CHEST

A 77-Year-Old Woman With Capillary Hypoxia and Perioral Cyanosis

Daniel Z. Hodson, MD; Giuliana G. Repetti, MD; Daniel T. Hoesterey, MD; Yejoo Jeon, MD; Kinan Bachour, MD; Roberto L. Mempin, MD; Tisha S. Wang, MD; and Michael Levine, MD

CASE PRESENTATION: A 77-year-old woman with asthma, hypothyroidism, irritable bowel syndrome, overactive bladder, and multiple rheumatologic conditions was sent from the clinic to the ED for evaluation of hypoxia. In the clinic, she reported dizziness without shortness of breath and was noted to have perioral cyanosis with an oxygen saturation measured by pulse oximetry (Spo_2) of 80%. She was given a nonrebreather mask delivering oxygen at 8 L/min, but the Spo_2 remained at 77% to 82%. In the ED, the patient reported intermittent shortness of breath, 2 to 3 days of mild left lower extremity swelling, and a brief episode of lightheadedness earlier in the day that had since resolved. She denied fevers/chills, upper respiratory symptoms, and chest pain. She had been referred to the pulmonology clinic 3 years earlier to evaluate mild hypoxia with Spo_2 readings in the low 90% range, but pulmonary function testing failed to identify an etiology. There was no history of VTE. Her rheumatologic conditions included osteoarthritis, rheumatoid arthritis, Sjögren's syndrome, and fibromyalgia.

CHEST 2022; 162(6):e295-e299

Physical Examination Findings

On arrival to the ED, the patient's initial vital signs revealed a heart rate of 70 beats/min; BP, 150/79 mm Hg; respiratory rate, 18 breaths/min; and an Spo_2 of 81% while receiving oxygen through a nonrebreather mask at 15 L/min. On initial examination by the medical ICU team, she was again noted to have perioral cyanosis and a grayish hue to her fingertips without clubbing. Pulmonary examination, completed with the patient received oxygen via a high-flow nasal cannula at 60 L/min with an Fio_2 of 100%, revealed a respiratory rate of 16 breaths/min and symmetric vesicular breath sounds bilaterally without any adventitious breath sounds. Her Spo_2 remained consistently in the mid-80% range during the interview and examination, and she was not in distress. She had minimal lower extremity edema, with the left lower extremity appearing slightly larger than the right lower extremity. The remainder of the examination yielded unremarkable results. The patient's venous blood appeared darker than the venous blood of a healthy control subject (Fig 1), and an arterial blood sample was also noted to be abnormally dark (Fig 2).

Diagnostic Studies

The CBC was notable for hemoglobin (11.8 g/dL), whereas the basic metabolic panel results were unremarkable. Arterial blood gas was notable for a pH of

AFFILIATIONS: From the Division of Internal Medicine-Pediatrics (D. Z. H.), the Department of Medicine (G. G. R., Y. J., and K. B.), the Division of Pulmonary and Critical Care Medicine (D. T. H., R. L. M., and T. S. W.), and the Department of Emergency Medicine (M. L.), David Geffen School of Medicine at the University of California Los Angeles, Los Angeles, CA.

CORRESPONDENCE TO: Daniel Z. Hodson, MD; email: dhodson@mednet.ucla.edu

DOI: https://doi.org/10.1016/j.chest.2022.06.006

Figure 1 – *Venous blood. Several hours after blood was drawn, the patient's venous blood (right) was darker than the venous blood (left) of a healthy control subject.*

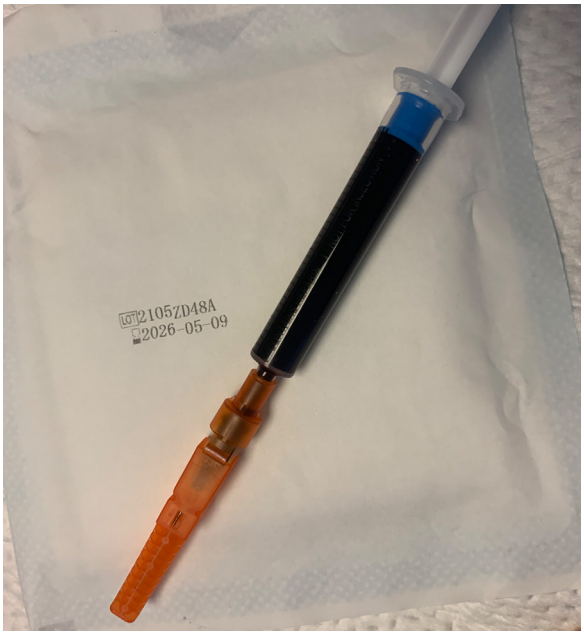

Figure 2 – *Arterial blood. The patient's arterial blood drawn for repeat arterial blood gas analysis was remarkably dark.*

7.58; $Paco_2$, 24 mm Hg; and Pao_2, > 500 mm Hg while receiving oxygen via a high-flow nasal cannula at 60 L/min with an Fio_2 of 100%. Single-view portable chest radiography and transthoracic echocardiography with bubble contrast produced unremarkable results. A chest CT angiogram with contrast did not indicate pulmonary embolism and showed only mild atelectasis and inflammatory changes consistent with her known asthma. Mass spectrometry did not reveal any evidence of hemoglobin variants.

The patient's cyanosis and the discrepancy in oxygen saturation, as measured by pulse oximetry and blood gas analysis, were concerning for methemoglobinemia. Thorough medication reconciliation (Table 1) revealed intermittent phenazopyridine use over several years, and the patient had recently restarted this medication approximately 3 days before presentation. A blood sample was sent to the laboratory for CO-oximetry testing, but unfortunately, the results could not be reported because of the presence of an interfering substance. The team therefore decided to proceed with administration of methylene blue for empiric treatment of suspected methemoglobinemia.

Unfortunately, the patient also reported current use of duloxetine and ginkgo biloba, so there was concern

TABLE 1] Active Medications at the Time of Presentation

Route	Medication
Oral	Azathioprine
	Carisoprodol
	Colchicine
	Duloxetine
	Estradiol
	Ginkgo biloba
	Levothyroxine
	Meclizine
	Meloxicam
	Mirabegron
	Multivitamin
	Oxycodone
	Phenazopyridine
	Pilocarpine
	Polyethylene glycol
	Rizatriptan/sumatriptan
	Upadacitinib
Inhaled	Albuterol
	Fluticasone
Topical	Diclofenac gel

for inducing serotonin syndrome with concurrent use of methylene blue and agents that inhibit serotonin reuptake. A trial of IV vitamin C was thus initiated first, without improvement in the patient's Spo_2. After discussion of the risks and benefits with the toxicology service and the patient, methylene blue treatment was initiated the next morning. The patient received IV methylene blue at 1.5 mg/kg without improvement, followed by an additional 1 mg/kg, also without improvement. The lack of improvement argued against methemoglobinemia as the culprit for her hypoxia. On further discussion with the laboratory, it was determined that the interfering substance precluding reporting of the CO-oximetry results was suggestive of the presence of sulfhemoglobin, but available equipment did not have the ability to confirm. Send-out testing for sulfhemoglobin by spectrophotometry was performed, and the sulfhemoglobin level was later reported at 20.0% (reporting limit, 2.0%).

What is the diagnosis?

Diagnosis: Sulfhemoglobinemia, likely secondary to phenazopyridine use

Discussion

Sulfhemoglobin is an abnormally altered hemoglobin molecule with a green pigment, and reports of sulfhemoglobinemia date back to the very beginning of the twentieth century. Sulfhemoglobinemia is a rare entity, and there are no estimates of population-level incidence in the literature. Early reports from the first half of the twentieth century linked sulfhemoglobinemia to nitro and amino compounds, specifically several compounds since removed from the market, including acetanilid and phenacetin (also called acetophenetidin). More recently, sulfhemoglobinemia has been associated with phenazopyridine, modern sulfonamides such as trimethoprim-sulfamethoxazole, dapsone, and metoclopramide, as well as toxins such as hydroxylamine sulfate. A list of implicated drugs was recently published by Rangan et al.

Normal hemoglobin is composed of globin molecules and a heme group, which contains an iron molecule surrounded by a porphyrin ring. The iron usually exists in the reduced (Fe^{2+}) state, and oxidative stress can oxidize iron from the reduced to the oxidized state (Fe^{3+}) to produce methemoglobinemia. Sulfhemoglobin results when a sulfur atom becomes incorporated into the porphyrin ring. Some offending agents may themselves contain sulfur, but hydrogen sulfide-producing gut flora or glutathione may serve as the sulfur source in some patients.

The presentation is dominated by cyanosis and fatigue without dyspnea. In 1907, West and Clarke described a 37-year-old woman with a "leaden hue, resembling in tint that of silver staining, which made her look when asleep as if she was moribund." In 1948, Finch noted that normal whole blood becomes bright red over time as the hemoglobin molecules bind oxygen, and a persistent dark shade suggests a dyshemoglobinemia. By the mid-twentieth century, it was known that sulfhemoglobin causes cyanosis at a much lower concentration (only 0.5 g/dL) compared with methemoglobin (1.5 g/dL) and deoxyhemoglobin (5.0 g/dL). Notably, patients do not usually exhibit signs of respiratory distress, and the results of cardiopulmonary examination are classically unremarkable. When the microbiome is involved in the generation of sulfur, constipation may be another presenting symptom.

Differentiation of methemoglobinemia and sulfhemoglobinemia is notoriously difficult. Pulse oximetry measures absorbance at 940 nm, which corresponds to oxyhemoglobin, and at 660 nm, which corresponds to deoxyhemoglobin. Methemoglobin absorbs equally well at the two measured wavelengths and therefore yields a consistent, artificially low Spo_2 reading. Absorbance by sulfhemoglobin is highest at approximately 620 nm and therefore also produces an artificially low saturation reading. Most CO-oximeters detect oxyhemoglobin, deoxyhemoglobin, carboxyhemoglobin, and methemoglobin, and therefore some CO-oximeters may erroneously report cases of sulfhemoglobinemia to be methemoglobinemia or, as occurred in this case, interference caused by sulfhemoglobin may be reported. Spectrophotometry can confirm and quantify the presence of sulfhemoglobin. Importantly, sulfhemoglobinemia does not respond to methylene blue, so a presumptive diagnosis can be made in suspected cases of methemoglobinemia/sulfhemoglobinemia that do not respond to methylene blue.

Two factors explain the more benign course of sulfhemoglobinemia compared with methemoglobinemia. First, whereas carboxyhemoglobin and methemoglobin shift the hemoglobin dissociation curve to the left and can therefore lead to dissociative shock and death due to the inability to offload oxygen in local tissue, sulfhemoglobin shifts the hemoglobin dissociation curve to the right. Second, it is unusual to have $>$ 25% to 50% of hemoglobin-binding sites affected by sulfur binding, whereas all oxygen-binding sites can be affected by either carbon monoxide (resulting in carboxyhemoglobin) or oxidation (resulting in methemoglobin). However, the oxidative stress itself in cases of sulfhemoglobinemia can result in severe hemolytic anemia. Sulfhemoglobin molecules persist for the duration of the life of the affected erythrocyte (up to 120 days), and there is no specific antidote. Management hinges on removal of the offending agent, and blood transfusions may be used to increase the overall oxygen-carrying capacity, and therefore overall oxygen content, of the blood in critically ill patients.

Clinical Course

In the medical ICU on hospital day 2, the patient received 2 units of packed RBCs for a hemoglobin level of 10.4 g/dL. The patient remained clinically stable without chest pain or shortness of breath during the 72-h hospitalization. Spo_2 remained 77% to 90% regardless of the degree of supplemental oxygen used. She remained ambulatory and at her physical baseline. The patient was advised to avoid

phenazopyridine, to stop all supplements, and to slowly reintroduce the most important supplements in discussion with her primary care physician. Eight to 10 weeks after discharge, the patient's sulfhemoglobin level had decreased to 6.1%, she was back to baseline with an Spo_2 of 95% to 96%, and her caregiver reported her cyanosis had resolved.

Clinical Pearls

1. *Cyanosis with a benign cardiopulmonary examination and a saturation gap between oxygen saturation as measured by pulse oximetry (Spo_2) and the Po_2 as measured by arterial blood gas analysis (Pao_2) should raise suspicion for dyshemoglobinemias.*
2. *When hemoglobin structure is altered, the oxygen saturation as measured by pulse oximetry is not accurate.*
3. *Knowledge of the local laboratory's capacity for CO-oximetry is crucial to understanding which hemoglobin alterations will be directly reported and which will be reported as interference.*
4. *Methemoglobinemia remains both more common and more dangerous than sulfhemoglobinemia.*
5. *There is no specific therapy for sulfhemoglobinemia aside from removal of the offending agent, and the condition does not respond to methylene blue. Blood transfusion can be used to augment the oxygen-carrying capacity in critically ill patients.*

Acknowledgments

Financial/nonfinancial disclosures: None declared.

Other contributions: *CHEST* worked with the authors to ensure that the Journal policies on patient consent to report information were met.

Suggested Readings

West S, Clarke TW. Idiopathic cyanosis due to sulph-hæmoglobinæmia: enterogenous cyanosis. *Med Chir Trans*. 1907;90:541-562.

Finch CA. Methemoglobinemia and sulfhemoglobinemia. *N Engl J Med*. 1948;239(13):470-478.

Brandenburg RO, Smith HL. Sulfhemoglobinemia; a study of 62 clinical cases. *Am Heart J*. 1951;42(4):582-588.

Park CM, Nagel RL. Sulfhemoglobinemia. *N Engl J Med*. 1984;310(24):1579-1584.

Lu HC, Shih RD, Marcus S, Ruck B, Jennis T. Pseudomethemoglobinemia: a case report and review of sulfhemoglobinemia. *Arch Pediatr Adolesc Med*. 1998;152(8):803-805.

Aravindhan N, Chisholm DG. Sulfhemoglobinemia presenting as pulse oximetry desaturation. *Anesthesiology*. 2000;93(3):883-884.

Gopalachar AS, Bowie VL, Bharadwaj P. Phenazopyridine-induced sulfhemoglobinemia. *Ann Pharmacother*. 2005;39(6):1128-1130.

Askew SW, Baranoski GVG. On the dysfunctional hemoglobins and cyanosis connection: practical implications for the clinical detection and differentiation of methemoglobinemia and sulfhemoglobinemia. *Biomed Opt Express*. 2018;9(7):3284-3305.

Morales A, Walsh R, Brown W, Checinski P, Williams SR. Case report: phenazopyridine-induced sulfhemoglobinemia in an 83-year-old presenting with dyspnea. *J Emerg Med*. 2021;61(2):147-150.

Rangan A, Savedra ME, Dergam-Larson C, et al. Interpreting sulfhemoglobin and methemoglobin in patients with cyanosis: an overview of patients with M-hemoglobin variants. *Int J Lab Hematol*. 2021;43(4):837-844.