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Clinical Case Study

A 70-Year-Old Man with Blue Skin

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CASE DESCRIPTION

A 70-year-old man with a history of hypertension, porcine aortic valve replacement, and chronic obstructive pulmonary disease began having dizziness and confusion. He had strange 1-word responses to his son, who took him to a hospital. A computed tomography scan was performed, showing a subarachnoid hemorrhage. There was no neurosurgeon at that hospital; therefore, the patient was transferred the next morning to our institution. The patient's son reported a remote history of falling and the patient hitting his head on a cabinet. The patient denied any headaches, nausea, vomiting, vision changes, or seizures, but he confirmed having a productive cough for the last 2 weeks for which he had been placed on levofloxacin. He smoked 1.5–2 packs of cigarettes a day. His physical examination showed no abnormal neurologic signs, and he was alert and oriented without acute distress. Laboratory tests revealed an increased white blood cell count, abnormal coagulation, and acute renal failure (Table 1). The patient received care and various medications (amiodarone, atorvastatin, azithromycin, benzocaine, citalopram, clonazepam, fluticasone, levalbuterol, metoprolol, and ropinirole) at admission to control his blood pressure, cough, throat pain, and subarachnoid hemorrhage.

Two days later (day 3), he developed fever (103.7 °F/39.8 °C) and atrial fibrillation, appeared very lethargic, and complained of mild shortness of breath, but he denied any chest pain, nausea, vomiting, or chills. His renal function had improved. His blood culture from the day of admission was positive for gram-positive cocci, and the physician was concerned for possible endocarditis. The patient was thus given vancomycin and cefepime, and he was scheduled for a transesophageal echocardiography (TEE)[2] procedure the next morning (day 4).

QUESTIONS TO CONSIDER

1. What clinical signs and laboratory results lead to a diagnosis of methemoglobinemia?
2. What can cause methemoglobinemia, and what was the cause for this patient?
3. What methods are available to measure Met-Hb?
4. How should patients with methemoglobinemia be treated?

The patient was treated with topical benzocaine spray before the TEE procedure. At the completion of TEE, the patient experienced respiratory failure, hypotension (87/48 mmHg), and decreased heart rate (57 beats/min), and he was noted to have a cyanotic appearance. The patient was awake and neurologically conversant, and he was able to follow commands. Arterial blood gas changes from day 3 to the morning of day 4 (2 draws that were 6 min apart) are shown in Table 2. Two heparin-containing syringe blood samples on day 4 had a dark-brown color, which was consistent with increased methemoglobin (Met-Hb) levels at 39.0% and 67.7% (reference interval, 0.0%–1.0%). The patient's pulse oximeter showed oxygen saturation at 77%. The patient's chest x-ray showed moderately enlarged heart size, atherosclerotic aorta, and minimal pulmonary vascular congestion, with no focal infiltrates or effusions.

DISCUSSION

Methemoglobinemia generally presents with signs of cyanosis and dark-brown colored arterial blood. Presenting clinical signs may correlate with the percentage of Met-Hb. Cyanosis occurs at 15%; anxiety, headache, and dizziness can occur at Met-Hb >20%; fatigue, confusion, and tachypnea can occur at 30%–50%; levels of >50% can be associated with arrhythmias, acidosis, seizures, and coma; and >70% is considered a lethal level *(1)*.

Met-Hb is a form of hemoglobin containing ferric ion (Fe^{3+}) oxidized from ferrous ion (Fe^{2+}). In this form the ability of hemoglobin to transport and deliver oxygen to tissues is disabled. In healthy individuals, methemoglobinemia is generally prevented by NADH-

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[2] Nonstandard abbreviations: TEE, transesophageal echocardiography; Met-Hb, methemoglobin, G6PD, glucose-6-phosphate dehydrogenase; O_2-Hb, oxygenated Hb; deoxy-Hb, deoxyhemoglobin; CO-Hb, carboxyhemoglobin; Po_2, O_2 partial pressure.

Table 1. Laboratory tests at admission.

Complete blood count (reference interval)		Coagulation (reference interval)		Basic metabolic panel (reference interval)	
White blood cells, $\times 10^9$/L (4.2–11.0)	15.2	Prothrombin time, s (9.4–11.4)	14.1	Na, mEq/L (135–150)	138
Red blood cells, $\times 10^{12}$/L (4.04–5.86)	4.54	Partial thromboplastin time, s (25.9–35.8)	30.1	K, mEq/L (3.5–5.0)	4.3
Hb, g/dL (13.0–17.3)	14.3	International normalized ratio (0.92–1.12)	1.31	Cl, mEq/L (100–109)	99
Hematocrit, % (34.0–45.0)	42.0			CO_2, mEq/L (24–32)	28
Mean corpuscular volume, fL (80–98)	92.5			Anion gap, mEq/L (7–15)	15
Mean corpuscular Hb, pg (27.0–34.0)	31.5			Blood urea nitrogen, mg/dL (7–18)	34
Mean corpuscular Hb concentration, g/dL (31.5–36.5)	34.0			Glucose, mg/dL (65–100)	117
Red cell distribution width–SD, fL (37.0–51.0)	48.6			Ca, mg/dL (8.6–10.7)	8.8
Platelets, $\times 10^9$/L (150–400)	109			Creatinine, mg/dL (0.8–1.5)	2.1
Mean platelet volume, fL (7.4–10.4)	11.6			Estimated glomerular filtration rate, $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$ (>90)	31

dependent cytochrome b5-Met-Hb reductase and, to lesser extent, NADPH-dependent Met-Hb reductase, which requires glucose-6-phosphate dehydrogenase (G6PD) *(2)*.

Causes of methemoglobinemia can be hereditary or acquired. One of the hereditary causes is cytochrome b5-Met-Hb reductase deficiency, an autosomal recessive condition. Methemoglobinemia may also arise in patients with congenital G6PD deficiency, but this occurs infrequently because the enzyme plays a minor role in maintaining the reduction state of hemoglobin compared to b5-Met-Hb reductase *(2)*. The acquired causes are mostly exposure to oxidizing toxins, including nitrates and chlorate compounds. Ash-Bernal et al. *(3)* reviewed 138 acquired methemoglobinemia cases, of which 42% were caused by dapsone, followed by benzocaine (4%) and primaquine (4%). The patient in this case was reported to have taken 1 benzocaine lozenge at admission due to his complaint of productive coughs despite taking the antibiotic levofloxacin for 2 weeks before his admission. He was then given benzocaine in a spray form to prepare for the TEE procedure indicated by the possible endocarditis from bacterial infections.

Table 2. Patient's arterial blood gas results on days 3 and 4.

Measurand (reference interval)	Day 3	Day 4, 11:07 AM	Day 4, 11:13 AM
pH (7.35–7.45)	7.48	7.36	7.38
Pco_2,[a] mmHg (35–45)	40.5	54.7	52
Po_2, mmHg (80–90)	56.9	82.1	274
O_2 saturation, % (95–100)	92	98.5	[b]
Base excess, mEq/L (−2 to 2)	6.02	3.8	[b]
Bicarbonate, mmol/L (21.0–28.0)	29.9	29.9	29.7
CO-Hb, % (0.0–1.4)	2.3	0.8	[b]
Met-Hb, % (0.0–1.0)	1.7	39.0	67.7
Hb, g/dL (14.0–18.0)	12.0	12.2	12.2

[a] Pco_2, carbon dioxide partial pressure.
[b] For the arterial blood gas sample on day 4 at 11:13 AM, O_2 saturation and base excess were not calculated as indicated by the instrument message; CO-Hb was not ordered for this sample.

Benzocaine is a local anesthetic commonly used as a topical pain reliever or in cough drops. As of March 2011, the Food and Drug Administration had received 21 case reports of methemoglobinemia from benzocaine application. Fifteen cases were in pediatric patients who had been administered a gel form of benzocaine for teething pain, and the rest were adult patients receiving the drug in a gel or liquid form to relieve toothache. Benzocaine is also used in a spray form in the settings of endoscopic procedures. Thirteen of 21 cases had reported Met-Hb percentages ranging from 4% to 70.4% (median 46%). In the literature, case reports of methemoglobinemia caused by benzocaine application rarely showed Met-Hb >45% *(4–5)*. Vallurupalli et al. *(5)* retrospectively studied methemoglobinemia as a complication of topical anesthetic sprays. They identified 9 out of 11 methemoglobinemia cases [mean (SD) Met-Hb, 40.8% (5.2%)] in their hospital caused by use of benzocaine spray during TEE procedures, and found that benzocaine caused more methemoglobinemia than lidocaine. More than 60% of 242

anesthetic-induced methemoglobinemia cases (highest Met-Hb recorded, 54.1%) were caused by benzocaine in another literature review *(6)*. The safety communications from the Food and Drug Administration suggested that the populations at highest risk for developing methemoglobinemia include infants <4 months old, elderly patients, and patients with congenital defects causing methemoglobinemia. The following health conditions also place individuals at great risk for methemoglobinemia: breathing problems (asthma, bronchitis, and emphysema), heart disease, active infection, anemia, and active smoking *(3)*. Our patient had many of these risk factors. At admission, the patient took 1 lozenge of benzocaine (15 mg) to control his productive cough and throat pain without developing methemoglobinemia. However, for a TEE procedure he was given benzocaine spray from a container with a concentration of 20 g benzocaine per 100 mL solution, which exceeded the amount in 1 benzocaine lozenge. We hypothesize that our patient's unusually high Met-Hb for adults (67.7%) may have resulted from the benzocaine spray given for the TEE procedure.

Met-Hb is usually measured by a multiwavelength oximeter that can directly measure different hemoglobin species, including oxygenated hemoglobin (O_2-Hb), deoxyhemoglobin (deoxy-Hb), and carboxyhemoglobin (CO-Hb). The instrument can thus derive the fraction of Met-Hb [Met-Hb/(O_2-Hb + deoxy-Hb + CO-Hb + Met-Hb)] and oxygen saturation [O_2-Hb/(O_2-Hb + deoxy-Hb)]. At the bedside, noninvasive pulse oximeters are generally used to estimate oxygen saturation. These oximeters typically use 2 wavelengths (660 and 940 nm) to measure only O_2-Hb and deoxy-Hb and to calculate oxygen saturation by the same definition as the multiwavelength oximeter in a blood gas instrument. In conditions of methemoglobinemia, the Met-Hb interferes at both wavelengths and falsely lowers oxygen saturation. When the Met-Hb fraction is above 30%, oxygen saturation measured by pulse oximeter plateaus at about 85% and cannot be corrected by administration of oxygen, which is another clue for diagnosing methemoglobinemia. The condition can also be diagnosed by determining the oxygen saturation gap (the oxygen saturation difference between the multiwavelength oximeter and pulse oximeter) *(2)*. O_2 partial pressure (P_{O_2}) is measured by amperometry on the blood gas instrument and should not be affected by the hemoglobin status. In this case, the P_{O_2} was 274 mmHg, reflecting hyperoxygenation status, and did not correlate with the pulse oximeter oxygen saturation at 77%.

The first-line treatment for methemoglobinemia in asymptomatic patients with relatively low Met-Hb is to remove the causative agents and wait for chemical reduction of methemoglobin to hemoglobin by NADH-Met-Hb reductase. Methylene blue treatment should be considered in symptomatic or asymptomatic patients with high Met-Hb. This drug can accelerate the hemoglobin reduction process through the NADPH-dependent G6PD pathway. This mechanism is not effective for patients who have a genetic defect of G6PD, and methylene blue can be dangerous to these patients, because it can increase risk of hemolysis and even rebound methemoglobinemia. This occurs due to the decreased NADPH production in G6PD deficiency, leading to inefficient reduction of methylene blue to leukomethylene blue and thereby Met-Hb conversion to hemoglobin *(7)*. G6PD deficiency is prevalent in the US among the African-American and Middle Eastern population and should be recognized *(8)*. Moderate doses of ascorbic acid may be given to treat methemoglobinemia in these patients.

POINTS TO REMEMBER

- Signs of methemoglobinemia include cyanosis that remains unresolved with oxygen supplementation, dark-brown arterial blood even after exposure to air, an oxygen saturation gap, very high oxygen partial pressure, and increased Met-Hb.
- The Evelyn–Malloy test and spectrophotometry resolving Met-Hb and methylene blue are methods to confirm the presence of increased Met-Hb. Multiwavelength oximetry available in many blood gas instruments is the most commonly used method in the clinical laboratory to measure both Met-Hb and oxygen saturation. Noninvasive pulse oximeters used at the bedside provide measures of oxygen saturation but can be misleading in cases of methemoglobinemia in which the low values of oxygen saturation reported by these instruments cannot be improved by oxygen supplementation.
- Causes of methemoglobinemia may be either hereditary or acquired. The acquired causes are primarily related to exposure to oxidizing toxins, such as benzocaine, a commonly used local anesthetic available in gel, liquid, cream, and aerosol forms. Such agents should be used with caution in patients at high risk of drug-induced methemoglobinemia, including active smokers, pediatric and elderly individuals, and G6PD-deficient patients.
- When methemoglobinemia is diagnosed, causative agents should be removed. Methylene blue can help accelerate the hemoglobin chemical reduction process, but this drug is ineffective and dangerous for G6PD-deficient patients. Ascorbic acid can be used as an alternative therapeutic agent.

Results of Met-Hb measurement by cooximetry should be carefully interpreted when methylene blue is administered, because methylene blue has a high absorption at the wavelength at which Met-Hb is determined. An Evelyn–Malloy test can be used as a confirmatory method to measure Met-Hb. The principle of the test is to add cyanide to bind with Met-Hb, which eliminates the absorption at 630–635 nm *(9)*. The amount of absorption elimination is proportional to the Met-Hb. An alternative confirmatory broadband diffuse optical spectroscopy method has also been developed by including methylene blue spectroscopic features into the deconvolution algorithm to improve Met-Hb absorptive resolution *(10)*.

The patient in this case was treated with methylene blue by intravenous injection, and his Met-Hb decreased to 5.1% within 3 h and was 1.9% the next morning. The patient recovered from bacteremia, became afebrile, and was discharged on day 10.

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Commentary

Sahar S. Abdelmoneim,[1,2] Sunil Mankad,[1] and Sharon L. Mulvagh[1]*

Shu et al. illustrate a case of potentially life-threatening acquired methemoglobinemia resulting from exposure to benzocaine-containing topical anesthetics. Methemoglobinemia occurs when red blood cells contain >1% Met-Hb. Benzocaine acts as an indirect oxidant of the hemoglobin, resulting in Met-Hb which is incapable of carrying oxygen to tissues.

Beyond the inciting benzocaine exposure, it is likely that the patient in this case had multifactorial predisposition for the development of acquired methemoglobinemia because of risk factors including prior intake of a medication accelerating the formation of Met-Hb (the antibiotic levofloxacin), a recent topical exposure to benzocaine (cough drop lozenges), and pharyngeal mucosal injury, accelerating benzocaine absorption. His septic condition also increased the risk of methemoglobinemia. Indeed, the arterial blood gas before the TEE already demonstrated slightly increased Met-Hb levels of 1.7%.

Key observations include the presence of cyanosis with absent cardiopulmonary symptoms, cyanosis unresponsive to oxygen, a saturation gap of >5%, and chocolate-colored blood, which should alert the astute clinician to the possibility of an intraerythrocytic Hb abnormality *(1)*. The diagnosis should be confirmed by an FDA-cleared cooximeter. The initial therapeutic goal is to improve oxygen delivery with assisted ventilation. The treatment of choice is low-dose methylene blue (1–2 mg/kg of 1% solution intravenously over 5 min), which restores the oxygen-carrying capacity of hemoglobin. Moderate doses of ascorbic acid (300–1000 mg/day orally) are recommended if methylene blue is contraindicated. In our TEE practice, we have stopped using benzocaine spray in favor of using a topical lidocaine 5% oral ointment, 1 inch, which is ap-

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