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Case Report

Simultaneous Methemoglobinemia and Hemolytic Anemia Related to Trimethoprim-sulfamethoxazole and Phenazopyridine

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ABSTRACT

Background: Methemoglobinemia manifests with cyanosis but no respiratory distress. Many substances implicated in methemoglobinemia also are known to cause either drug-induced hemolysis or oxidative stress on erythrocytes, leading to hemolysis. This case report described a patient presenting acutely with both cyanosis and jaundice.

Case Presentation The patient is a 76-year-old female with a history of chronic obstructive pulmonary disease and a recently diagnosed urinary tract infection (UTI) who presented to the emergency department with urinary frequency and dysuria. She had recently been started on trimethoprim-sulfamethoxazole (TMP-SMX) and phenazopyridine for her UTI. On physical exam, she had both cyanosis and jaundice, giving her skin a dull, gray color. She had hypoxia to 75% oxygen saturation, which did not remarkably respond to supplemental oxygen. She also had hyperbilirubinemia and anemia. Laboratory errors confounded the evaluation; however, there was high concern for methemoglobinemia, and empiric treatment was initiated. Methemoglobinemia was later confirmed and the patient improved, although she required multiple blood transfusions. After removing the offending agents, treating the methemoglobinemia, and providing supportive care for her hemolytic anemia, she improved and was discharged home.

Conclusion: Although methemoglobinemia has a classic presentation of cyanosis without respiratory distress, additional coincident pathologies can easily confuse the clinical picture. Understanding the pathophysiology of methemoglobinemia is key to understanding why our patient also developed hemolysis. When cyanosis and jaundice are both present, simultaneous management of methemoglobinemia and hemolytic anemia may be needed. Special attention to glucose 6-phosphate dehydrogenase status is required in these circumstances to avoid patient harm with methylene blue.

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Introduction

Methemoglobinemia is an uncommon diagnosis with a puzzling presentation of cyanosis without respiratory distress [1-3]. Jaundice, alternatively, represents hyperbilirubinemia, which can be secondary to numerous pathologies involving bilirubin excretion or processing either intravascularly or within hepatocytes. Many substances implicated in methemoglobinemia also are known to cause either drug-induced hemolysis or oxidative stress on erythrocytes, leading to hemolysis. This can happen in patients regardless of their glucose 6-phosphate dehydrogenase (G6PD) status, an important mechanism of cellular protection from oxidative stress [4]. This case report described a patient presenting acutely with both cyanosis and jaundice.

Case Presentation

The patient is a 76-year-old female with a recently diagnosed urinary tract infection (UTI), chronic obstructive pulmonary disease with no need for chronic supplemental oxygen and hypothyroidism who was presenting to the emergency department with urinary frequency and dysuria. She had recently been started on trimethoprim-sulfamethoxazole (TMP-SMX) and phenazopyridine for her UTI three days before referral. She denied fever, nausea, shortness of breath, cough, chest pain, abdominal pain, or any other symptoms of systemic illness.

On initial physical exam, her color was a mix of jaundice and cyanosis, giving her skin a dull gray appearance. Her daughters agreed that her color was "off" but were not sure if this happened over the course of days or hours. The patient was in no distress and resting comfortably in the bed. Her initial vital signs showed a respiratory rate of 18 bpm, heart rate of 78 bpm, blood pressure of 127/59 mm Hg, body temperature of 98.2°F, and an oxygen saturation of 72%. She was escalated to 15 L/min oxygen flow through a non-rebreather mask with an improvement of her oxygen saturation to 75%.

The patient did not exhibit any respiratory symptoms and was clinically stable. However, due to her history of COPD and the emergence of new hypoxia, she received a nebulizer treatment containing 5 mg of albuterol and 0.5 mg of ipratropium, but her oxygen saturation did not improve. Subsequently, she was placed on high-flow nasal cannula therapy with humidification and heating, at a flow rate of 40 liters per minute and a fractional inspired oxygen percentage of 100%. Her oxygen saturation improved marginally, reaching a range of 80 to 85%.

Laboratory assessment revealed several findings: A total bilirubin level of 9 mg/dL, normal direct bilirubin, normal values for the remaining liver tests, an undetectably low haptoglobin level, and an elevated lactate dehydrogenase level at 411 U/L. COVID-19 and influenza tests yielded negative results. During the collection of arterial blood gas samples, it was observed to have a dark, almost chocolate-like color.

Given the high clinical suspicion of methemoglobinemia, we contacted poison control, and a methemoglobin level was obtained.

The arterial blood gas sample showed a pH of 7.43, partial pressure of oxygen of 421 mm Hg, partial pressure of carbon dioxide of 36 mm Hg, and bicarbonate of 23 mmol/L. However, the methemoglobin level could not be determined despite multiple samples being run through the machine. After consulting with laboratory staff and the analyzer software company, it was concluded that the machine analyzer was being affected by an unknown substance in her blood. Consequently, the physician and the local poison control toxicologist decided to initiate empiric treatment with methylene blue.

She was hospitalized for six days. She ultimately received two doses of methylene blue during her hospital stay. After recalibrating the device, a methemoglobin level of 4.6% was recorded on hospital day 5 (normal is <1.5%). Her indirect hyperbilirubinemia was found to be secondary to hemolytic anemia, likely triggered by TMP-SMX, which necessitated three units of blood transfusions due to her hemoglobin frequently dropping as low as 5.9 mg/dL. Testing for direct agglutination and G6PD deficiency returned negative results. Ultimately, her hemolysis, UTI, and methemoglobinemia resolved, and she was discharged home.

Discussion

Dyshemoglobinemias resulting from toxins are generally rare. Several drugs, foods, and drinks lead to increased levels of methemoglobin (Table 1) [1]. These disorders affect hemoglobin's ability to carry oxygen and lead to changes in the oxygen-hemoglobin dissociation curve. Methemoglobinemia is unique in its puzzling presentation of cyanosis, low measured oxygen saturation, and yet the absence of clinical respiratory distress. Many agents that cause methemoglobinemia also add oxidative stress to cells, sometimes to a degree that re-

Table 1. Exposures associated with methemoglobinemia

Drugs	
Local anesthetics	Phenacetin
	Phenazopyridine
	Dapsone
	Chloroquine
	Primaquine
	Trimethoprim
	Sulfonamides
	Rasburicase
	Cyclophosphamide
	Flutamide
	Metoclopramide
	Benzocaine
Nitrate derivatives	Lidocaine
	Prilocaine
	Articaine
	Nitroglycerin
Industrial products	Nitroprusside
	Amyl nitrate
	Nitric oxide
	Nitrate salts
	Aniline dyes
At risk sources	Naphthalene
	Aminophenols
	Chlorates
	Bromates
	Herbiides
	Pesticides
	Well water
Clinical condition	Food grown in areas contaminated by excessive nitrates from fertilizers
	Areas suspected of inappropriate manure utilization
	Infantile enteritis*

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*There are multiple mechanisms proposed for this including increased susceptibility to oxidative stress in infant erythrocytes and about 60% activity of infant cytochrome B5 reductase enzyme. This puts infants at risk of methemoglobinemia in the setting of nitrate production from intestinal organisms.

sults in hemolytic anemia, regardless of the patient's G6PD status. Additionally, many drugs implicated in methemoglobinemia have been associated with cases of drug-induced immune hemolysis as well as hemolysis secondary to oxidative stress [2-5]. The presented case demonstrated oxidative stress-related hemolysis and methemoglobinemia due to the antibiotic TMP-SMX and analgesic phenazopyridine combination.

The iron moiety within deoxyhemoglobin exists as Fe^{2+} referred to as the ferrous state. Oxidizing agents will convert the ferrous iron to ferric iron (Fe^{3+}). Consequently, the hemoglobin molecule with this form of iron is referred to as methemoglobin and will not bind oxygen. The methemoglobin pigment gives the blood a dark brown and chocolate color. Methemoglobinemia occurs when the body's mechanisms for reducing ferric iron, namely by cytochrome B5 reductase and to a much lesser extent NADPH-methemoglobin reductase, are affected. In addition to reducing the oxygen-carrying capacity, the oxygen-hemoglobin dissociation curve shifts to the left, and as a result, the capacity of the molecule to discharge oxygen to the tissue decreases [1, 2, 4, 5].

Management of methemoglobinemia in the acute setting starts with a thorough history to identify the causative agent. In addition, the patient's history should be scrutinized to evaluate the possibility of G6PD deficiency. This is because the treatment of choice, methylene blue, will not work in patients with G6PD deficiency and induces hemolysis from its oxidative properties before metabolism. The dose of methylene blue varies from 0.3 up to 5.5 mg/kg infused intravenously over 3-5 minutes. Methylene blue is metabolized to leucomethylene blue, which acts as a reducing agent to convert the ferric iron back to its ferrous state in erythrocytes. Oxygen supplementation should also be applied simultaneously. After the administration of methylene blue, the dose can be repeated if improvement is not noted within 30 minutes. The patient's methemoglobin percentage obtained from the laboratory should also improve significantly about 1 hour after administration [1, 3].

In addition to, or as an alternative to methylene blue therapy, ascorbic acid can also be used as a reducing agent to treat methemoglobinemia. Ascorbic acid, or vitamin C, dosing has not been standardized, and 0.5 g up to 10 g per dose has been documented. N-acetylcysteine may act as a cofactor to enhance reduction by increasing intracellular glutathione and has been suggested in patients with G6PD deficiency. Other strategies to combat the hypoxemic effect of methemoglobinemia, particularly in refractory cases, are blood transfusions, exchange transfusions, and hyperbaric oxygen [6-8].

Conclusion

Although methemoglobinemia has a classic presentation of cyanosis without respiratory distress and dark chocolate blood, additional concomitant pathologies can easily confuse the clinical picture. Understanding the pathophysiology of methemoglobinemia is key to understanding why our patient also developed hemolysis. When cyanosis and jaundice are both present, simultaneous management of methemoglobinemia and hemolytic anemia may be needed. Special attention to G6PD status in this situation is necessary to avoid methylene blue injury to the patient.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

Conceptualization: Michael Reis; methodology, software, formal analysis, investigation, resources, data Curation, writing, supervision, and project administration: All authors.

Conflict of interest

The authors declared no conflicts of interest.

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