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Methemoglobinemia: a potential confounder in COVID-19 respiratory failure

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INTRODUCTION

Methemoglobinemia is a state of excessive methemoglobin (metHb) in the blood which reduces oxygen-carrying capacity and hence tissue oxygen delivery. Most cases of methemoglobinemia are acquired from exposure to oxidizing agents. A metHb level > 30% can result in fatal hypoxia**.** We describe a case of methemoglobinemia (metHb level 41.6% (0.4-1.5%) in a patient with coronavirus disease 2019 (COVID-19) presenting with low peripheral oxygen saturation (SpO_2). The patient is a migrant worker in the construction industry, with exposure to industrial solvents. As > 90% of the cases of COVID-19 in Singapore have been diagnosed in migrant workers, most of whom work in construction, physicians need to be aware of other potential causes of a low SpO_2 in this group of patients.

CASE DESCRIPTION

Our patient is a 45-year-old Indian man who was admitted to the ICU in May 2020 with a fever and SpO_2 91% (95-100%) on room air. He lived in a dormitory and had been recently been diagnosed with COVID-19. He had no past medical history and he was not on chronic medications. Despite escalating oxygen therapy, his SpO_2 remained <92% (95-100%). An arterial blood gas (ABG) on a fraction of inspired oxygen (FiO_2) of 60% and a flow rate of 60 liters per minute on high-flow nasal cannula revealed chocolate-colored blood (Fig. 1), an arterial partial pressure of oxygen (PaO_2) 264mmHg (75-100mmHg) and SaO_2 100% (95-100%). He was of dark complexion and cyanosis was not immediately apparent to the clinicians in the emergency department. His chocolate-coloured blood and the stark discrepancy between SaO_2 and SpO_2 (the “saturation gap”) prompted us to perform co-oximetry, which revealed methemoglobinemia.

Fig. 1 Chocolate-colored blood on ABG

Despite a metHb level of 41.6% (0.4-1.5%), his serum lactate was 1.1mmol/L (0.5-2.2mmol/L). Biochemically there was no evidence of haemolysis (haemoglobin 17.5g/dL (13.6-16.6g/dL), haptoglobin 91mg/dL (36-200mg/dL) and LDH 432U/L (270-550U/L). As he was clinically stable and his glucose-6-phosphate dehydrogenase (G6PD) status was unknown, we treated him with 1.5g of intravenous ascorbic acid(AA) 6-hourly rather than methylene blue (MB). The patient was monitored with twice-daily co-oximetry and his oxygen therapy titrated according to his PaO_2. MetHb levels decreased to 13.3% (0.4-1.5%) over 48 hours, and AA was continued orally at 1g every 8 hours.

While the patient's metHb levels decreased, his PaO_2 also decreased from progression of COVID-19 pneumonia over the next 3 days. He did not receive any specific therapies for COVID-19. Furthermore, we ensured that hydroxychloroquine was not used in the treatment of COVID-19 in this patient because it could potentially worsen his methemolgobinemia.[1,2] Awake prone positioning strategies were applied and he did not require intubation. He was discharged from the ICU with a metHb level of 10.6% (0.4-1.5%).

Since the patient was asymptomatic despite significant methemoglobinemia and also had polycythaemia (hemoglobin17.5g/dL (13.6-16.6g/dL)), this pointed to a longstanding hypoxia resulting in an increase in haematopoiesis to improve oxygen carrying capacity of

blood. He was thus investigated for congenital methemoglobinemia. He had no family history of blood disorders, and haemoglobin electrophoresis was normal. However, we were unable to completely exclude a congenital cause as he declined genetic testing. His occupational history of a 15-year exposure to industrial solvents for waterproofing and polishing surfaces constitutes a risk factor for acquired methemoglobinemia.

DISCUSSION

Oxidative stress results in the conversion of hemoglobin to metHb, as heme iron is oxidized from the normal ferrous (Fe^{2+}) state to the ferric (Fe^{3+}) state. Ferric heme is unable to bind to oxygen, and also increases the oxygen affinity of the remaining ferrous hemes within the same haemoglobin molecule. Reduction in the oxygen-carrying capacity of blood results in a left-shift of the haemoglobin-oxygen dissociation curve – leading to hypoxia. In healthy individuals, several pathways (predominantly cytochrome b5 reductase) convert metHb back to haemoglobin, thus ensuring that metHb comprises only about 1% of total haemoglobin.

Methemoglobinemia can be congenital or acquired. Congenital methemoglobinemia is rare, but can be caused by cytochrome b5 reductase deficiency (most common), haemoglobin M disease, or cytochrome b5 deficiency. Most cases of methemoglobinemia are acquired from exposure to oxidizing substances. The most commonly implicated substances are local anaesthetics (e.g. benzocaine) and antibiotics (in particular dapsone).[3,4] However, nitrates and nitrites, as well as solvents and dyes like nitrobenzene and aniline (used in the painting and dye industries) have also been implicated.[5,6] Chronic dapsone use can also cause chronic haemolysis, thus patients with methemoglobinemia should be assessed for chronic haemolysis.

Symptoms of methemoglobinemia arise from tissue hypoxia. At metHb levels of 20%, patients may experience light-headedness and headache. At 30-50%, there may be confusion and loss of consciousness. MetHb levels $\geqslant$ 50% can cause seizures, dysrhythmias, coma, and

death.[7] However, patients with chronic methemoglobinemia usually have compensatory polycythemia and may be relatively asymptomatic (as seen in our patient).

A diagnosis of methemoglobinemia may be suspected with a low SpO_2 refractory to oxygen supplementation, chocolate-coloured blood, or a saturation gap. Standard pulse oximetry uses light-emitting diodes that absorb light at 2 wavelengths of 660nm and 940nm, and hence only provides an accurate measure of oxyhaemoglobin as a percentage of total haemoglobin in the absence of dyshaemoglobins (e.g. carboxyhemoglobin and metHb). The diagnosis of methemoglobinemia requires co-oximetry, which uses multiple wavelengths to distinguish percentages of oxyhaemoglobin, deoxyhaemoglobin, carboxyhaemoglobin, and MetHb.

Treatment of methemoglobinemia includes removal of the precipitating agent (if acquired), supplemental oxygen and other supportive measures. Administration of intravenous MB or AA in patients with severe symptoms and/or metHb levels > 30% may be required. MB works by acting as an electron carrier intermediate for the nicotinamide adenine dinucleotide phosphate hydrogen-metHb reductase pathway, an alternative pathway capable of converting metHb back to haemoglobin. MB is preferred because it acts rapidly. However, its use in patients with G6PD deficiency may precipitate haemolysis, and in patients taking serotonergic agents, MB can precipitate serotonin syndrome. AA also has reducing potential and is an alternative when MB is contraindicated. Patients should also be counselled on avoiding substances that can induce metHb formation.

The dominant respiratory feature of severe COVID-19 is arterial hypoxemia and a low SpO_2 or SaO_2.[8] COVID-19 pneumonia causes hypoxemia through ventilation/perfusion mismatch, shunt, and diffusion limitation. Methemoglobinemia decreases the oxygen-carrying capacity of blood. In combination, these can compromise oxygen delivery and cause fatal tissue hypoxia. This case highlights the possible discrepancy between SpO_2 and the arterial partial

pressure of oxygen/the arterial oxygen saturation. A low SpO_2 in the setting of normal/supranormal indices of oxygenation on the ABG should prompt the consideration of a diagnosis of methemoglobinemia, especially in patients with a history of exposure to industrial chemicals. This is especially important in Singapore, where migrant workers, many of whom are exposed to industrial chemicals, account for the vast majority (94%) of COVID-19 cases.[9] Thus, it should not be assumed that a low SpO_2 in such a patient is due to COVID-19 pneumonia alone.

In conclusion, methemoglobinemia is a rare but potentially life-threatening disease that typically presents with symptoms of tissue hypoxia. We report a case of methemoglobinemia in a patient with COVID-19, possibly secondary to industrial solvent exposure. There are similar reports of methemoglobenimia in COVID-19 patients, although these patients had received COVID-19 treatment agents. Singapore has experienced an outbreak of COVID-19 among migrant workers living in dormitories. As such, with a large population at risk of COVID-19 infection who are also exposed to industrial agents that potentially cause methemoglobinemia, both pathologies may arise in a single patient. Clinicians should thus be wary of premature diagnostic closure in patients with COVID-19, and be cognisant of other causes of a low SpO_2.

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