CASE REPORTS

Hemolytic Anemia in a Glucose-6-Phosphate Dehydrogenase-Deficient Patient Receiving Hydroxychloroquine for COVID-19: A Case Report

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ABSTRACT

Introduction: The growing coronavirus disease 2019 (COVID-19) pandemic initially led to widespread use of hydroxychloroquine sulfate as an off-label experimental treatment of this disease.

Case Presentation: Acute hemolytic anemia developed in an African American man with COVID-19-related pneumonia and glucose-6-phosphate dehydrogenase (G6PD) deficiency who completed the standard 5-day experimental course of hydroxychloroquine. Although the trigger leading to our patient's hemolytic sequelae will never be known with certainty, his clinical course suggests that hydroxychloroquine use and/or COVID-19 infection may trigger hemolysis in susceptible patients with G6PD deficiency.

Discussion: This case confirms recent findings that the potential risks of hydroxychloroquine therapy for COVID-19 may outweigh the benefits.

INTRODUCTION

Hydroxychloroquine is an oral medication used for the treatment of malaria and several rheumatologic diseases, and it recently was used widely as an experimental drug to treat pneumonia due to coronavirus disease 2019 (COVID-19). Hydroxychloroquine information resources and drug package inserts recommend caution when prescribing this medication to patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, presumably because of a risk of hemolytic anemia. This risk by association is loosely connected to rare reports of hemolysis and death in G6PD-deficient patients who received primaquine, an antimalarial medication similar to hydroxychloroquine, for the treatment of malaria.[1] In more than 6 decades of primaquine use by approximately 200 million people, 14 deaths have been reported.[2] However, to our knowledge, there is no evidence in the literature of an association between hydroxychloroquine and hemolytic anemia.[3] In this case report, we describe a case in which a patient with previously unknown G6PD deficiency experienced acute hemolytic anemia in the setting of hydroxychloroquine therapy for COVID-19-related pneumonia.

CASE PRESENTATION

Presenting Concerns

A 51-year-old African American man with type 2 diabetes, hypertension, and morbid obesity presented to our hospital with approximately 2 to 3 weeks of subjective fevers, myalgias, dry cough, and worsening shortness of breath. One week earlier, he presented to an outside hospital's Emergency Department, where community-acquired pneumonia was diagnosed. He was discharged to home with a prescribed 7-day course of levofloxacin that was reportedly completed. On general worsening of his cough and dyspnea, he arrived at our hospital and was subsequently admitted.

On admission, the patient tested positive for COVID-19, with chest radiographic findings consistent with COVID-19 pneumonia. He initially demonstrated a supplemental oxygen requirement of 2 L/minute via nasal cannula, but this need resolved within 24 hours of hospitalization.

Therapeutic Intervention and Treatment

On day 1, the standard experimental 5-day course of hydroxychloroquine (400 mg twice daily on day 1, and 400 mg once daily on days 2-4) for treatment of COVID-19-induced pneumonia was initiated. Testing for G6PD deficiency was done on admission; however, the result was found to be abnormal only on the sixth day of hospitalization. Notably, the patient was also found to have a creatine kinase level elevated to 4399 U/L and creatinine level of 10.1 mg/dL (1.2 mg/dL before admission), which were concerning for acute kidney injury. The patient was initially managed with intravenous fluids but soon required hemodialysis.

Follow-up and Outcomes

On the sixth day of hospitalization, one day after completion of hydroxychloroquine therapy, the patient became hypoxic and required supplemental oxygen via nasal cannula, correlating with a decrease in hemoglobin level to 8.4 g/dL (14.5 g/dL on admission). Additional studies in the subsequent 3 days revealed a reticulocytosis of more than 3%, increasing lactic dehydrogenase level to 2575 U/L, increasing total bilirubin level to 1.5 mg/dL (0.3 mg/dL on admission) with relatively unchanged direct bilirubin levels (maximum = 0.4 mg/dL throughout hospitalization), low haptoglobin concentration to less than 10 mg/dL, and positive schistocytes on a peripheral blood film, suggestive of an acute intravascular hemolytic anemia. All other laboratory tests, including complete blood cell count, urine analysis, and

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coagulation profiles had either normal results or nonspecific findings consistent with COVID-19 infection.

The patient consequently required red blood cell transfusions on days 9, 10, and 11 of hospitalization. Afterward the patient's hemoglobin levels stabilized to between 8 and 9 g/dL. During this hemolytic process, the patient's hemodialysis catheter irreversibly clogged twice, requiring 2 separate urgent catheter replacements. The patient became able to breathe comfortably on room air on day 16 and was discharged home with outpatient hemodialysis scheduled. A case timeline appears in Table 1.

DISCUSSION

Glucose-6-phosphate dehydrogenase deficiency is a recessive X-linked blood disorder characterized by a defective mutation in G6PD, an enzyme that plays a critical role in protecting erythrocytes from oxidative damage.[4] In the setting of infection (eg, pneumonia) or exposure to certain foods or medications, oxidative stress leads to excessive accumulation of free radicals, causing G6PD-deficient erythrocytes to burst and ultimately leading to hemolytic anemia.[5] The 2 most clinically significant genetic variants of G6PD deficiency are the Mediterranean and African types, which are both highly prevalent in geographical areas where malaria is endemic. It is widely accepted that this distinct geographic distribution of G6PD deficiency is the product of positive selection, because these mutations may confer protection against malaria.[6]

Antiparasitic medications have been commonly used to treat or prevent malaria for more than a century. Among them, the quinolone hydroxychloroquine has been in use as an antimalarial agent for more than 65 years, with a warning to prescribers that hydroxychloroquine may lead to hemolytic anemia in patients with G6PD deficiency. This warning was based on solid evidence that a similar quinolone to hydroxychloroquine, primaquine, rarely causes hemolytic anemia in G6PD-deficient patients.[2] However, until the time of this writing, there have been no published clinical case reports or scientific evidence establishing an association between hydroxychloroquine and hemolysis. One recent study specifically investigating this possible association did not reveal episodes of suspected hydroxychloroquine-induced hemolysis in 11 G6PD-deficient patients who received a combined 700 months of hydroxychloroquine therapy for various rheumatologic disorders.[7] Moreover, the American College of Rheumatology does not recommend screening for G6PD deficiency before initiation of therapy with hydroxychloroquine.[8]

Nearly all patients with G6PD deficiency remain asymptomatic in the steady state, and hemolysis develops only in the setting of food or drug interactions or severe infection. Indeed, our patient was unaware of his G6PD deficiency until this hospitalization.

Although the trigger leading to our patient's hemolytic sequelae will never be known with certainty, a few potential explanations merit consideration. First, our patient's hypoxia on initial presentation may have served as the trigger. Although the patient's hypoxia was mild and resolved after 24 hours, the duration and/or degree of hypoxia before presentation is unknown and may have been sufficient to trigger hemolysis. Second, unknown hydroxychloroquine-dependent interactions alone may have served as the trigger. Although, to our knowledge, no reports of hydroxychloroquine-induced hemolysis exist in the published literature, the loading dose of 800 mg of hydroxychloroquine in our COVID-19 pneumonia protocol is twice the normal dose in standard rheumatologic therapy and in published studies examining the potential association between hydroxychloroquine and hemolysis. Levofloxacin-induced hemolytic anemia also remains on the differential diagnosis but is considered extremely rare. Autoimmune hemolytic anemia is typically associated with conditions that our patient lacked; thus, no direct testing for it was performed. Last, there is the possibility that COVID-19 infection alone may trigger hemolytic anemia in susceptible patients with G6PD deficiency. To our knowledge, this is the first reported case of hemolytic anemia in a patient with COVID-19 infection or in a patient who received hydroxychloroquine therapy.

Since we submitted this article for publication, the US Food and Drug Administration revoked its emergency use authorization to use hydroxychloroquine to treat COVID-19 in certain hospitalized patients, because recent results from a large, randomized clinical trial in hospitalized patients found this medicine did not decrease the likelihood of death or of hastening recovery.[9]

CONCLUSION

As the COVID-19 pandemic continues to grow in the United States, we may learn of more cases of hemolytic anemia in patients with G6PD-deficiency who received treatment with hydroxychloroquine. If so, these additional cases would further support the FDA's decision to revoke the Emergency Use Authorization (EUA) for hydroxychloroquine sulfate for the treatment of COVID-19 disease.❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Authors' Contributions

Jorge Aguilar, MD, PhD, and Yelena Averbukh, MD, participated equally in the drafting, critical review, and submission of the final manuscript. Both authors have given final approval to the manuscript.

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Table 1. Case timeline

Relevant Medical History and Interventions

A 51-year-old African American man with type 2 diabetes, hypertension, and morbid obesity received a diagnosis from another hospital of community-acquired pneumonia

Date	Summaries from initial and follow-up visits	Diagnostic testing (including dates)	Interventions
3/31/2020	Patient presents with 2-3 weeks of subjective fevers, myalgias, dry cough, and worsening shortness of breath, demonstrating a supplemental oxygen requirement.	Chest X-Ray: pneumonia COVID-19 PCR: positive G6PD: positive (resulted on 4/6)	Supplemental oxygen provided via nasal cannula or non-rebreather mask.
4/1/2020	Patient no longer required supplemental oxygen.	Creatine kinase level el-evated to 4399 U/L and Creatinine level of 10.1 mg/dL (1.2 mg/dL be-fore admission) were concerning for acute kidney injury (AKI).	5-day course of Hydroxychlo-roquine initiated; AKI was initially managed with intravenous fluids but soon required serial he-modialysis.
4/6/2020	Patient completed 5-day course of Hydroxychlo-roquine; Patient became hypoxic, requiring sup-plemental oxygen.	Hg 8.4 d/gL (down from 14.5 g/dL on ad-mission)	Supplemental oxygen provided via nasal can-nula or non-rebreather mask
4/7/2020	Persistence of lethargy, dyspnea, and hypoxia, requiring supplemental oxygen.	Hemolysis workup find-ings (CBC, reticulocyto-sis, LDH, bilirubin, hap-toglobin, and peripheral blood smear) suggestive of an acute intravascular hemolytic anemia	Supplemental oxygen provided via nasal can-nula or non-rebreather mask.
4/9/2020	Persistence of lethargy, dyspnea, and hypoxia, requiring supplemental oxygen.	Hg 5.9	Red Blood Cell (RBC) Transfusion
4/10/2020	Persistence of lethargy, dyspnea, and hypoxia, requiring supplemental oxygen.	Hg 6.7	RBC Transfusion
4/11/2020	Persistence of lethargy, dyspnea, and hypoxia, requiring supplemental oxygen.	Hg 6.6	RBC Transfusion
4/16/2020	Significant clinical improvement; Reso-lution of hypoxia.	Hg 8.6	
4/21/2020	Patient was discharged to home.		