CASE REPORT

Blue Patient and Brown Blood: A Case Series

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Abstract

With several contradictory reports on the efficacy of hydroxychloroquine (HCQ) on COVID-19, the Indian Council of Medical Research (ICMR) recommended its use for prophylaxis and treatment of mild cases during the first wave of the pandemic. Amidst all the controversies, there have been a few cases reported of significant methemoglobinemia and hemolysis in COVID-19 cases being treated with HCQ. The diagnosis of methemoglobinemia amidst this COVID-19 crisis is really challenging owing to similar clinical manifestations. We present a case series where methemoglobinemia was promptly detected and managed efficiently, resulting in the uneventful discharge of all three cases. This is to be understood that undiagnosed cases of methemoglobinemia can be potentially fatal due to hypoxic stress on the body. If the condition is not being detected timely, leading to dangerous levels of untreated methemoglobinemia may cause a case of fatality falsely attributed to COVID-19. However, when the HCQ is not being used for COVID-19 presently, still clinicians must know different drugs that can cause methemoglobinemia and should promptly intervene to avoid any catastrophe.

Keywords: Ascorbic acid, COVID-19, Cyanosis, Hydroxychloroquine, Methemoglobinemia.

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Introduction

COVID-19 is the global challenge that we are facing at present. Lack of effective therapy has led to lots of experimentation with all sorts of medicines like antimalarials, antivirals, antihelminthic, antibiotics, etc. Some preliminary studies from China and France have shown that chloroquine and HCQ decrease the viral load and decreased the total duration of disease in COVID-19.[1,2] ICMR's initial recommendations for HCQ for chemoprophylaxis and treatment of mild to moderate COVID-19 cases were based on these studies.[3] But, a case-control study conducted by ICMR demonstrated a major reduction (>80%) in the odds of getting COVID-19 infection with the intake of more than four HCQ doses, and thus HCQ was an agent for prophylaxis and therapy in mild cases as per Indian guidelines during the first wave of the pandemic.[4] However, preliminary results from the RECOVERY trial and the SOLIDARITY trial have shown no reduction in mortality of hospitalized COVID-19 patients treated with HCQ.[5,6] Hence, HCQ is no longer recommended for prophylaxis or treatment. During the first wave of the pandemic when HCQ was being used, few cases have been reported showing significant methemoglobinemia and hemolysis in COVID-19 cases.[7,8] Due to impaired oxygen transport the clinical manifestations of methemoglobinemia range from cyanosis, breathlessness, altered sensorium, acidosis due to anaerobic respiration, and in severe cases coma and death.[9] Similar symptoms may represent clinical deterioration in COVID-19 cases requiring invasive ventilation. Thus diagnosing methemoglobinemia amidst this COVID-19 crisis is really challenging. This underestimation of actual incidences is further accentuated in resource-limited settings lacking CO-oximetry. Alternately, if the condition is not being detected timely, leading to dangerous levels of untreated methemoglobinemia causing case-fatality falsely attributed to COVID-19. We present a case-series where methemoglobinemia was promptly detected and efficiently managed.

Case 1

A 28-year-old female presented with complaints of high-grade fever with chills for five days and a history of contact with a COVID-19 positive case in the past 10 days. Her vitals were pulsed 78/min, BP 110/70 mm Hg, temp 100°F with the respiratory rate (RR) 26/min, and oxygen saturation (SpO_2) 96% on room air. Crepitations were present in the left lower zone on chest auscultation. Her initial investigations were hemoglobin (Hb) 7.1 g/dL, total leucocyte count (TLC) 7090/µL with 65% neutrophils, and platelets 2.74 lakh/µL. Her renal and liver function tests and urinalysis and electrocardiographic (ECG) were within normal limits (WNL) except for serum bilirubin 1.4 mg/dL (conjugated 0.5 mg/dL and unconjugated 0.9 mg/dL). Her chest X-ray (CXR) suggested of left lower zone pneumonia and arterial blood gases (ABG) showed pH 7.47, pO_2 72.9 mm Hg, pCO_2 35 mm Hg, bicarbonate-25.2 mmol/L. She was started on oxygen (O_2) by face mask, oral paracetamol, HCQ, and intravenous (IV) cefoperazone-sulbactam. On day 2 of admission, she became restless, agitated, and breathless with falling SpO_2 (85%). She was immediately intubated and kept on mechanical ventilation. Her immediate postintubation ABG showed pH 7.34, $PaCO_2$ 50 mm Hg, PaO_2 132 mm Hg [fraction of inspired oxygen (FiO_2) 100%], bicarbonate 26 mmol/L. Her COVID-19 RT-PCR, Typhidot, and malaria antigen test reports were negative. Her Hb further dropped to 5.6 gm/dL on day 4 of admission, for which two units of packed red blood cells (PRBC) were transfused. Her TLC increased to 17,540/µL with 84% neutrophils and worsening of CXR. Her endotracheal aspirate grew pseudomonas resistant

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to cefoperazone-sulbactam. She was switched on to piperacillin-tazobactam as per the sensitivity report and continued on lung-protective ventilation. Her serum bilirubin also increased to 3.5 mg/dL (conjugated 1.5 and unconjugated 2.0 mg/dL). Despite 100% FiO_2 her SpO_2 never exceeded >88% and surprisingly there was no effect of increasing positive end-expiratory pressure on oxygenation. Gradually the FiO_2 was titrated to 40%, accepting a target SpO_2 of 89% on day 3 of invasive ventilation (hospital admission day 5). Her ABG showed pH 7.42, pCO_2 40.6 mm Hg, pO_2 164 mm Hg (FiO_2 40%), bicarbonate 26.4 mmol/L. Despite improvement in her blood gases, her ABG sample was abnormally brownish in color. This allowed us to think retrospectively about methemoglobinemia and hemolysis possibly due to HCQ exposure. Her samples were sent for CO-oximetry and Glucose 6 Phosphate dehydrogenase (G6PD) activity estimation. Her methemoglobin (MetHb) value was 37.2% and G6PD was 25.8 U/gm Hb (high). Reticulocyte count was 2.5%, serum lactate dehydrogenase (LDH) 973 U/L and Hb electrophoresis showed normal peaks and no HbM. She was started on IV ascorbic acid 1.5 gm 6 hourly. She was extubated on day 5 of invasive ventilation and her MetHb levels showed a gradual decline. On day 12 of hospital admission, she was discharged on request at MetHb level of 10.3%. On a follow-up visit after 1 week, her MetHb level was 12.9%, G6PD activity was 18.8 U/gm Hb with serum bilirubin 1.4 g/dL without any symptoms. This suggested we to think of other causes of methemoglobinemia. Further work-up with genetic testing for cytochrome B5 reductase deficiency was planned but she didn't turn up for further follow-up visits.

Case 2

A 43-year-old man with no comorbidities presented with complaints of fever and cough for two days and a history of contact with a COVID-19 case. His vitals were pulse 92/min, BP 142/78 mm Hg, temp 102°F with RR 24/ min, and SpO_2 97% on room air. He was admitted and was started on oral paracetamol, azithromycin, and an HCQ regimen. His reports were Hb 14.3 g/dL, TLC 5800/µL with 84% neutrophils, and platelets 2.3 lakh/ µL. His renal and hepatic parameters, CXR, and ECG were WNL. His COVID-19 RT-PCR report was positive. On day 2 of admission, he became cyanosed with SpO_2 around 86–88 % which didn't improve on supplemental O_2. However, besides cyanosis, there were no other symptoms. His CXR was repeated and blood gases were analyzed. There was no worsening of CXR and ABG was also WNL, but SpO_2- PaO_2 mismatch was suspected with SpO_2 (88%) and PaO_2 183 mm Hg on O_2 @10 l/min by face mask and SaO_2 97% in ABG. This mismatch alerted us to possible methemoglobinemia and HCQ was stopped. His G6PD activity and MetHb levels were sent. G6PD activity was below 0.5 U/g of Hb and MetHb was 12%. He was given oral ascorbic acid 500 mg thrice daily. His cyanosis improved over the next two days and he was discharged on day 10 (repeat COVID-19 report negative).

Case 3

A 58-year-old diabetic man with a fever and COVID-19 positive report was admitted to our hospital. His vitals were pulsed 96/min, BP 136/76 mm Hg, RR 26/min, temp 99°F, SpO_2 96% on room air. His initial lab reports including CBC, liver and renal function tests, urinalysis, ECG, and CXR were WNL with HbA1c 6.8% and D-dimer 589 ng/mL. He was managed with oral hypoglycemics, paracetamol, azithromycin, and HCQ as per the regimen. On day 2, he became breathless and cyanosed with SpO_2 around 88–90% on room air. His saturation did not improve on oxygen @ 10 L/min by face mask. His ABG sample was abnormally muddy brown in color. His ABG showed pH 7.41 $PaCO_2$ 31 mm Hg, PaO_2 226 mm Hg, and SaO_2 99%. Because of our previous experiences, HCQ was stopped, IV ascorbic acid (500 mg TID) started and G6PD activity (qualitative) and MetHb (quantitative) levels were sent for estimation. G6PD activity was low and MetHb level was 17%. His TLC increased to 12,800/µL with 85% neutrophils and his CXR showed gradual worsening with the appearance of bilateral infiltrates on day 3. His O_2 requirement progressively increased with SpO_2 93% on a high flow nasal cannula (flow 45–60 L/min), and his cyanosis improved. He was started on IV remdesivir, cefoperazone, dexamethasone 6 mg OD, and subcutaneous low molecular weight heparin 0.6 mg OD. His oral hypoglycemics were switched to subcutaneous regular insulin. On day 8 of admission, his oxygen requirement decreased, requiring @ 8 L/min by face mask with the subsequent clearing of CXR. He was discharged on day 20 of admission when he was asymptomatic (repeat COVID–19 report negative) and MetHb level of 1.6%.

Discussion

Methemoglobinemia is a condition characterized by high blood MetHb content (normal <1.5%). MetHb is an oxidized iron state of normal Hb, ferrous to ferric, that lacks the O_2 and CO_2 transportation ability. Due to impaired O_2 transport, the clinical features of methemoglobinemia range from cyanosis, breathlessness, altered sensorium, and acidosis (due to anaerobic respiration) to coma and death.[9] Methemoglobinemia can be acquired or congenital. Congenital methemoglobinemia is due to cytochrome b5 deficiency of cytochrome b5 reductase deficiency, or due to abnormal Hb M.[10] Acquired methemoglobinemia is due to exposure to oxidizing agents, drugs like local anesthetics, sulfa drugs, chloroquine, and HCQ, especially in a susceptible population with G6PD deficiency.[11]

The first case of this case series might be a case of type 1 hereditary methemoglobinemia. Her two siblings died in infancy, however, she and her family denied any cyanosis which can be explained by her coexisting anemia. Completely normal infancy and very late presentation of hereditary methemoglobinemia have already been reported.[12] Being this condition rare in India as only eight cases has been detected till now.[13] Further workup was planned, but the patient did not turn up for subsequent visits. Her low Hb at presentation may have a wide range of possible causes. But the significant drop in Hb after admission and raised LDH definitely indicates some underlying hemolysis. Raised G6PD activity is also indirect evidence of immature RBCs coming into circulation. As she had already received two units of PRBC for anemia, hence commenting on peripheral blood smear or reticulocyte count is not justified.

Interestingly, we could not find any ECG changes in all the three patients treated with HCQ, which is a known side-effect of this drug. The most common ECG change associated with HCQ administration is QTc prolongation. However, it is usually not more than 450 ms and an overall increase of more than 60 ms was not observed.[14–16] A multicenter retrospective cohort study has shown a 7% incidence of clinically actionable ECG changes after HCQ administration.[17] Another observational study from India where HCQ was used as prophylaxis against COVID-19, has not shown abnormal QTc duration.[18]

All three cases might be just the tip of the iceberg. Because of the lack of CO-oximetry at several centers, the actual incidence of

methemoglobinemia after HCQ might be missing, especially in a country of 0–15% of the incidence of G6PD deficiency.[19] Prompt detection of methemoglobinemia and immediate discontinuation of HCQ was an important step in the management of these cases. Though routine screening for G6PD deficiency is not advisable and methemoglobinemia can happen in non-G6PD deficient persons also, as in cases of cytochrome b5 reductase deficiency (congenital methemoglobinemia).[13] In absence of CO-oximetry, simple validated color charts have been advocated for crude estimation of methemoglobinemia at the bedside, which will allow the clinician for appropriate decision making in resource-limited settings.[20] However, in a breathless desaturating patient, it is difficult to ascertain whether the arterial blood color change is due to true hypoxia (deoxygenated blood) or methemoglobinemia. Hence, there should be a high index of suspicion when there is a significant mismatch between arterial PaO_2 and SpO_2 by pulse oximetry. Classical cyanosis is not always observable in methemoglobinemia especially in cases of coexisting anemia, as was evident in our first case. Methylene blue has long been known as an antidote for methemoglobinemia, but it may be catastrophic in G6PD deficient patients.[21] Thus, this case series also shows that methemoglobinemia should be managed conservatively with ascorbic acid and avoiding methylene blue until G6PD levels are not available. More severe cases may require erythrocytapheresis or whole blood exchange.[22] However in a resource-limited setting, PRBC should be transfused cautiously avoiding fluid overload with diuretics. We should understand that undiagnosed cases of methemoglobinemia can be potentially fatal due to hypoxic stress on the body. With the daily increase in the number of COVID-19 cases and more and more people receiving HCQ, treating clinicians must be aware of this complication and its treatment. Hence, being clinically vigilant of the side-effects of the drug and their varied manifestations is a much-desired attribute for the clinicians at the bedside. Undiagnosed cases of methemoglobinemia can be potentially fatal due to hypoxic stress on the body. If the condition is not being detected timely, leading untreated lethal levels of methemoglobinemia may result in case-fatality falsely attributed to COVID-19.

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