CASE REPORT FROM THE EMERGENCY DEPARTMENT

A Case of Acquired Methemoglobinemia

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OBJECTIVE

While methemoglobinemia is a rare diagnosis, it is a potentially life-threatening condition.[1] The following case report of acquired methemoglobinemia emphasizes the importance of maintaining a wide differential diagnosis in patients presenting with refractory acute hypoxic respiratory failure, cyanosis, and topical lidocaine use. As part of the case presentation, the etiology, pathophysiology, and treatment of methemoglobinemia are reviewed.

CASE PRESENTATION

A 56-year-old male with a past medical history of essential hypertension, bicuspid aortic valve status post aortic valve replacement, chronic bronchitis, chronic cigarette abuse, and gastroesophageal reflux disease (GERD) presents to the Emergency Department (ED) with dizziness, headache, shortness of breath, and cyanosis. The patient reports he awakened to let his dog out the night prior to admission and felt dizzy and more short-of-breath than baseline. He and his wife have noticed his lips and fingers are purple, and he checked his pulse oximetry at home and found his level to be 70% on room air.

Upon arrival to the ED, his hypoxia is worse and he is placed on high-flow nasal cannula. He is tachycardic, dyspneic, and cyanotic.

A review of his history reveals he is compliant with prescribed inhaled corticosteroids and a long-acting beta-agonist, and has a therapeutic INR on Coumadin® one week before his presentation to the ED.

He relates that he has previously undergone hospitalizations for hypoxia, which improved with steroids and antibiotics. Of note, during the most recent admission, he required high-flow nasal cannula in the intensive care unit due to hypoxic respiratory failure and cyanosis after a syncopal event while in the garage with space heaters. A carbon monoxide level had been checked during that admission and was normal, yet it had been checked 24 hours after being hospitalized.

Although he is not on any newly prescribed medications, he reports that he has been using over-the-counter lidocaine patches, sometimes two or three at a time, over the past 8-12 months for chronic knee pain.

He works in landscaping but denies any recent significant exposures to unusual chemicals, nor illicit drug use. He has functioning carbon monoxide detectors in his home, and it is notable that his wife does not have similar symptoms. He has not recently traveled outside the area nor consumed well water. He smokes about 10 cigarettes per day and does not use oxygen at home.

The ED workup includes an elevated D-dimer at 0.82 µ/mL (normal ≤0.4 µ/mL), and an INR in the therapeutic range. Lactic acid is normal. Troponins are elevated at 38.33 ng/dL but a repeat check has no delta at 38.36 ng/dL. The initial EKG shows no significant changes from baseline. An ABG is normal for someone on supplemental oxygen, yet the respiratory therapist notes the blood is very dark in color, "almost the color of chocolate." A lactate level, to evaluate for cyanide poisoning, is negative.

A chest x-ray is negative for signs of acute heart failure or infection. A computed tomography (CT) angiogram had been completed six days prior and, because it was negative for any acute pathology, a repeat CT is not immediately repeated.

The carbon monoxide hemoglobin level is normal at 6% (normal for smokers is ≤7%), the oxyhemoglobin is low at 60.7% (normal range 90% to 99.9%), and the methemoglobin is elevated at 27.0% (normal range 0.0% to 1.5%).

After the ED team consults with Lehigh Valley Health Network toxicology, the patient is treated with a 2 mg/kg infusion of methylene blue. The patient's hypoxia, cyanosis, and shortness of breath rapidly improve (see Fig. 1), and a repeat methemoglobin completed approximately 60 minutes afterward is normal-

ized to 0.6%. The hospital medical team admits the patient for further evaluation and management with a request for consultation by a hematologist.

Given his complex past medical history of cyanotic and hypoxic episodes, glucose-6-phosphate dehydrogenase (G6PD) deficiency levels and cytochrome B5 reductase enzyme labs are sent to evaluate for congenital methemoglobinemia. A repeat echocardiogram (EKG) shows no new changes, and the patient maintains a stable pulse oximetry on room air with no new symptoms related to his chronic medical conditions.

While the congenital testing is pending, the suspected etiology of his methemoglobinemia is use of multiple lidocaine patches. He is advised to stop using lidocaine patches and is discharged to home in stable condition.

At his follow-up with a hematology service clinician, his G6PD and cytochrome B5 reductase enzyme levels are normal, ruling out common congenital etiologies.

DISCUSSION

While rare, methemoglobinemia is a potentially life-threatening condition if not treated promptly.[1] Methemoglobinemia is caused by an elevated level of methemoglobin in the blood, which diminishes the oxygen-carrying capacity of circulating hemoglobin. Hemoglobin's normal ferrous (Fe2+) state can be converted to the ferric (Fe3+) state by oxidizer agents such as lidocaine. This ferric species does not bind oxygen, decreasing the capacity to oxygenate tissues. Methemoglobin does occur in small amounts during routine delivery of oxygen to the tissue; in normal red blood cell function, levels are kept low through a reduction process utilizing the red blood cell enzyme cytochrome B5 reductase (Cyb5R).[2] Oxidizers can potentially diminish the natural reduction capacity of any individual.

Causes of methemoglobinemia can be congenital or acquired. Congenital methemoglobinemia most commonly is due to cytochrome B5 reductase deficiency, hemoglobin M disease, and G6PD deficiency.[1,3]

In acquired methemoglobinemia, exogenous substances increase the oxidation of hemoglobin to methemoglobin. Acquired methemoglobinemia can be due to use of dapsone, exposure to nitric oxide or nitrates in food or well water, or recreational inhalants like amyl or isobutyl nitrates. Another potential culprit is exposure to topical anesthetics such as benzocaine and lidocaine.[1]

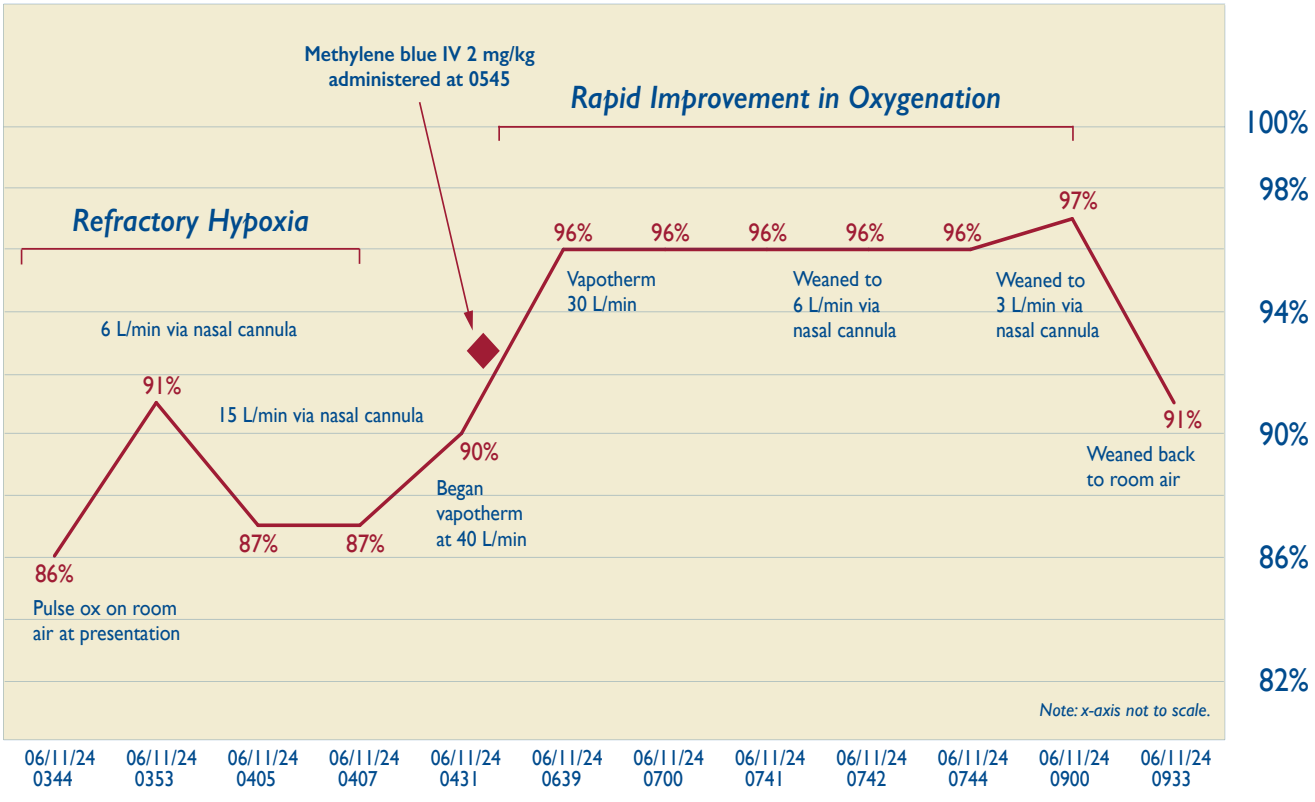

Fig. 1. Patient's pulse oximetry trend over time with methylene blue treatment.

Lidocaine has been commercially available for more than 70 years, and its potential as a cause of methemoglobinemia has been recognized for nearly as long.[4,5] Topical benzocaine use has dramatically decreased after being implicated as a cause of methemoglobinemia.[5]

Signs and symptoms of acquired methemoglobinemia are cyanosis, refractory hypoxia due to reduced oxygen binding capacity, dizziness, syncope, tachypnea, dark brown chocolate-colored blood, and death. Methemoglobin levels will be elevated.[6]

Treatment of acquired methemoglobinemia includes removal of the offending agent and supportive treatment with oxygenation. Methylene blue is the primary treatment of choice to decrease methemoglobin levels, as it can rapidly reduce hemoglobin from the ferric (3+) state back to the functional ferrous (2+) state. As demonstrated in this case, 2 mg/kg intravenously dosing is recommended[6]; rapid improvement of oxygen-binding capacity, and thus oxygen delivery to peripheral tissues, can occur.

Of note, caution must be taken with use of methylene blue in patients with G6PD deficiency, SSRI use, pregnancy, and renal failure. In G6PD deficiency, methylene blue may induce hemolysis and worsen methemoglobinemia, while methylene blue may precipitate serotonin syndrome in patients who are simultaneously using SSRIs. Methylene blue may also be teratogenic. An alternative option is ascorbic acid, but the reaction rate is slow and this agent may be ineffective when used alone.[6]

After administration of methylene blue, a follow-up methemoglobin level should be obtained 30-60 minutes later.[6]

CONCLUSION

Topical lidocaine is a valuable option for pain management as part of a multimodal treatment approach.[7] This case demonstrates that acquired methemoglobinemia is a rare but potentially life-threatening adverse condition to consider when evaluating a patient who presents with hypoxia and cyanosis.

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