Case Report

A rare cause of acquired methemoglobinemia

Jahnavi Vurimi[1], Anirban Sarkar[2], N Fahim Abdullah[2], Komal Krishna Jayanth[3]

From [1]Post Graduate, [2]Associate Professor, Department of General Medicine, ESIC Medical College and PGIMSR, Bengaluru, Karnataka, [3]MBBS, Department of General Medicine, All India Institute of Medical Sciences, Rishikesh, India

ABSTRACT

Methemoglobinemia is a life-threatening clinical condition with a favorable outcome when diagnosed and treated promptly. It should be suspected in patients with oxygen saturation of around 85% that does not improve despite supplemental oxygen therapy. We report the case of a 48-year-old male with acquired methemoglobinemia due to the consumption of complementary alternative medicine (Ayurvedic medication for chronic kidney disease), who had a good outcome on treatment with Methylene blue. In refractory cases not responding to methylene blue, exchange transfusion is an effective alternative treatment.

Key words: Acquired methemoglobinemia, Alternative medicine toxicity, Drug-induced methemoglobinemia, Methylene blue, Refractory hypoxia

Methemoglobinemia is a rare disorder characterized by oxidation of the bivalent ion to the trivalent ion (ferrous to ferric form) in the hemoglobin molecule. Oxygen binds to hemoglobin in ferrous form [1]. This shifts the oxygen dissociation curve to the left, resulting in functional anemia without a reduction in hemoglobin concentration [1]. Some substances have the ability to maintain oxygen in ferric form, thus causing decreased oxygen binding capacity. There are two mechanisms in the body that reduces methemoglobin to hemoglobin. Cytochrome *B*5 reductase pathway (also called nicotinamide adenine dinucleotide [NAD]-dependent methemoglobin reductase) is the major pathway. The other mechanism is through NAD phosphate (NADPH)-dependent methemoglobin reductase, which requires a cofactor such as Methylene blue or riboflavin for activation. There are two types of methemoglobinemia. Methemoglobinemia type 1: Mostly asymptomatic, characterized by blue slate gray-like skin discoloration that does not improve on supplemental oxygen. It is present from birth and is rare. Methemoglobinemia type 2: Predominantly neurological manifestations, including microcephaly, hypotonia, growth retardation, choreo-athetoid movements, seizures, strabismus, and non-progression of psychomotor skills [2].

CASE REPORT

A 48-year-old male presented with complaints of fatigue, myalgia, and giddiness for 2 weeks. The patient has been a known case of diabetes mellitus and chronic kidney disease (CKD) with an estimated glomerular filtration rate of 54 mL/min/1.73 m^2 (stage 3A) for 12 years and 5 years, respectively. He had been consuming Ayurvedic medications for CKD for the preceding 20 days.

On examination, the patient had pallor but no cyanosis. Room air oxygen saturation was 86% while arterial blood gas (ABG) analysis showed a SaO_2 of 96%. Skin was slate-gray in color. Blood pressure was 90/60 mmHg. The patient had a drop in hemoglobin from 9 g/dL to 6.6 g/dL within 2 weeks with peripheral smear showing normocytic normochromic anemia with schistocytes, polychromatophils, and few spherocytes, target cells, and acanthocytes (Fig. 1).

Laboratory investigations of the patient are shown in Table 1. Due to a saturation mismatch, methemoglobinemia was suspected. The methemoglobin spot test was done (Fig. 2) and yielded positive results. Methemoglobin level was 10.4%.

The patient was treated with Methylene blue 1 mg/kg intravenous (IV) over 5 min. Patient improved clinically, and room air saturation increased to 96%. The patient was also advised to stop the Ayurvedic medication, after which no recurrence was observed.

DISCUSSION

Common drugs causing methemoglobinemia are (a) anesthetics: Benzocaine, lidocaine; (b) club drugs like cocaine, MDMA (ecstasy), gamma-hydroxybutyrate; (c) nitrates like nitroglycerin, inhaled nitric acid;

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Correspondence to: Jahnavi Vurimi, General Medicine, ESIC Medical College and PGIMSR, Bengaluru, Karnataka, India. E-mail: jahnavi.vurimi@gmail.com

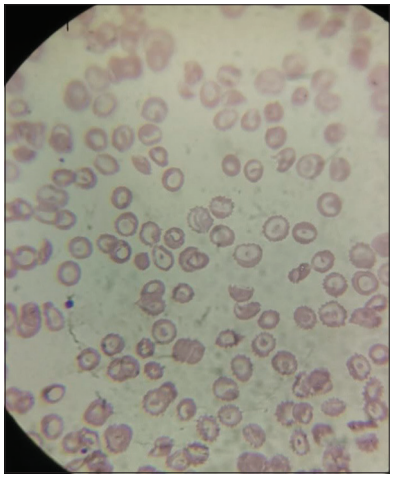

Figure 1: Peripheral smear of the patient

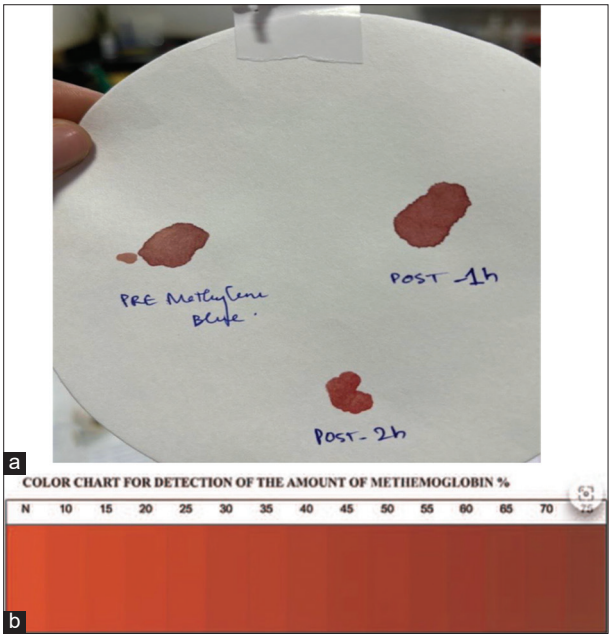

Figure 2: (a) Methemoglobin spot test, (b) Brown color chart for detection of the amount of methemoglobinemia

(d) fertilizers and herbicides; (e) metoclopramide and cyclophosphamide; (f) dapsone, rifampicin, and antimalarials; (g) nitrite-containing well water and manure oil; (h) infections such as *Escherichia coli*, *Klebsiella,* and *Pseudomonas*; and (i) laundry detergents, bathroom and kitchen cleaning agents, nail polish removers [3].

Pulse oximetry can be used for investigation as it measures light absorption at two wavelengths (oxy and deoxy hemoglobin) [2]. Co-oximetry measures light absorption at four wavelengths 600 nm (carboxyhemoglobin), 631 nm (methemoglobin), 660 nm (deoxyhemoglobin), and 940 nm [1]. Calculation of Saturation Gap - that is, the difference between the measured saturation in ABG and that in pulse oximetry. A difference of more than 5% may raise suspicion of methemoglobinemia [4]. Various factors can cause discrepancies between SpO_2 and SaO_2 readings. These include inadequate peripheral blood flow, variations in skin pigmentation, motion-induced interference, and blood-related conditions such as hemoglobin disorders, methemoglobinemia, and carboxyhemoglobinemia and sulfhemoglobinemia [3].

Table 1: Investigations of the patient

Investigations	Results
Direct Coombs test	Negative
Indirect Coombs test	Negative
Urine hemoglobin	Negative
LDH	600 U/L (high)
ANA	Negative
Complement protein C3	21.73 mg/dL (normal)
Complement protein C4	94 mg/dL (normal)
Haptoglobin	<20 mg/dL
Reticulocytes	13%
Hb electrophoresis	Negative
G6PD	15 U/g of hemoglobin (normal)
USG abdomen	Bilateral grade-2 renal parenchymal disease and no hepatosplenomegaly
Initial methemoglobin levels	10.4%
Methemoglobin levels after treatment	1.4%
pO_2	87.5 mmHg
SO_2	96.4%
pH	7.38

Clinical presentation of methemoglobinemia depends on percentage of methemoglobin levels [5]: (a) <10% - asymptomatic or mild symptoms - low pulse oximetry reading and alteration of skin color; (b) 10–30% - cyanosis and dark brown blood- confusion; (c) 30–50% - dyspnea, syncope, dizziness, confusion, chest pain, palpitations, and headache; (d) 50–70% - seizures, arrhythmia, delirium, coma; (e) >70% - death.

Treatment of methemoglobinemia is primarily based on supportive care and discontinuation of the drug or toxin. Definitive treatment involves the reduction of methemoglobin to the non-oxidized state using methylene blue. It is a cofactor of the enzyme NADPH-Methemoglobin reductase, which converts ferric to ferrous forms. Methylene blue accepts electrons from NADPH and forms leukomethylene blue which converts Fe^{3+} to $^{2+}$ ion [6]. It is indicated in symptomatic methemoglobinemia and when methemoglobin levels are between 10 and 30%. Methylene blue is a Monoamine Oxidase Inhibitor and can lead to the development of serotonin syndrome in interaction with other drugs [5]. The drug dose is 1–2 mg/kg IV over 5 min. Cyanosis resolves within 1 h of application. If there is a failure of response to 2 mg/kg, suspicion of G6PD deficiency arises. If there is rebound methemoglobinemia after 12 h, infusion can be considered. It is contraindicated in G6PD deficiency, where patients lack NADPH. Administration of methylene blue consumes available NADPH, causing decreased glutathione levels and thus hemolysis. The prominent side effect of methylene blue is that the risk of worsening of methemoglobinemia increases with repeated doses of methylene blue with toxic levels of methylene blue reached at a total dose >7 mg/kg [5]. It is due to the bioaccumulation of methylene blue, leading to the reversal of the reductive action. It is contraindicated

in pregnancy due to teratogenic concerns and possible intestinal atresia [5]. It should be cautiously administered in patients with renal failure and in anesthetized patients where it inhibits guanylate cyclase, decreasing nitric oxide-mediated vasodilatation, leading to systemic and pulmonary hypertension [5]. Other treatment modalities are: High doses of Vitamin C are considered (1.5-3 g IV every 6 h), and exchange transfusion may be attempted [7]. The role of N-acetyl cysteine remains unclear. Hyperbaric oxygen was tried in some case reports but there is no clear-cut indication [4]. Riboflavin (Vitamin B2) can be used in hereditary methemoglobinemia, which acts as an electron acceptor [5]. Therapeutic whole blood exchange led to a survival rate of 81.6% in patients refractory to methylene blue [8-10].

CONCLUSION

Methemoglobinemia is a life-threatening clinical condition with a favorable outcome when diagnosed and treated promptly. In refractory cases not responding to methylene blue, exchange transfusion is an effective alternative treatment.

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