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Pseudo-methemoglobinemia Induced by Phenazopyridine, a Diagnostic Challenge

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Introduction:

Cyanosis, blue discoloration of the skin and mucous membranes, is classified as central or peripheral based on the location on the body that is affected. Peripheral cyanosis involves the hands and feet while central cyanosis involves the lips, tongue and sublingual tissues. Patients with peripheral cyanosis typically have normal hemoglobin oxygen saturation (SaO_2) but reduced peripheral blood flow due to vasoconstriction. Contrarily, central cyanosis is caused by increased concentrations of deoxy-hemoglobin due to reduced SaO_2 or by the presence of a dysfunctional hemoglobin (Hb) variant.[1] Thus, while peripheral cyanosis is typically transient and reversible, central cyanosis may indicate impending or ongoing respiratory or cardiac failure.

In the evaluation of a patient with central cyanosis, cardiac, pulmonary and Hb disorders must be considered.[1] A provider must first rule out acute respiratory or cardiac conditions or decompensated chronic conditions capable of causing hypoxia or poor tissue perfusion. Chest X-ray, EKG, pulse oximetry and arterial blood gas analysis may be useful in the initial evaluation.

In the absence of pulmonary or cardiac pathology, a provider may then consider cyanosis caused by a hemoglobinopathy. Two diagnoses of clinical relevance are methemoglobinemia and sulfhemoglobinemia. Both of these non-functioning Hb variants can be acquired disturbances from the effects of oxidizing drugs.[3, 4] Methemoglobin (MetHb) is formed from the oxidation of Fe^{2+} to Fe^{3+} of Hb which makes it unable to bind O_2.[5] Not only does MetHb disable Hb molecules from binding O_2, but it also indirectly effects non-denatured Hb. The presence of MetHb induces a *left* shift in the oxyhemoglobin dissociation curve which decreases the ability of remaining Hb to unload O_2 in the tissues (Figure 1).[2, 6, 7] This effect has important clinical implications. Cyanosis develops at levels near 10% (1.5g/dL), headaches, shortness of breath and altered mental status occur at 20-45% and life threatening hypoxia occurs when levels reach 50-60%.[6, 7] Thus, methemoglobinemia is an important diagnosis to consider because symptoms can be non-specific and the condition can be rapidly fatal if left untreated.

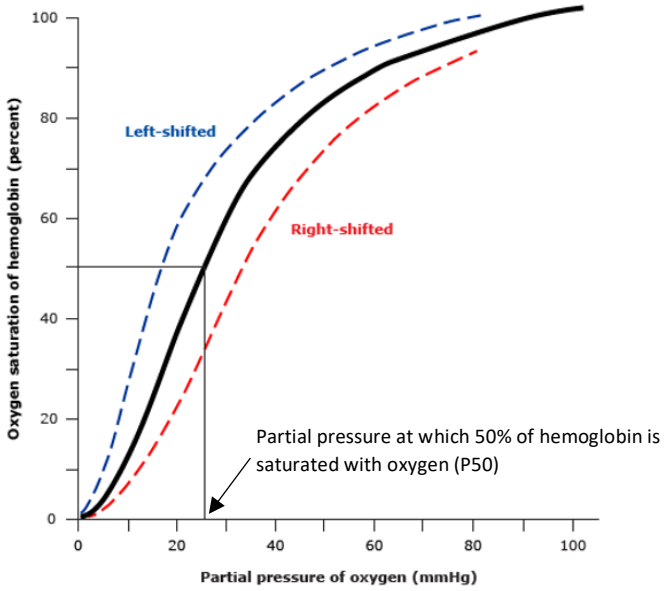

Figure 1: Oxyhemoglobin disassociation curve with normal unloading demonstrated by the solid black line and examples of left-shift which increases oxygen affinity to hemoglobin and reduces unloading of oxygen to tissues and right shift which decreases oxygen affinity to hemoglobin and enhances oxygen unloading to tissues[2]

Sulfhemoglobinemia has some similar characteristics to methemoglobinemia but differs substantially in physiological effects and clinical significance. Like MetHb, SulfHb is unable to carry O_2 due to an oxidative denaturation effect and it too indirectly effects non-denatured Hb.[5] In contrast to

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MetHb, however, SulfHb causes a *right* shift in the oxyhemoglobin dissociation curve which allows the unaffected Hb molecules to more efficiently deliver oxygen to tissues (Figure 1).[2, 8] This has important clinical significance, as even at high levels (20-60%) patients can remain asymptomatic and the condition is rarely life-threatening.[5] Furthermore, very low levels of SulfHb (0.5 g/dL or 3-4%) cause central cyanosis so these patients will typically present early, have low levels of SulfHb and are asymptomatic outside of central cyanosis.[8]

Importantly, while sulfhemoglobinemia does not have an effective treatment, methemoglobinemia rapidly resolves with administration of methylene blue. In sulfhemoglobinemia, cyanosis will resolve after removal of the offending agent and physiologic turnover of red blood cells.[5, 6]

Case Presentation:

A 58-year-old female presented to clinic with a chief complaint of "blue fingers and blue toes for the last several days." She stated that overall, she had been feeling well and was having no shortness of breath, chest tightness or fevers. Further review of systems was negative for any cardiovascular or respiratory complaints, but it did reveal dysuria over the last two weeks. Past medical history included iron deficiency anemia, hypertension, hypothyroidism, breast malignancy, and arthritis. Medications included Armour thyroid 15 mg daily, aspirin 325 mg daily, acetaminophen 500 mg as needed, losartan 50 mg-hydrochlorothiazide 12.5 mg daily, and iron 65 mg daily. Additionally, she had started using phenazopyridine (Azo urinary pain relief®) for recent onset dysuria. She had been taking 100 mg, 2-3 times daily over the last two weeks despite the recommended dosing of 190 mg up to 3 times daily for a maximum of two days. She also reported taking several other supplements including calcium, magnesium, fish oil, and flaxseed oil. Past surgical history included a left total hip arthroplasty without complication six weeks previously as well as abdominal hysterectomy in 1997 and left mastectomy in 1999. She denied tobacco usage and drinks alcohol socially but not excessively.

Physical exam showed a female in no acute respiratory distress sitting comfortably. Her vital signs were blood pressure 122/82, heart rate 68 BPM, temperature 98.4 F and oxygen saturation 84% via pulse oximetry on room air. Skin exam showed perioral and nailbed cyanosis in the fingers and toes. Cardiopulmonary examination was normal. CBC and C-reactive protein were normal including a normal Hb level of 12.0 g/dL (N=11.0-15.5 g/dL). CMP was normal outside of slightly elevated liver function enzymes with AST 49 (N= 13-39 U/L), ALT 59 (N=5-25 U/L). Urinalysis was unrevealing. D-Dimer was elevated to 1.41 (0-0.49). Arterial Blood Gas (ABG) revealed values within the reference range. Further investigation with CO-oximetry was performed and showed MetHb level elevated to 33.2%. The patient was treated with methylene blue (2 mg/kg) and admitted to the hospital out of concern for methemoglobinemia.

Several hours later MetHb remained elevated to 32.7% and an additional dose of methylene blue was administered. On hospital day two, MetHb was again measured and remained high at 31.7%. All three of these measurements were reported from the same CO-oximeter. During this time, the patient did not report any respiratory distress and CBC and CMP remained nearly unchanged. Out of suspicion for erroneous measurements, a specimen was sent to a reference laboratory which measured the MetHb level to be 0.2% using a blood gas analyzer (Rapid Point 500 ABG analyzer). In the presence of cyanosis, a low MetHb level and with the patient remaining asymptomatic, sulfhemoglobinemia was presumed to be the diagnosis.

The patient was discharged, scheduled for close follow-up, given instructions to stop the use of phenazopyridine and asked to return if symptoms developed. A specimen was sent to a larger laboratory for further analysis which revealed an elevated SulfHb level of 2.6% (N: 0-0.4%) and again confirmed normal MetHb. This result was received ten days after the patient's initial presentation and confirmed sulfhemoglobinemia as the patient's diagnosis. In her follow-up visit two weeks after initial presentation her cyanosis was improving but still present and she remained asymptomatic. She was lost to further follow-up.

Discussion:

Clinically differentiating sulfhemoglobinemia and methemoglobinemia can be challenging in an asymptomatic patient. Phenazopyridine is known to induce the formation of both SulfHb and MetHb and other commonly used drugs have been known to induce both Hb variants as well [3, 4, 9, 10] (Table 1). Interestingly, the source of sulfur in SulfHb is often unknown as many drugs that induce its formation do not contain sulfur.[4]

Table 1: Drugs or chemicals associated with inducing both MetHb and SulfHb
• Acetanilide • Aniline • Bismuth Subnitrate • Hydroxylamine • Nitrites • Nitroglycerin • Phenazopyridine • Phenacetin • Sulfonamides • Trinitrotoluene

It is important to note that significantly less SulfHb (0.5 g/dL) causes cyanosis compared to that of MetHb (1.5 g/dL).[7] Thus, this asymptomatic cyanotic patient demonstrates a common presentation for a patient with sulfhemoglobinemia. Interestingly, this patient's SulfHb was measured to be 2.6% which correlates to a SulfHb level of 0.31 g/dL, a value less than what is commonly reported in the literature as capable of causing cyanosis. It is known that absolute rather than relative quantity of abnormal hemoglobin (SulfHb, MetHb or deoxy-Hb) is associated with cyanosis so the amount that produced cyanosis in this patient may be attributed to skin pigmentation or reduced dermal thickness.[11]

This case shows that in a patient with sulfhemoglobinemia, both the pulse oximetry and CO-oximetry can be misleading. Pulse oximetry relies on variations in the infrared (IR) spectrum to differentiate oxygenated and deoxygenated Hb.[6] The presence of SulfHb and MetHb cause the IR absorption to peak at a value that correlates to 80-85% oxygenation.[6] In this case, pulse oximetry was 84% but the normal pO_2 and normal Hb indicate that the patient was not experiencing poor tissue oxygenation. The next step in the workup involves using CO-oximetry or blood gas analysis to identify MetHb. These instruments work by detecting variations in absorbance using spectrophotometry.[6] The presence of SulfHb disrupts this analysis because it shares an absorption peak at 626 nm with MetHb, thus leading to false positive MetHb levels.[12] Depending on model and age of these instruments there is variability in sensitivity of identifying MetHb and SulfHb.[13] In instruments unable to differentiate them, the reported level of MetHb is vastly overestimated because the molar absorptivity of MetHb is several times that of SulfHb.[13] This was evident in this case as the reported level of MetHb was between 31.7-33.2% while the actual value of SulfHb was only 2.6%. The false positive MetHb level and lack of rapid identification of SulfHb led the provider to administer an additional dose of methylene blue with no benefit for the patient.

Conclusion:

This is a case of sulfhemoglobinemia or pseudo-methemoglobinemia induced by phenazopyridine, a commonly used urinary pain relieve agent. While SulfHb and MetHb have unique physiological effects, at lower concentrations distinguishing them is difficult because they both cause apparent oxygen desaturation on pulse oximetry and many drugs have been associated with inducing the formation of both variants. Further complicating the diagnosis is that false positive MetHb can occur because of similar absorption on spectrophotometry analysis. In this case, SulfHb was only identified after sending a specimen to a second reference laboratory. Providers should be aware of the capabilities of the CO-oximeters and blood gas analyzers at their institution in identifying these two entities so they are able to more rapidly arrive at a diagnosis and initiate appropriate treatment. Sulfhemoglobinemia should be strongly considered in an otherwise asymptomatic, cyanotic patient with laboratory reported methemoglobinemia that is unresponsive to methylene blue therapy.

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