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A Case Report of Methemoglobinemia and Hemolytic Anemia in the Setting of COVID-19 Pneumonia and G6PD Deficiency

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INTRODUCTION

It is well known that hereditary or acquired methemoglobinemia can cause hypoxia due to the oxidation of heme, which impairs its ability to offload oxygen (**Figures 1 & 2**), and that acquired methemoglobinemia is most often caused by exposure to drugs and toxins that oxidize hemoglobin to methemoglobin, directly or indirectly[1]. Recently, a few case reports have highlighted methemoglobinemia in patients with COVID-19 pneumonia. Some of these reports were due to treatment with hydroxychloroquine and others from unidentifiable causes[2-4]. We present a case in which a patient with COVID-19 pneumonia was diagnosed with methemoglobinemia and acute hemolysis from G6PD deficiency in the setting of worsening hypoxia after receiving treatment with dexamethasone, remdesivir, and high-dose vitamin C.

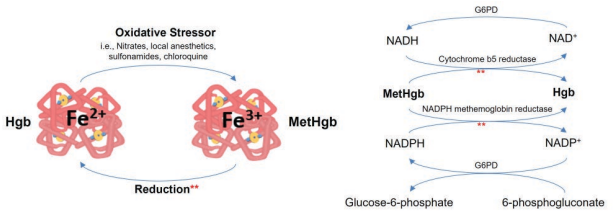

Figure 1: Hemoglobin-Methemoglobin Redox Mechanism

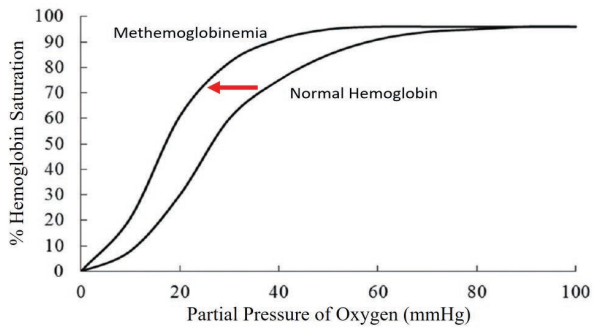

Figure 2: Oxygen–Dissociation Curve

CASE PRESENTATION

A 32-year-old African American male with no significant past medical history presented to the emergency room with exertional shortness of breath and non-productive cough for 6 days. He was febrile to 103°F and had an oxygen saturation of 91% on room air. He had no evidence of crackles or wheezes on lung auscultation, but his chest x-ray showed bilateral patchy opacities and a COVID-19 nasopharyngeal swab was positive. He was admitted and started on Remdesivir and dexamethasone 6 mg/day. On hospital day (HD) 2, he enrolled in a COVID high-dose vitamin C trial where he was randomized to the treatment arm and received 34g of vitamin C (0.3g/kg) IV on HD 2 and 68g (0.6g/kg) IV on HD 3. He was removed from the trial on HD 4 for worsening hypoxia. On HD 5, his oxygen saturation was 80% on 15L of oxygen. Despite his low oxygen saturation, he had no shortness of breath or increased work of breathing. An arterial blood gas while on 15L showed: pH 7.39, $PaCO_2$ 43 mmHg, PaO_2 110 mmHg, measured O2 saturation 88%, and calculated O2 saturation 99%. He was subsequently transferred to the intensive care unit for closer monitoring.

Due to the discrepancy between his pulse oximeter (SpO_2) and arterial oxygen saturation (PaO_2), a co-oximetry panel was sent. This revealed a mildly elevated methemoglobin level of 8.1%. Notably, his hemoglobin had declined from 13.7 on admission to 6.8 g/dL by HD 8, and his creatinine climbed to 3.6 mg/dL from 1.0 mg/dL. In addition to methemoglobinemia, he was found to have a non-immune hemolysis, and review of his peripheral blood smear showed bite and blister cells with the presence of Heinz bodies. A serum G6PD level obtained at the time of active hemolysis was inappropriately low at 3.5 U/g Hg. Hematology recommended treatment of his methemoglobinemia with 1.5g of vitamin C every 8 hours for a total of 4 days, which improved his methemoglobin level to 4%. Methylene blue was not used given his diagnosis of G6PD deficiency

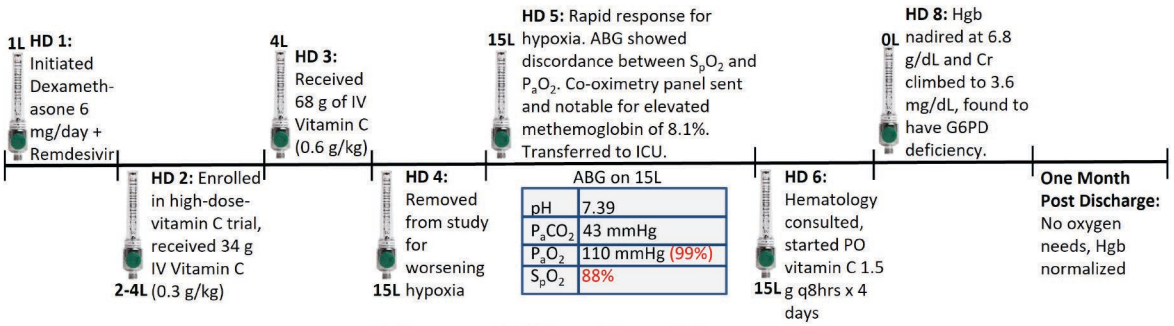

Figure 3: Timeline of Events

and his methemoglobin level was only mildly elevated. Methylene blue is considered in patients with moderate to severe elevations in methemoglogin (>20-30%). By HD 8, he was maintaining 95-100% oxygen saturation on room air, and his hemoglobin eventually recovered to 12 g/dL one month later without additional treatment (see **Figure 3** for complete timeline of events).

DISCUSSION

Undoubtedly, this patient's hypoxia from COVID-19 pneumonia was exacerbated by methemoglobinemia and acute hemolysis from underlying G6PD deficiency, but the cause of the methemoglobinemia remains unclear.

Since he was only exposed to three medications (remdesivir, dexamethasone, and high-dose vitamin C), there is concern that one of these pharmacotherapies acted as an oxidative stressor inducing both methemoglobinemia and hemolytic anemia. While physiologic doses of vitamin C act as a reducing agent, there are case reports that suggest supraphysiologic doses of vitamin C (30g or more) can act as an oxidizing agent. This mechanism is due to the production of hydrogen peroxide as a byproduct of ascorbic acid in high serum concentrations cycling between its ionized and radical forms, allowing hydrogen peroxide to oxidize hemoglobin and cause lipid peroxidation of the cell membrane leading to intravascular hemolysis[5].

It is worth noting that there is another case report similar to ours (but without the use of Vitamin C) where no known inducer of methemoglobinemia was identified and the authors discussed the possibility of COVID-19 acting as an oxidative stressor itself like that of other viral infections that produce reactive oxygen and nitrogen species[3]. Thus, it is also possible that the viral insult may have contributed to the development of this patient's methemoglobinemia.

Despite the unknown etiology of our patient's methemoglobinemia, this case emphasizes the importance of keeping a broad differential and recognizing the discrepancy between the patient's SpO_2, PaO_2, and clinical exam. It is imperative to recognize this abnormality and obtain an arterial co-oximetry panel once erroneous causes of this discordance are ruled out such as: poor probe positioning, hypothermia, and acrylic/painted nails. It also has important implications for the management of COVID-19, especially when considering treatments known to cause methemoglobinemia or trigger hemolysis in G6PD deficiency, like hydroxychloroquine and supraphysiologic doses of vitamin C.

KEY POINTS

- It is important to keep a broad differential for hypoxia in the setting of COVID-19 pneumonia and recognize discrepancies between SpO_2, PaO_2, and the clinical exam.
- It is imperative to recognize this abnormality and obtain an arterial co-oximetry panel once erroneous causes of discordance are ruled out such as: poor probe positioning, hypothermia, and acrylic/painted nails.
- Although vitamin C is a treatment for mild methemoglobinemia due to its reduction potential, it has been reported to be an oxidizing agent at supraphysiologic doses (>30 grams).

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