CLINICAL VIGNETTE

Dapsone Induced Methemoglobinemia in a Rheumatoid Arthritis Patient

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Case Presentation

A 69-year-old female with seropositive erosive rheumatoid arthritis (RA) presents with shortness of breath and hypoxia. She initially presented with worsening dyspnea on exertion two weeks prior and was admitted for hypoxemic respiratory failure. She received high dose prednisone and nasal oxygen for interstitial lung disease either drug-induced from methotrexate or related to rheumatoid arthritis. The patient was on atovaquone for Pneumocystis pneumonia (PCP) prophylaxis due to sulfa allergy. Atovaquone was switched to dapsone because of worsening thrombocytopenia. Three days after discharge, she was briefly admitted for right lower extremity deep vein thrombosis (DVT) without pulmonary embolism and started on apixaban. The patient reported pulse oximeter saturations (SpO2) of 85% after discharge, which remained in the 80s despite increasing nasal oxygen to 5L/min. In the ED, her vital signs were within normal limits except for a respiratory rate of 26 and SpO2 of 87% on room air. Venous blood gas (VBG) showed pH 7.43, partial pressure of CO2 ($PvCO_2$) 33mmHg, partial pressure of oxygen (PvO_2) 32mmHg, venous O_2 saturation (SvO2) of 49.1%, and an elevated methemoglobin (MetHgb) level of 15.9%. Prior MetHgb level on arterial blood gas (ABG) was 1.3%. Labs were otherwise significant for anemia with Hgb 8.2g/dL, hematocrit 24.6%, reticulocyte count 6.2%, haptoglobin <15mg/dL, and LDH 450 U/L. Her prior thrombocytopenia had resolved with platelet 293K/cumm. Other labs included creatinine kinase (CK) elevated at 1240 U/L and basic metabolic panel (BMP) with mildly decreased Na of 133mmol/L. Her glucose-6-phosphate dehydrogenase (G6PD) levels returned normal. Dapsone was stopped, and she was given 2mg/kg of methylene blue and cimetidine with improvement in her methemoglobinemia to 5.1%. She also received intravenous fluids for mild rhabdomyolysis with improvement in CK. The patient's respiratory distress improved, and she was weaned off nasal oxygen. She was restarted on atovaquone for PCP prophylaxis and continued on a steroid taper with outpatient rheumatology follow-up.

Discussion

This patient with rheumatoid arthritis developed methemoglobinemia while taking dapsone for PCP prophylaxis. In methemoglobinemia the normal ferrous (Fe^{2+}) form of heme is oxidized to the ferric (Fe^{3+}) state. Unlike ferrous hemoglobin, the ferric variant in MetHgb does not bind O_2 and causes the remaining molecules in the tetrameric hemoglobin to hold O_2 with greater affinity. This leads to decreased O_2 tissue delivery due to a leftward shift in the oxygen-Hgb dissociation curve, resulting in a functional anemia.[1] Our patient with Hgb of 8.2 and MetHgb level of 15.9%, had functional Hgb level of about 6.9. Normally, MetHgb is maintained at ~1% of total Hgb by the cytochrome b5 reductase enzyme, the nicotinamide adenine dinucleotide phosphate (NADPH)-dependent MetHgb reductase in conjunction with G6PD, and alternative pathways with nonenzymatic antioxidants ascorbic acid and glutathione. Methemoglobinemia occurs when MetHgb level exceeds 1%. It can be categorized into hereditary/genetic such as enzyme deficiencies or acquired from exposure to oxidizing agents.[2]

Mild methemoglobinemia (2-10% of total Hgb) is usually well tolerated in otherwise healthy individuals. At levels above 10-15%, cyanosis of the skin and mucous membranes can be present. Unlike the classic blue seen in other causes of cyanosis, this has a brown, "pasty" appearance. Symptoms of severe tissue hypoxia begin to appear with MetHgb higher than 20-30%. These include headache, fatigue, dizziness, and tachycardia. As MetHgb levels approach 60%, acidosis, paralysis, arrhythmias, coma, and seizures can develop. Levels >70% are usually lethal.[1,2] Patients with comorbidities that compromise tissue oxygenation such as anemia, respiratory and cardiovascular disease, symptoms of methemoglobinemia can be seen at MetHgb levels below 15%.[2,3]

Pattern recognition is key in diagnosis of methemoglobinemia since symptoms of hypoxia are non-specific, and cyanosis may not be readily apparent on exam depending on skin tone and concentration of circulating MetHgb. Laboratory measurement of MetHgb may not be readily available and the "saturation gap" observed between ABG and pulse oximetry readings may hint at underlying methemoglobinemia. The saturation gap results from limitations of pulse oximetry measuring only oxyhemoglobin and Hgb measurement using noninvasive spectrophotometry which does not account for abnormal Hgb. As the level of MetHgb increases, the O_2 saturation on pulse oximetry (SpO2) falls and plateaus at ~85%,[1,4] while O_2 saturation measured by ABG (SaO2) can appear normal, creating the "saturation gap." Basic laboratory tests that may be helpful include complete blood count to check for anemia, reticulocyte count to monitor hemolysis, and G6PD level. If available, CO-oximetry can non-invasively measure peak light absorbance for

MetHgb to detect methemoglobinemia compared to conventional pulse oximetry.[2]

Dapsone is a drug used for leprosy, PCP prophylaxis, and the treatment of dermatitis herpetiformis. A study of 138 cases of methemoglobinemia at two hospitals reported dapsone as the most common cause of acquired methemoglobinemia in 42% of cases.[5] Dapsone is metabolized by the cytochrome P450 system in the liver to its hydroxylamine metabolites, which are potent oxidants hypothesized to cause hemolytic anemia and methemoglobinemia while undergoing enterohepatic circulation with a half-life of 24-30 hours. It is estimated that 4-13% of patients receiving dapsone develop these side effects.[2,6]

The primary treatment of dapsone-induced methemoglobinemia is intravenous methylene blue. 1-2 mg/kg is given in a 1% solution over 5 minutes.[7] Methylene blue acts as a cofactor in the NADPH-dependent MetHgb reductase regulatory pathway in conjunction with G6PD to convert MetHgb to Hgb. The mechanism involves the reduction of methylene blue by NADPH-dependent MetHgb reductase to leukomethylene blue, which subsequently acts as an electron donor to MetHgb, converting the Fe^{3+} heme to the normal F^{2+} form in Hgb. As such, methylene blue should not be administered to patients with G6PD deficiency as they will not have adequate production of NADPH to reduce methylene blue to leukomethylene blue. In addition, the maximum dose of methylene blue should not exceed 7mg/kg due to increased side effects such as dyspnea, restlessness, nausea, diarrhea, and diaphoresis. At the 15mg/kg dosage range, methylene blue can paradoxically become an oxidizing agent causing Heinz body formation and hemolysis.[1-3,7]

Alternative therapies for methemoglobinemia include ascorbic acid and cimetidine. When methylene blue is not available or contraindicated due to G6PD deficiency, ascorbic acid can be used as a nonenzymatic reducing agent for MetHgb.[8,9] Cimetidine is usually given prophylactically to inhibit the liver cytochrome P450 enzyme system reducing hepatic metabolism of dapsone to its toxic hydroxylamine form. Some studies recommend against acute cimetidine use due to its slow onset of action.[5]

Our patient started dapsone for PCP prophylaxis because of a sulfa allergy precluding the use of trimethoprim-sulfamethoxazole as first-line medication and was switched off atovaquone due to thrombocytopenia. On presentation, a VBG was done instead of an ABG. While there is a correlation of pH, PCO_2, and base excess values between VBG and ABG, the PO2 and O_2 saturation is typically lower in deoxygenated venous blood.[10] Therefore, the "saturation gap" dependent on the arterial PO_2 and O_2 saturation values cannot be seen on a VBG. Fortunately, a MetHgb level was obtained and showed a level of 15.9%. While this level is lower than the usual 20-30% where one would begin to see symptoms of hypoxia, our patient's underlying anemia and interstitial lung disease likely lowered the symptom threshold and caused worsening dyspnea. Methylene blue and cimetidine were given with improvement of her MetHgb level and respiration. Hemolysis with elevated reticulocyte count and LDH, along with low haptoglobin levels in our patient were likely a byproduct of oxidative stress caused by dapsone. She was switched from dapsone to atovaquone after thrombocytopenia stabilized, and one year later she is tolerating atovaquone without further episodes of methemoglobinemia.

Conclusion

Dapsone remains one of the most common causes of acquired methemoglobinemia due to its oxidative metabolites. Clinicians should recognize the nonspecific presentation of methemoglobinemia and that a "saturation gap" on ABG may be a clue to high levels of MetHgb. At the correct dose, methylene blue is an effective antidote for methemoglobinemia in patients without G6PD deficiency, while ascorbic acid can be an alternative option in those who lack the enzyme.

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