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CASE REPORT

Methemoglobinemia in the Setting of G6PD Deficiency and SARS-CoV-2 Infection

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Abstract

We report a case of a 58 year old African American male patient with Coronavirus Disease-2019 (COVID-19) in the setting of multiple concomitant hematologic disorders, including Glucose-6-phosphate dehydrogenase deficiency (G6PD deficiency) and sickle cell trait. Typically, G6PD deficiency remains clinically silent, and only a minority of patients will show signs of chronic hemolytic anemia. However, all G6PD deficient patients are at risk of non-immune hemolysis after exposure to a variety of infectious pathogens, including COVID-19. Our patient displayed evidence of methemoglobinemia and subsequent tissue anoxia. We review the theories and mechanisms behind the increased risk of complications and severity of illness in the context of COVID-19 and hematologic disorders. These patients may require alternative treatment pathways due to their comorbidities. This case emphasizes the complications that can arise in this setting, and highlights important considerations for patient treatment.

Keywords: Methemoglobinemia, COVID-19, G6PD

Essentials

- Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common enzyme deficiency in humans
- SARS-CoV-2 prompts a pro-oxidant response while simultaneously suppressing the antioxidant system which contributes to increased severity of disease in G6PD patients
- Hemolysis due to G6PD can lead to worsening respiratory status in COVID-19 infection through several mechanisms
- Methylene blue is contraindicated and ineffective in G6PD patients with methemoglobinemia, and alternative therapies like ascorbic acid should be used

1. Introduction

The Coronavirus Disease-2019 (COVID-19) pandemic is caused by SARS-CoV-2, a novel coronavirus that causes multisystem illness, usually most pronounced as severe respiratory disease. COVID-19 infection with concomitant hematologic disorders may predispose patients to increased severity of condition and treatment complications. Therefore, these patients require special consideration of widely varying symptoms and potential alternative treatment pathways due to underlying preexisting hematologic disorders.

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common enzyme deficiency in humans, affecting about 400 million people worldwide.[1] G6PD is a cytosolic enzyme that

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catalyzes the pentose phosphate shunt. It is required to maintain the level of nicotinamide adenine dinucleotide phosphate (NADPH), which protects the red blood cells from oxidative injury. Sickle cell disease is an inherited spectrum of disorders characterized by two abnormal beta-globin chains of hemoglobin. On the other hand, sickle cell trait is present in individuals with only one abnormal beta-globin chain of hemoglobin.[2] Herein, we report a rare case of COVID-19 infection in the setting of G6PD deficiency and sickle cell trait, highlighting the complications and treatment challenges.

2. Case presentation

A 58-year-old African-American male with a history of G6PD deficiency, sickle cell trait, and surgically managed localized prostate cancer mcr presented to the emergency department with altered mental status and shortness of breath. On presentation, the patient was tachycardic (HR of 120 bpm), tachypneic (RR 25 bpm), and hypoxic (SpO2 of 80% on room air). Complete blood count revealed WBC 29.14 mm3/mcL, Hgb 8.9 g/dL and platelet count of 181 mm3/mcL. The physical exam was remarkable for somnolence, tachypnea, and bilateral coarse lung sounds. Complete metabolic panel revealed hyperglycemia (glucose of 844 mg/dL), acute kidney injury (creatinine of 2.99 mg/dL, with a baseline of 0.80 mg/dL), and elevated AST/ALT (336/113 U/L). A non-contrast computed tomography (CT) of the chest was obtained in the setting of respiratory distress, which showed diffuse bilateral ground-glass airspace opacities. SARS-CoV-2 PCR testing was positive. The patient was treated with broad-spectrum antibiotics, insulin infusion for hyperglycemia, and supplemental oxygenation. Dexamethasone/Remdesivir as a treatment of COVID-19 was also initiated. Due to increasing confusion and respiratory distress, the decision was made to intubate the patient.

On post-admission day 1, the patient had worsening liver function (AST/ALT >7000/5287 units/L), which prompted stopping the remdesivir. Repeat laboratory testing also showed a hemoglobin of 6.7 g/dL (without overt signs of bleeding), requiring transfusion with two units of packed red blood cells. Workup showed no signs of hemolysis or sickle cell crisis.

On post-admission day 2, the patient had SpO2 in the 80 s mmHg despite maximal mechanical ventilator settings. ABG showed PaO2 of 174 mmHg and the development of methemoglobinemia (0.3 g/dL on admission, peak of 9.6 g/dL). Repeat hematologic workup demonstrated hemolysis with sickling of red blood cells. Given that the typical treatment for methemoglobinemia with methylene blue would be ineffective in this patient due to the history of G6PD deficiency, the patient was started on ascorbic acid infusion and red cell exchange transfusion. Despite maximal vasopressor therapy, mechanical ventilation, and methemoglobin improvement, the patient continued to worsen clinically and passed away.

3. Discussion

Typically, G6PD deficiency remains clinically silent, and only a minority of patients will show signs of chronic hemolytic anemia. However, all G6PD deficient patients are at risk of non-immune hemolysis after exposure to oxidative stressors such as medications, infections, or fava beans. G6PD deficiency leads to methemoglobinemia, wherein failure to generate adequate NADPH in RBCs leads to heme iron in the oxidized ferric state rather than the ferrous state, which does not carry oxygen adequately. This leads to a left shift in the oxygen-hemoglobin dissociation curve and secondary tissue hypoxia.

G6PD deficiency has been hypothesized to exacerbate the severity of Covid-19 infection, as the virus prompts a pro-oxidant response through activation of macrophages while simultaneously suppressing the antioxidant system.[2] Given that G6PD deficiency results in a compromised antioxidant system, it is postulated that these patients might suffer more severely from COVID-19.[3] Wu et al. have demonstrated an increased susceptibility of G6PD deficient cells to SARS-CoV infection in an ex vivo study.[4] A retrospective study of 182 patients in Sardinia, Italy, showed that G6PD deficiency has a negative influence on the outset of COVID-19.[5] This leads to a more complicated treatment process, especially when greater oxidative stress, created by treating COVID-19, makes patients more susceptible to medically induced methemoglobinemia.

Severe hemolysis due to G6PD deficiency may manifest as methemoglobinemia, in which heme iron is in the oxidized ferric state rather than the ferrous state.[6,7] The discrepancy in our patient's SpO2 and PaO2 with elevated methemoglobin levels demonstrates this biochemical process. In G6PD deficiency, the typical standard treatment of methemoglobinemia with methylene blue is ineffective because the reduction of methemoglobin is NADPH dependent. Methylene blue is also

potentially dangerous in this situation since it has an oxidant potential that may induce hemolysis in G6PD deficient patients.[8] Instead, our patient was treated with ascorbic acid infusion.

Using a murine hemolysis model,[9] Hu et al. found that the acute hemolysis-induced increase in pulmonary arterial pressure leading to right ventricle failure caused sudden death. Reduced nitric oxide bioavailability and massive platelet activation/aggregation leading to massive thrombosis, specifically in the pulmonary microvasculature, played critical roles in the pathogenesis of acute hemolysis-associated fatal pulmonary arterial hypertension. Albertsen et al. reported a deadly hemolytic crisis with disseminated intravascular coagulation and pulmonary microthrombi in a G6PD-deficient African male.[10] Those studies provide a plausible explanation for worsening respiratory disease in G6PD deficient patients in the context of COVID-19 infection.

Further complicating our patient's hematologic history, sickle cell trait may have played a role in his multi-organ system dysfunction and subsequent death. COVID-19's ability to increase inflammatory cytokines such as interleukin-6 can induce vaso-occlusive crises.[11] COVID-19 has also been shown to cause endothelial and microvascular dysfunction through complement-mediated processes.[12] Patients with sickle cell disease have a higher rate of developing pulmonary complications in the setting of COVID-19 infection.[13] Typically, sickle cell trait is clinically benign without significant symptomatology as sickle cell crisis is related to sickle cell disease. However, in rare cases, an occlusive crisis can also affect patients with sickle cell trait under severe stressors such as low oxygen levels, dehydration, or high altitude.[14,15] With the complication of COVID-19, this crisis is more likely to occur.

4. Conclusion

The COVID-19 pandemic has proven that management of the infection in even otherwise healthy adults can be challenging for clinicians, nevertheless in patients with multiple hematological disorders. Our case adds to the sparse literature about this specific situation and highlights the complications and treatment difficulties associated with this clinical dilemma. In clinically worsening COVID-19 patients, with no clear etiology, it may be reasonable to consider G6PD as a part of comprehensive evaluation. Early recognition of these challenges is essential for earlier interventions and improved patient outcomes.

Contributors

All authors had full access to all the data and manuscript materials and take responsibility for the integrity of data and the accuracy of the paper.

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Conflict of Interest

All authors have no conflict of interest.

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