direct antiglobulin test (DAT), also known as the direct Coombs test, was negative. Co-oximetry demonstrated methemoglobinemia, with levels reaching 9.1%. A pneumonia molecular panel detected *Haemophilus influenzae*, while the patient also reported possible fava-bean ingestion, suggesting an additional potential oxidative trigger. His clinical course was complicated by acute kidney injury, with creatinine rising to 2.17 mg/dL. Management included transfusion of four units of warmed packed red blood cells, intravenous hydration, supplemental oxygen, and antibiotic therapy. Methylene blue was not administered in the setting of severe G6PD deficiency and concurrent hemolysis. This case describes the concurrent occurrence of severe oxidative hemolysis, methemoglobinemia, and acute kidney injury in G6PD deficiency, emphasizing the importance of recognizing potential oxidative triggers and considering the risks associated with methylene blue treatment.

Categories: Hematology, Medical Education, Internal Medicine
Keywords: acute kidney injury, g6pd deficiency, haemophilus influenzae, hemolytic anemia, hyperbilirubinemia, methemoglobinemia, oxidative stress

Introduction

Glucose-6-phosphate dehydrogenase (G6PD) helps red blood cells withstand oxidative stress. It generates nicotinamide adenine dinucleotide phosphate (NADPH) through the pentose phosphate pathway, allowing cells to maintain reduced glutathione and protect hemoglobin and red-cell membranes from damage [1].

G6PD deficiency is X-linked and is among the most common inherited red-cell enzymopathies [2]. It most commonly affects male individuals. Many affected individuals have no symptoms until an oxidative challenge occurs. Recognized triggers include infection, certain medicines, and fava beans [3]. Acute hemolytic episodes may present with fever, chills, jaundice, marked pallor, tachycardia, abdominal pain, and dark urine. Severe cases can lead to profound anemia, acute kidney injury, and possible shock.

Methemoglobinemia occurs when the iron in hemoglobin is oxidized from Fe^{2+} to Fe^{3+}, reducing its capacity to carry oxygen. It can accompany oxidative hemolysis, although the two are separate manifestations of red-cell injury [4,5]. When both occur together, assessing oxygenation and determining the most appropriate treatment can be challenging, particularly in patients with severe anemia. Methylene blue, commonly used to treat significant methemoglobinemia, relies on NADPH-dependent reduction and may be ineffective or even worsen hemolysis in patients with severe G6PD deficiency [6,7].

We describe severe hemolysis with concurrent methemoglobinemia and acute kidney injury in a man with marked G6PD deficiency. A recent respiratory infection was documented, while an additional food-related trigger remained uncertain. This case highlights the diagnostic and management challenges associated with these concurrent complications.

Case Presentation

A 44-year-old man presented to the emergency department with generalized weakness, jaundice, dark urine, vomiting, diarrhea, and shortness of breath. He reported feeling generally unwell for approximately five days, following a cold-like illness about one week before admission. Two days before presentation, he developed frequent vomiting, approximately seven to eight episodes, along with loose stools and poor oral intake. The following day, he noticed dark, cola-colored urine, which he initially described as hematuria.

The patient also reported consuming restaurant-prepared hummus before his illness. He suspected that it might have contained fava beans, although the ingredients could not be confirmed.

On examination, the patient appeared markedly unwell, with pronounced jaundice, pallor, and shortness of breath. Initial vital signs showed a heart rate of 106 beats/min, blood pressure of 126/86 mmHg, respiratory rate of 20 breaths/min, oxygen saturation (SpO_2) of 89%, and temperature of 36.8°C. Bilateral breath sounds were reduced on chest examination. The abdomen was soft, with tenderness in the right upper quadrant. He was conscious and oriented.

Initial laboratory investigations revealed severe anemia with reticulocytosis, elevated lactate dehydrogenase (LDH), low haptoglobin, predominantly indirect hyperbilirubinemia, and elevated inflammatory markers, together with impaired renal function (Table *1*). The direct antiglobulin test (DAT) was negative. Initial venous blood gas (VBG) analysis revealed an elevated methemoglobin level of 8.9%.

Laboratory parameter	Result	Reference range
Hemoglobin	5.5 g/dL	13.5-17.5 g/dL
White blood cell count	29.9 × 10^9/L	4.0-11.0 × 10^9/L
Reticulocyte count	11.36%	0.5%-2.5%
LDH	3,409 U/L	120-246 U/L
Haptoglobin	0.14 g/L	0.30-2.00 g/L
Total bilirubin	11.1 mg/dL	0.3-1.2 mg/dL
Indirect bilirubin	9.9 mg/dL	0.0-1.2 mg/dL
Creatinine	1.83 mg/dL	0.72-1.18 mg/dL
Serum urea	141.2 mg/dL	19.3-49.2 mg/dL
CRP	126 mg/L	<10 mg/L
Procalcitonin	2.78 ng/mL	<0.1 ng/mL

TABLE 1: Initial laboratory investigations on admission.

Initial laboratory findings demonstrating severe hemolytic anemia, elevated inflammatory markers, and renal impairment.

LDH: lactate dehydrogenase; CRP: C-reactive protein

Diagnostic assessment

Together, the laboratory findings indicated severe hemolytic anemia. Quantitative G6PD activity was 0.0 IU/g hemoglobin. The sample had been collected before transfusion. Other causes of DAT-negative hemolysis, including paroxysmal nocturnal hemoglobinuria (PNH) and paroxysmal cold hemoglobinuria (PCH), were considered and investigated. PNH flow cytometry detected no type II or type III CD59-deficient red-cell population and no abnormal monocyte or granulocyte population. The laboratory found no evidence of a PNH clone. Blood gas analysis revealed a methemoglobin level of 8.9% on the initial VBG, which subsequently increased to 9.1% on arterial blood gas (ABG) analysis.

Treatment and clinical course

The patient was admitted to the intensive care unit (ICU) for management of severe symptomatic anemia and associated complications. On ICU admission, oxygen saturation was 92% while receiving 15 L/min of oxygen through a non-rebreather mask, although his work of breathing was normal. He initially received two units of warmed packed red blood cells (PRBCs), along with intravenous fluids and supplemental oxygen. Blood warming is generally used during rapid or large-volume transfusions to prevent transfusion-associated hypothermia. He was treated with ceftriaxone and azithromycin for suspected pneumonia. Hemoglobin, biochemical markers of hemolysis, renal function, and urine output were monitored throughout hospitalization.

On Day 2, hemoglobin remained 5.8 g/dL after the initial transfusions, LDH was 2,886 U/L, and dark urine persisted. Creatinine increased to 2.17 mg/dL. Gastrointestinal fluid losses and pigment-related renal injury were considered possible contributors to the renal impairment.

The patient had reported a cold-like illness approximately one week before admission and presented with dyspnea, reduced breath sounds bilaterally, and an initial requirement for supplemental oxygen. Laboratory investigations demonstrated leukocytosis and elevated inflammatory markers, while a pneumonia molecular panel detected *Haemophilus influenzae*. These findings supported a suspected respiratory infection, which was considered a possible oxidative trigger for the hemolytic episode. However, its role as the definitive precipitating factor could not be established.

A third PRBC unit was administered, raising hemoglobin to 6.9 g/dL. Serial blood gas analyses showed an initial methemoglobin level of 8.9%, followed by measurements of 9.1% and 8.6%. The level subsequently declined to 3.6% and eventually 2.6% during hospitalization. Methylene blue was not administered, and management remained supportive.

By Day 3, jaundice and dark urine had improved, and his oxygen requirements had decreased. He was transitioned from an oxygen face mask to nasal cannula before being weaned to room air. Hemoglobin reached 7.7 g/dL, and the white blood cell count decreased to 16.9×10^9/L. Creatinine declined to approximately 1.59 mg/dL, total bilirubin to 1.7 mg/dL, C-reactive protein (CRP) to 54 mg/L, and procalcitonin to approximately 0.46 ng/mL.

On Day 4, the patient was clinically stable on room air, with adequate urine output. Hemoglobin was 7.3 g/dL, LDH had decreased to 1,786 U/L, creatinine was 1.57 mg/dL, and total bilirubin was 1.9 mg/dL. He received a fourth PRBC unit, bringing the total to four units during hospitalization.

Despite significant clinical and biochemical improvement, anemia and elevated markers of hemolysis persisted. Continued inpatient monitoring was recommended, but the patient chose to leave against medical advice following counseling.

Peripheral blood film

Peripheral blood-film examination revealed anisopoikilocytosis, erythrocytes with irregular contours suggestive of bite and blister cells, and Heinz body-like changes, consistent with oxidative hemolysis. Representative microscopic findings are shown in Figure *1*.

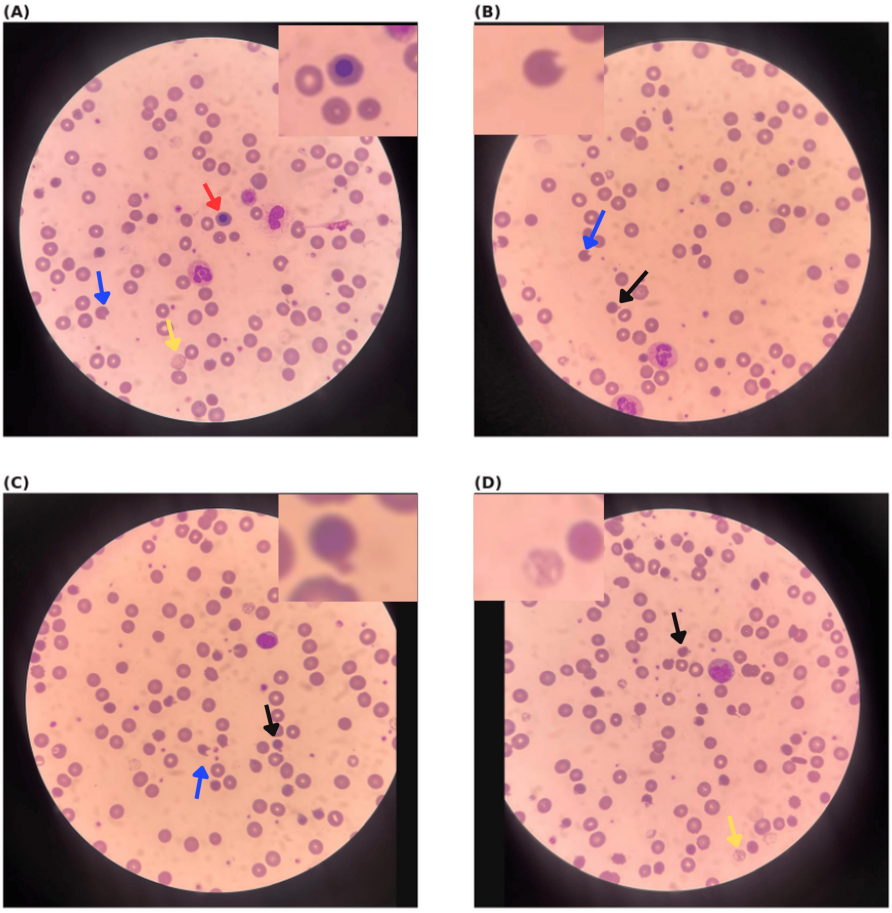


FIGURE 1: Peripheral blood smear findings in a patient with G6PD deficiency. (A-D) Representative peripheral blood smear photomicrographs demonstrating red blood cell morphological abnormalities associated with oxidative erythrocyte injury. Blue arrows indicate bite cells (degmacytes), black arrows highlight erythrocytes with irregular membrane projections suspected to be associated with Heinz body formation, yellow arrows indicate a blister cell, and the red arrow indicates a suspected nucleated red blood cell. Enlarged insets provide a closer view of selected abnormal cells. Supravital staining was not performed; therefore, the presence of Heinz bodies could not be confirmed.

G6PD: glucose-6-phosphate dehydrogenase

Outcome

Following blood transfusions, intravenous hydration, antibiotics, and supportive care, the patient showed significant clinical and biochemical improvement. Hemoglobin increased from 5.5 g/dL on admission to 7.3 g/dL on Day 4, while LDH decreased from 3,409 to 1,786 U/L. Total bilirubin fell from 11.1 to 1.9 mg/dL, and creatinine improved from a peak of 2.17 to 1.57 mg/dL. Jaundice and dark urine resolved, and the patient no longer required supplemental oxygen. Although anemia and elevated LDH persisted, his overall condition had improved considerably. Continued inpatient monitoring was recommended to assess further hematological recovery, but the patient chose to leave against medical advice. No subsequent laboratory results were available to assess his longer-term recovery.

Discussion

Three findings distinguish this episode: very severe G6PD-associated hemolysis, concurrent methemoglobinemia, and transient renal impairment. The biochemical evidence of hemolysis was clear, but

the contribution of each possible oxidative trigger was not.

The hemoglobin of 5.5 g/dL, reticulocytosis, high LDH and indirect bilirubin, low haptoglobin, and dark urine together supported intravascular hemolysis. Bite and blister cells reported on the peripheral smear were compatible with oxidative red-cell injury. A negative DAT and undetectable G6PD activity further supported G6PD-associated non-immune hemolysis [3].

Creatinine rose from 1.83 to 2.17 mg/dL before declining with supportive treatment. Both hemoglobin-related tubular injury and dehydration from vomiting and diarrhea may have contributed. Renal impairment has been described in other cases combining G6PD-related hemolysis and methemoglobinemia [5].

The methemoglobin fraction peaked at 9.1%. Although this is a modest level compared with severe isolated methemoglobinemia, the patient's profound anemia and respiratory illness reduced his reserve for oxygen delivery. Co-oximetry was important because pulse oximetry cannot reliably measure methemoglobin; PaO_2 alone does not reflect the loss of functional hemoglobin [6].

The respiratory panel detected *H. influenzae*, and the patient had recent respiratory symptoms and marked inflammation. Infection was therefore a credible oxidative stressor. He had also eaten restaurant-prepared hummus, but its ingredients were unknown. Fava beans can provoke hemolysis and methemoglobinemia in G6PD deficiency [7]; however, favism cannot be diagnosed here from an unverified dietary exposure.

Management of methemoglobinemia in G6PD deficiency requires caution. Methylene blue relies on NADPH-dependent reduction and may be ineffective or worsen hemolysis in patients with severe G6PD deficiency [6,7]. In this case, methylene blue was not administered given the patient's profound G6PD deficiency and ongoing severe hemolysis. Management instead focused on blood transfusions, supportive care, and treatment of the underlying illness.

The G6PD sample was obtained before transfusion, strengthening interpretation of the undetectable activity. During acute hemolysis, selective destruction of older red cells and reticulocytosis may affect enzyme activity measurements, while recent transfusion can introduce donor red cells with normal G6PD activity [8]. Thus, the pre-transfusion timing is an important feature of this case.

The patient's urine color, bilirubin, creatinine, and oxygen requirements improved during the four-day admission. His hemoglobin remained low, however, and departure against medical advice prevented assessment of full hematologic recovery.

The principal limitation is uncertainty about the oxidative trigger: a respiratory infection was documented, but it cannot be shown to be the only cause. Fava-bean exposure was unconfirmed. Follow-up results were also unavailable.

Conclusions

This case describes severe acute hemolysis with methemoglobinemia and acute kidney injury in a patient with profound G6PD deficiency. A recent respiratory infection was considered a likely precipitating factor, although possible dietary exposure to fava beans could not be confirmed. The patient showed significant clinical and biochemical improvement following blood transfusions, intravenous hydration, and treatment of the underlying infection, although anemia persisted at discharge. This case emphasizes the importance of obtaining a thorough clinical history, including targeted questions about underlying medical conditions, recent infections, medication use, and dietary exposures, as these can help identify potential triggers and guide early diagnosis and management. Recognition of concurrent methemoglobinemia, close monitoring of renal function, and awareness of the potential risks of methylene blue are also important when managing patients with severe G6PD-associated hemolysis.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Nada Abdelmaksoud, Laian Hamod, Arunodaya Mohan

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Supervision: Arunodaya Mohan, Kshitij Anand

Disclosures

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