An Interesting Case of Missed Lifelong Chronic Methemoglobinemia

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Abstract

Congenital methemoglobinemia is a rare hematological condition with variable presentation from asymptomatic to debilitating. We describe a case where we drastically improved the health of an individual with previously undiagnosed and unmanaged congenital methemoglobinemia. Methemoglobinemia should be considered in the differential when presented with acute or chronic symptoms of cyanosis.

Case Presentation

History of Presenting Illness

A 22-year-old Middle Eastern female was referred to the emergency department (ED) for evaluation of dark blood and very low oxygen saturation during wisdom teeth removal.

She endorsed always having dusky fingers, blue tinted lips and toes and poor cardiovascular endurance and frequently being cold. She reported regular shortness of breath upon mild and was frequently fatigued as a child with minimal activity compared to her peers. She denied chest pain, diarrhea, constipation, dizziness, fevers, seizures, chills, or unintentional weight loss. She denied eating any seeds or any known exposure to pesticides or cyanide.

The patient presented to the ED 3 years ago due to chest pain, shortness of breath, and cyanosis around her lips. On arrival, she was found to have a pulse oximetry oxygen saturation of 91% on room air. She was given ketorolac and an inhaled dose of ipratropium bromide and albuterol. Her oxygen saturation did not change at the time, but the pulse oximeter was then moved to her ear and read 98% saturation on room air. The ED suspected she had poor circulation possibly due to Raynaud's disease. She was discharged being told to monitor her response to cold exposure and to follow up with her primary care provider.

Pertinent Physical Exam Findings

Central cyanosis
Conjunctival pallor
Peripheral cyanosis in fingertips and pale lips

Pertinent Lab Findings

Initial oxygen saturation of 88% on pulse oximetry
Hemoglobin 13.4 g/dL (normal range 12.0-16.0 g/dL)
Mean corpuscular volume 82.9 μ^3 (normal range 81.0-99.0 μ^3)
Methemoglobin 31.6% (normal range 0-3%)
pH arterial 7.44 (normal range 7.35-7.45)
Arterial PCO_2 36 mmHg (normal range 35-45 mmHg)
Arterial PO_2 334 mmHg (normal range 80-100 mmHg)
Arterial blood gas O2 saturation 67.3% (normal range 94-97%)
Arterial HCO_3^- 23.3 mEq/L (normal range 22-28 mEq/L)

Medications, chemicals, and environmental substances that could cause methemoglobinemia were discussed with the patient, but she could not recall any chronic exposures to these agents. Given lab results, a single 58 mg IV dose (1 mg/kg) of methylene blue was given.

Patient Progress

Methemoglobin levels measured an hour after methylene blue administration improved to 0.7% and was within normal limits.

Due to the chronicity of symptoms and lack of exposure to agents that cause chronic methemoglobinemia, a genetic cause was most likely responsible for her symptoms. The patient's blood was tested for cytochrome b5 reductase levels and was found to be 2.1 units per gram of hemoglobin (normal range 7.8-13.1 U/gHgb). This result indicated cytochrome b5 reductase deficiency.

The patient was kept for observation overnight with morning labs showing her iron level, ferritin level, iron percent saturation, and reticulocyte hemoglobin level were low at 34 ug/dL, 7.0 ng/mL, 10.8%, 24.5 pg, respectively (normal ranges for iron, ferritin, iron percent saturation, and reticulocyte hemoglobin is 42-135 ug/dL, 10-291.0 ng/mL, 15.0-50.0%, 32.0-39.0 pg, respectively). The transferrin was within normal limits 251 mg/dL (normal range 250-380 mg/dL). The patient follows a non-vegan, non-vegetarian halal diet

As the methemoglobinemia was likely chronic, the patient was discharged on 1000 mg of ascorbic acid three times a day prior with outpatient hematology follow-up.

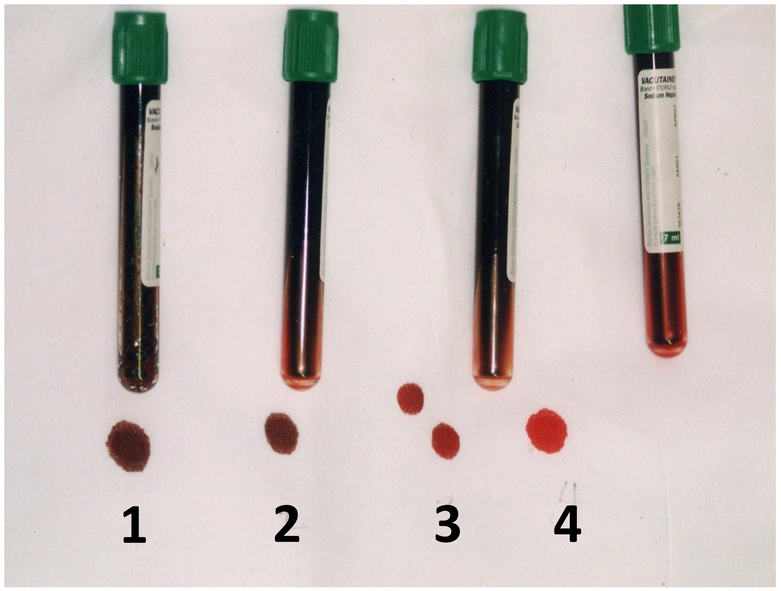

Figure 1. The dark chocolate brown color of blood in methemoglobinemia. Tubes 1 and 2 have a methemoglobin concentration of 70%. Tube 3 has a concentration of 20% and tube 4, a normal concentration.[1]

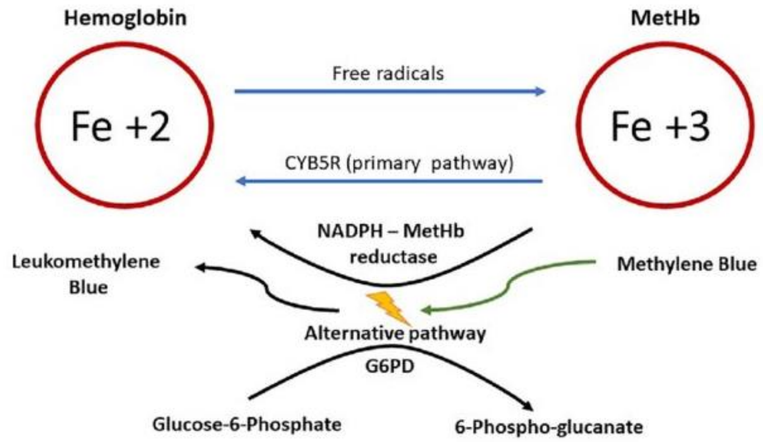

Figure 2. Methemoglobin (MetHb) formation, primary and alternative pathway of metabolism. Free radicals convert ferrous iron (Fe+2) to ferric iron (Fe+3) generating MetHb. MetHb reduced back to hemoglobin by cytochrome B5 reductase (CYB5R). Methylene blue enables alternative pathway activity for MetHb reduction to hemoglobin.[2]

Discussion

Methemoglobinemia is a when methemoglobin levels are elevated above normal levels in the blood (approximately 1%). Methemoglobin is a form of hemoglobin where iron has been oxidized from a ferrous (Fe2+) state to a ferric (Fe3+) state. Methemoglobin does not bind oxygen like hemoglobin and therefore leads to tissue hypoxia. While methemoglobinemia is most commonly due to acquired exogenous factors causing oxidation of ferrous iron in hemoglobin, it can also be due to congenital causes such as the autosomal recessive disorder of cytochrome b5 reductase deficiency. Normally, Cytochrome b5 reductase catalyzes the reduction of methemoglobin to hemoglobin (Fig. 2).[2] Ascorbic acid's reducing potential[3,4] and methylene blue's ability to activate NADPH methemoglobin reductase[2] can be used to treat acquired and congenital causes of methemoglobinemia.

To our knowledge, this is the first documented case of unrecognized chronic methemoglobinemia related to cytochrome b5 reductase deficiency. Routine pulse oximetry is unable to accurately determine oxygen saturation in methemoglobinemia, as seen in this case. The patient's iron deficiency likely explained the lack of appropriate absolute polycythemia in a state of chronic methemoglobinemia.

This case highlights the importance of considering methemoglobinemia when presented with a patient with acute or chronic symptoms of cyanosis and symptoms sometimes can be resolved with a simple intervention.

Conclusions

Consider methemoglobinemia when presented with a patient with either acute or chronic symptoms of cyanosis.

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