Title

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CLINICAL VIGNETTE

Confused about the Hypoxia: A Case of Dapsone-induced Methemoglobinemia

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A 66-year-old female with history of depression, Crohn's disease in remission, and recent diagnosis of interstitial nephritis on prednisone presented to emergency room with altered mental status for two weeks.

History was mostly obtained from husband given patient's confusion. The patient had been started on prednisone 60mg daily 6 weeks prior to admission by her nephrologist for interstitial nephritis. She had worsening creatinine from 1.6 mg/dl (ref 0.6-1.3 mg/dl) to 2.0 mg/dl over the past several months, which had prompted a kidney biopsy. Biopsy showed acute and chronic interstitial nephritis and 6-8 week course of prednisone was started, along with pantoprazole and dapsone 100 mg daily for *Pneumocystis jirovecii* prophylaxis.

In the two weeks prior to her presentation, patient had episodes of confusion associated with personality changes and insomnia. The patient would intermittently speak in incoherent sentences and was also noted to have obsessive thoughts and grandiose delusions. The patient could not recall these episodes but acknowledged confusion and poor sleep. She denied fever, headache, weakness, numbness, respiratory or gastrointestinal symptoms.

Upon presentation to emergency room, vital signs included temperature 36.6° C, blood pressure 113/78 mmHg, pulse 69/min, respirations 17 /min and oxygen saturation of 90% on room air. Physical exam was essentially normal; heart with regular rate and rhythm without gallops, murmurs, or rubs, jugular venous pulse was not elevated, lungs were clear to auscultation bilaterally, and extremities were without edema. Mental status exam was notable for loud speech and bursts of emotional lability from crying to laughing but easily reorientable and cooperative. Laboratory values notable for WBC 13.28 X 10^3/microL (ref 4.16-9.95 X 10^3/microL) with 82.7% neutrophils, hemoglobin 11.1 g/dl (ref 11.6-15.2 g/dl), platelets 136 X 10^3/microL (ref 143-398 X 10^3/microL), blood urea nitrogen 43 mg/dl (ref 7-22 mg/dl), creatinine 1.8 mg /dl (ref 0.6-1.3 mg/dl), bicarbonate 17 mmol/L (ref 20-30 mmol/L), troponin 0.57 ng/ml (ref <0.1 ng/ml) that decreased to 0.48 ng/ml on repeat testing. EKG and echocardiogram on day of admission were notable for T-wave inversions in anterior leads and preserved ejection fraction without evidence of structural abnormalities. Portable chest X-ray showed minimal consolidation versus atelectasis in the left lung base. MRI/MRA brain/neck did not show any acute abnormal findings.

After admission to medicine, psychiatry was consulted and her behavioral changes were attributed to toxic-metabolic encephalopathy due to steroids. Prednisone dose was reduced by 50% given lack of improvement in kidney function and tapered. She received olanzapine for episodes of agitation and insomnia and was started on azithromycin and ceftriaxone for possible community acquired pneumonia given infiltrate on chest X-ray.

On hospital day 2, the bedside nurse placed the patient on oxygen via nasal cannula up to 5 liters/min for low oxygen saturation, persistently 88%, without improvement. Patient also developed sinus tachycardia with heart rate of 110 bpm. Repeat examination at that time was unchanged from admission with no evidence of cyanosis or heart failure. Arterial blood gas showed a pH of 7.36 (ref 7.37-7.41), pCO2 of 30 mmHg (ref 38-42 mmHg), pO2 of 91 mmHg (ref 98-118 mmHg), and bicarbonate of 17 mmol/L (ref 22-26 mmol/L). Co-Oximetry was significant for oxyhemoglobin 85% (ref >94%), elevated methemoglobin 11% (ref 0.5-1.5%) and hemoglobin of 7.9 g/dl (ref 11.6-15.2 g/dl).

Dapsone was discontinued and tests for hemolysis and glucose-6-phosphate dehydrogenase (G6PD) levels obtained. Lactate dehydrogenase was elevated at 464 U/L (ref 125-256 U/L) and haptoglobin levels were <8 mg/dl (ref 21-210 mg/dl). Peripheral blood smear was significant only for a few schistocytes. By hospital day 3, patient's clinical status worsened to symptomatic dyspnea with a persistent tachycardia with heart rates up to 150 bpm with ambulation and oxygen saturation of 88% on 5 liters nasal cannula. Given patient's progressive symptoms, methylene blue 25 mg/m^2 was given over 15 minutes along with oral ascorbic acid 1000 mg twice daily. Repeat Co-Oximetry in one hour intervals showed decreasing methemoglobin levels of 8.6% and 2.4%. Patient's dyspnea, oxygen requirements, and tachycardia improved over this time period. She required 1 unit of packed red blood cell transfusion with stabilization of her hemoglobin. She remained stable was discharged to acute rehab one week later.

Discussion

This case is an example of acquired, dapsone-induced methemoglobinemia. Methemoglobin is an oxidized form of hemoglobin (Fe^{2+}->Fe^{3+}) that binds to oxygen irreversibly and also causes remaining normal ferrous hemes (Fe^{2+}) in the hemoglobin tetramer to have increased oxygen affinity, leading to an overall decreased oxygen delivery to the tissues. One

pathway to reduce ferric iron (Fe^{3+}) is by electrons provided by G6PD using NADPH methemoglobin reductase. Methylene blue works by activating this pathway. As a result, methylene blue is contraindicated in patients with G6PD as it may be ineffective and potentially harmful as the oxidative potential can precipitate hemolysis. In our case, G6PD levels had not resulted at the time of methylene blue administration but we felt the risk of deficiency was low as G6PD is an X-linked disorder (mostly in males) and prevalent in African and Mediterranean ancestry, while our patient was Western European. In cases where methylene blue is contraindicated or where G6PD status is not known, ascorbic acid may be given as a reducing agent as we also started.

Patients with acute toxic methemoglobinemia can become critically ill due to worsening hypoxia that does not improve with supplemental oxygen. Pulse oximetry readings are inaccurate and typically register an oxygen saturation below 90%. Our patient lacked evidence of cyanosis most likely because of relatively lower methemoglobin levels. Severity of symptoms correlates with methemoglobin levels. Dapsone, topical anesthetics (lidocaine and benzocaine), and anti-malarials are common causes of drug-induced cases, and it is important to note that many illicit drugs sold on the street contain dapsone. Therefore, it is critical for clinicians to have high suspicion for methemoglobinemia when such medications are involved. Dapsone has a long half-life of more than 30 hours as it undergoes enterohepatic recirculation. Thus, serial methemoglobin levels should be checked and treatment may need to be repeated if symptoms persist.[1]

The best ways to detect methemoglobinemia is with blood gas and co-oximetry. Discoloration of blood (brownish to blue) may be a clue to diagnosis. Diagnosis of methemoglobinemia is made when methemoglobin levels are > 5 percent. Patients often become symptomatic when levels exceed 10 percent but ones with underlying lung disease may have a lower threshold. Levels > 30 percent can be life-threatening. An oxygen "saturation gap" can also be observed which is defined as when there is a more than 5% difference in the oxygen saturation measured by pulse oximetry and the calculated oxygen saturation from a blood gas.[2]

In addition to stopping the offending agent and providing supportive care, methylene blue is the drug of choice for acute toxic methemoglobinemia. Treatment with methylene blue is recommended depending on severity of symptoms and/or when levels exceed 20 percent. In our patient, it was given due to severity of her symptoms. Dosing is weight-based (1-2mg/kg) depending on gravity of symptoms. G6PD levels should be checked prior to initiation of dapsone but if levels are not known, the patients' gender and ethnicity can be helpful in assessing the overall risk of G6PD. Ascorbic acid is a reducing agent that can be co-administered with methylene blue in patients with G6PD and severe symptoms or if G6PD status is not known.

In conclusion, clinicians should perform a thorough medication reconciliation and substance use history in patients who present with hypoxia, not responsive to administration of oxygen with an unremarkable cardiopulmonary evaluation and consider obtaining an arterial blood gas with co-oximetry.

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