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NEUTROPENIA, HYPOXIA, AND THE COMPLEXITIES OF EMERGENCY MEDICINE: A CASE OF DAPSONE-INDUCED METHEMOGLOBINEMIA

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☐ **Abstract—Background: Methemoglobinemia is a rare dyshemoglobinemia that can be difficult to diagnose due to its nonspecific symptomatology and infrequent occurrence. A number of commonly used medications have been known to contribute to this disease process that results in acute hypoxemia. Case Report: A 60-year-old man with history of acquired immunodeficiency syndrome presented to the Emergency Department (ED) with asymptomatic hypoxia. Supplemental oxygen proves to be ineffective in treating his low oxygen saturation. Numerous testing modalities are performed in the ED focused on an infectious versus pulmonary etiology prior to coming to the conclusion that the source is methemoglobinemia induced by dapsone therapy. Why Should an Emergency Physician Be Aware of This?: This article discusses the basic pathophysiology of the disease and the expected clinical findings. Patient outcome is correlated with prompt identification and discontinuation of the offending agents leading to the excessive accumulation of methemoglobin in the circulatory system. This makes it crucial that emergency providers know the symptomatology of the disease to facilitate appropriate treatment therapy. - Published by Elsevier Inc.**

☐ **Keywords—methemoglobinemia; dapsone; AIDs; acquired immunodeficiency syndrome; neutropenia; methemoglobin; methylene blue**

INTRODUCTION

Methemoglobinemia is a congenital or acquired functional anemia that causes an excess of methemoglobin (MetHb) to accumulate in the bloodstream. MetHb is produced when ferrous iron, found in heme, is oxidized into ferric iron, rendering the hemoglobin molecule incapable of carrying oxygen (1). In healthy individuals, a certain amount of MetHb is a normal byproduct of physiologic oxidative stress. When compensatory mechanisms fail to convert MetHb back to hemoglobin, the baseline concentration rises above 1%, leading to pathologic methemoglobinemia. Due to its inability to transport oxygen, tissue hypoxia and cyanosis are primary findings of the disease (2). Acquired methemoglobinemia is a consequence of toxin exposure, medications, or environmental conditions that accelerate the oxidative process. An extensive number of medications have been documented to potentiate methemoglobinemia. The most common medications include dapsone, phenazopyridine, nitrites/nitrates, lidocaine, and benzocaine (3).

Symptoms associated with methemoglobinemia vary based on methemoglobin concentration (Table 1). Many individuals remain asymptomatic or show minimal signs of cyanosis at MetHb levels up to 15% (4). Skin discoloration develops at levels near or exceeding 15%, these patients develop visible blue tinging most commonly to the nailbed, ears, and lips (4). As levels rise above 25%, patients may have symptoms of headache, altered mental status, and dyspnea consistent with acute hypoxia (5). Seizure activity, cardiac dysrhythmias, and fatality occur when the MetHb concentration surpasses 50% (6).

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Table 1. Stages of Methemoglobinemia

% MetHgb	Severity	Symptoms
< 2	Normal	None
2–15	Mild	None in healthy individuals*
15–30	Mild to moderate	Headache, fatigue, exercise intolerance
30–50	Moderate	Dizziness, syncope, confusion, dyspnea
> 50	Severe	Seizures, coma, dysrhythmias, acidosis, death

MetHgb = methemoglobin.
* Subjects with concomitant lung disease, sickle cell, or extremes of age may experience symptoms at lower levels.
Source (3): Taleb M, Ashraf Z, Valavoor S, Tinkel J. Evaluation and management of acquired methemoglobinemia associated with topical benzocaine use. Am J Cardiovasc Drugs 2013; 13:325–30.

CASE PRESENTATION

A 60-year-old white man with history of acquired immunodeficiency syndrome and chronic neutropenia, with a last known CD4 count of 81 per microliter, presented to the Emergency Department (ED) from his primary care office for findings of acute hypoxia. His oxygen saturation on room air in the clinic was measured at 87% by triage pulse oximetry. Notably, the patient was in the clinic for a follow-up appointment after being treated for pneumonia. The computed tomography of the chest from the month prior was positive for persistent lung infiltrates.

In the ED, the patient had no complaints. He was currently taking dapsone 100 mg daily for *Pneumocystis jirovecii* pneumonia prophylaxis and had been on this regimen for 3 years. His home medications also included abacavir-lamivudine, amlodipine, aspirin, cyanocobalamin, darunavir, docusate sodium, escitalopram oxalate, folic acid, mirtazapine, pregabalin, raltegravir, ritonavir, and tramadol. The patient reported compliance with his antiretroviral therapy. He was afebrile at presentation, temperature was 36.8°C, blood pressure was 143/73 mm Hg, heart rate was 75 beats/min, respiratory rate was 18 breaths/min, and SpO_2 84%. Physical examination revealed a cachectic male with a chronically ill appearance; the remainder of his examination was unremarkable. He was immediately placed on 15 L nonrebreather (NRB) 100% FiO_2 for hypoxia in the 80s. The patient remained awake and oriented with nonlabored breathing and spoke in complete sentences.

Initial arterial blood gas and co-oximetry on NRB was as follows: pH 7.45, pCO_2 31.3 mm Hg, pO_2 376 mm Hg, HCO_3 23, hemoglobin (Hgb) total 9.7 g/dL, OxyHgb 81%, MetHgb 18.7%, DeoxyHgb 1.1%, and CarboxyHgb 0.0%.

Lactate dehydrogenase was elevated at 335 U/L. The lactic acid and basic metabolic profile were within normal limits. Complete blood count with differential was significant for neutropenia and showed chronic pancytopenia. Electrocardiogram was negative for cardiac dysrhythmias or ischemia. Respiratory polymerase chain reaction was negative for viral etiology. The patient's recent infection with pneumonia, further complicated by his history of acquired immunodeficiency syndrome, led to a broad list of differential diagnoses. Chest x-ray study confirmed that there was not a large infectious consolidation, pleural effusion, or pneumothorax requiring immediate intervention. Computed tomography angiogram was negative for findings of subtle areas of consolidation not readily seen on chest x-ray study in addition to other cardiopulmonary emergencies such as pulmonary emboli or neoplasms.

The patient was weaned off NRB and placed on 2 L nasal cannula. A repeat physical examination demonstrated cyanosis of his nose, lips, and oral mucosa. He continued to be asymptomatic despite the cyanosis and showed no physical signs of respiratory distress. A repeat arterial blood gas and co-oximetry demonstrated pH 7.43, pCO_2 35.9 mm Hg, pO_2 127 mm Hg, HCO_3 24, Hgb total 10.3 g/dL, OxyHgb 79%, MetHgb 19.7%, DeoxyHgb 2.2%, and CarboxyHgb 0.0%. The respiratory therapist notified the provider of concerning findings of dark brown blood sample.

A methylene blue infusion was administered in the ED at 1 mg/kg; the patient tolerated it well without complications. Despite concerning laboratory results and comorbidities, the patient was cleared by the intensive care unit and deemed stable for admission to the medical-surgical floor. Dapsone was immediately discontinued upon admission and the patient was placed on atovaquone for *Pneumocystis jirovecii* pneumonia prophylaxis. His MetHb level decreased to 13.7% on day 2 of admission. Given the rapid decrease in MetHb, repeat levels were not drawn on subsequent days. The patient was observed until he was able to maintain an oxygen saturation above 95% while ambulating without supplemental oxygenation, indicating that MetHb was clearing from his system. He was weaned off oxygen and stable for discharge on day 6 of admission.

DISCUSSION

Oxygen deficiency in the blood results in its "chocolate brown" appearance, a clinical finding that is highly suggestive that MetHb levels are near or exceeding 15% (4). A hallmark finding of methemoglobinemia is a decrease in oxygen saturation that is out of proportion to the clinical presentation. This is the result of how pulse oximetry relies on the absorption of light wavelengths to calculate oxygenation levels. A pulse oximeter measures 2 wavelengths—660 nm and 940 nm—this data is then utilized to determine the ratio of oxyhemoglobin to

deoxyhemoglobin (6). MetHb absorbs light at both wavelengths, providing an inaccurately low reading that does not improve with supplemental oxygen (6). Pulse oximetry readings will plateau at approximately 85% SpO_2 regardless of increasing MetHb concentration levels (5). An arterial blood gas is commonly within normal range during the initial stage of the disease, and alone cannot be used as a diagnostic tool (1). Confirmation of methemoglobinemia is made through fixed-wavelength co-oximetry. It is the gold standard due to its ability to absorb multiple wavelengths of light, however, access is limited by cost and availability (2).

Identification and elimination of the source of methemoglobinemia is the primary and most critical step in treating the disorder. Patients with MetHb concentrations below 20% often will have spontaneous resolution without intervention; however, in cases where immediate reversal is needed, the most effective treatment has been found to be methylene blue. Intravenous administration of 1% methylene blue should be administered at 1–2 mg/kg over 5 min; the dose may be repeated if a dramatic decrease in MetHb is not seen within the first hour or if MetHb levels are moderate to severe at initiation of treatment (2).

It is important to note that methylene blue is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency due to increase in hemolysis and acceleration of methemoglobinemia (4). Other lesscommon side effects of methylene blue include mild bladder irritation, dizziness, headache, increased sweating, nausea, vomiting, abdominal pain, and diarrhea. Medical providers would benefit from being well versed in alternative treatment options in these rare instances, or in the case that methylene blue is not readily available. High-dose ascorbic acid has been found to reduce MetHb levels at a slower rate than methylene blue, but is an effective substitute. There is no conclusive dosing for ascorbic acid, however, studies have shown its success in reducing MetHb with intravenous infusion of 60 g/day over 6 h as well as 2 g/day (7,8). Other treatment options include activated charcoal, depending on the offending toxin and timing of exposure, hyperbaric oxygen, and exchange transfusion (1).

WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?

Emergency Medicine providers work in an area of contained chaos. We are responsible for primary assessment, identifying and treating life-threatening conditions, while simultaneously managing a number of critically ill patients. In the brief interview we have with our patients, we attempt to gather years of medical history in a matter of minutes and assemble a comprehensive emergent differential diagnosis. These factors make Emergency Medicine unique and challenging, and add a layer of complexity to diagnosing an uncommon condition.

The diagnosis of methemoglobinemia may be delayed in the ED, as the presence of hypoxia and signs of cyanosis often lead providers to primarily assess for pulmonary and cardiovascular etiologies. Given our patient's prior history of a pulmonary infection and immunocompromised state, the differential was broad, and a good example of how drug poisoning is not always at the forefront.

Our goal in presenting this case is that methemoglobinemia will be included in a differential when presented with symptoms of cyanosis, hypoxia, and darkened "chocolate color" blood samples. Despite being a drug-induced syndrome, it is unlikely that most providers will be able to diagnose the condition simply by reviewing a patient's medication list, as the number of possible offending agents is extensive. Identification of the condition is key, followed by withdrawing the causative agent and treatment with methylene blue or alternative therapies discussed previously.

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