CLINICAL VIGNETTE

Methemoglobinemia and Behcet's Disease

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A 42-year-old Egyptian woman with Behcet's disease, rheumatoid arthritis and relapsing polychondritis was hospitalized for generalized weakness, dyspnea on exertion and chest tightness. She had been on a tapering regimen of high dose methylprednisolone for two weeks for Behcet's disease flare. On this regimen, she developed progressive, generalized weakness and dyspnea on exertion with chest tightness, prompting ED evaluation. Her other outpatient medications included azathioprine 150 milligram(mg) daily, methylprednisolone 40 mg every morning and 24 mg every afternoon, and atovaquone 1700mg daily. Inpatient evaluation included computed tomography scan of the chest, echocardiogram, pulmonary function testing, and nerve conduction studies with electromyogram -- all of which were unrevealing. She was eventually diagnosed with steroid-induced myopathy and continued with methylprednisolone taper to 40 mg in the morning and 20 mg at night, with symptomatic improvement. On hospital day 9, atovaquone was discontinued due to concerns for potentially contributing to symptoms of dyspnea. Due to prior gastrointestinal intolerance to Trimethoprim-sulfamethoxazole, she was started on dapsone for *Pneumocystis* prophylaxis after testing negative for glucose-6-phosphate dehydrogenase (G6PD) deficiency. Two days later, she developed acute dyspnea after returning from a walk in the hallway.

Vital signs were notable for sinus tachycardia (130 bpm), blood pressure 132/91 mmHg, and respiratory rate of 28 with oxygen saturation of 88% on room air. Her oxygen saturation improved to 91% on 5 L of oxygen via nasal cannula. On examination, the patient had labored breathing with use of accessory muscles, lungs clear with good air movement. No cyanosis of mucosa or skin noted. Electrocardiogram demonstrated sinus tachycardia without ischemic changes. Initial labs demonstrated hemoglobin 11.9 g/dL and normal electrolytes. Venous blood gas demonstrated respiratory alkalosis with pH 7.51 and partial pressure of carbon dioxide (pCO2) of 34. Serial troponins were negative. Chest radiograph demonstrated a clear chest with no consolidation or infiltrates, and computed tomography angiogram of the chest was negative for pulmonary embolism.

Arterial blood gas (ABG) was drawn; and a dark brown appearance was noted. The results showed pH of 7.46, pCO2 of 36, with partial pressure of oxygen (pO2) of 181 and oxygen saturation (SaO2) of 98.5%. A co-oximetry was performed and showed oxyhemoglobin of 88.4 and Methemoglobin (MetHb) level of 10.4%.

Dapsone was suspected to be the culprit and was discontinued immediately. Methylene blue 1 mg per kilogram was given, and high-dose oral ascorbic acid was started. Repeat ABG with co-oximetry showed MetHgb level of 1.5%. Patient's dyspnea improved, and she was weaned off of nasal oxygen.

Further testing was done to rule out any other cardiopulmonary process. Repeat echocardiogram with bubble did not demonstrate shunt pathology. Pharmacologic nuclear stress test was negative for myocardial ischemia. The patient continued to improve and was discharged on hospital day 16.

Discussion

Methemoglobinemia is a rare cause of hypoxia. It is difficult to diagnose and potentially fatal. Abnormal forms of hemoglobin, such as methemoglobin (MetHb) may occur in two ways - congenital or acquired leading to reduced oxygenation of tissues. Acquired methemoglobinemia is commonly due to adverse effects of medications - most notably dapsone and topical anesthetic agents such as benzocaine.[1] Dapsone is used for multiple indications including leprosy, dermatologic conditions and for *Pneumocystis* prophylaxis. It is important to note that many street drugs also contain dapsone. Because methemoglobinemia has a non-specific presentation of hypoxia and cyanosis, diagnosis may pose as a challenge; thus, clinicians must have a high suspicion for this diagnosis in certain settings.

Physiologic levels of MetHb exists at < 1%, and methemoglobinemia is diagnosed when methemoglobin level is > 5%, and patients usually become symptomatic when MetHb level is > 10%. Methemoglobinemia concentrations between 20% and 45% are associated with dizziness, fatigue, headache, tachycardia, and weakness.[2] Concentrations above 45% are associated with acidosis, cardiac arrhythmias, coma, dyspnea, and seizures.[2] Methemoglobinemia is formed when ferrous state (Fe2+) iron is further oxidized to ferric state (Fe3+). Heme-containing iron in its ferric form (Fe3+) cannot bind oxygen. This in addition to allosterically increasing hemoglobin oxygen affinity results in a leftward shift in oxygen binding curve. These processes can lead to classic presenting symptoms such as central and or peripheral cyanosis, dyspnea, tachycardia, and weakness with chocolate-brown appearing blood.

Methemoglobinemia is generally managed by discontinuing the inciting agent and providing symptomatic support. Symptomatic patients, however, can be treated with Methylene blue,

which is given intravenously 1mg per kg administered over five minutes. The dose is re-administered if initial clinical response is insufficient within the next hour. Methylene blue acts as a cofactor for nicotinamide adenine dinucleotide phosphate hydrogen (NADPH)-MetHb reductase. This leads to formation of leukomethylene blue which reduces ferrous iron to ferric, reducing levels of MetHb.

Cimetidine has also been studied as treatment for methemoglobinemia due to its inhibitory effects on cytochrome P450 which decreases dapsone metabolism to its toxic hydroxylamine metabolite.[3] Patients on dapsone for dermatological conditions with associated methemoglobinemia showed cimetidine was effective in reducing cyanosis and dyspnea without interference with dapsone dermatological effects.[4] However, these cases were chronic cases of methemoglobinemia and looked at cimetidine effects over a number of weeks. It is not recommended in acute settings. Ascorbic acid has also been used to increase enzymatic reduction of MetHb; however, is not commonly used as monotherapy in patients with acute symptomatic methemoglobinemia.[5]

Dapsone-associated methemoglobinemia behaves in a dose dependent manner.[6] Our case provides a unique presentation as this patient became profoundly dyspneic after receiving only two doses of dapsone and did not show the classic central and peripheral signs of cyanosis. Persistent hypoxia despite oxygen supplementation was key to suggest methemoglobinemia in setting of recent dapsone use.

Methemoglobinemia poses as a diagnostic challenge due to its rarity and nonspecific symptoms. Our case highlights the diagnostic difficulty. The key to diagnosis includes thorough medication review, recognizing the oxygen saturation gap, noting abnormal ABG blood coloration, and checking co-oximetry to test for methemoglobinemia when suspicion is high. Early recognition may be life-saving to remove the offending agent and start early treatment.

REFERENCES

1. **Ash-Bernal R, Wise R, Wright SM**. Acquired methemoglobinemia: a retrospective series of 138 cases at 2 teaching hospitals. *Medicine (Baltimore).* 2004 Sep;83(5):265-73. doi: 10.1097/01.md.0000141096.00377.3f. PMID: 15342970.
2. **Ward KE, McCarthy MW**. Dapsone-induced methemoglobinemia. *Ann Pharmacother*. 1998 May; 32(5):549-53. doi: 10.1345/aph.17003. PMID: 9606476.
3. **Mehta M**. Cimetidine and dapsone-mediated methaemoglobinaemia. *Anaesthesia*. 2007 Nov;62(11): 1188. doi: 10.1111/j.1365-2044.2007.05332.x. PMID: 17924910.
4. **Goolamali SI, Macfarlane CS**. The use of cimetidine to reduce dapsone-dependent haematological side-effects in a patient with mucous membrane pemphigoid. *Clin Exp Dermatol.* 2009 Dec;34(8):e1025-6. doi: 10.1111/j.1365-2230.2009.03710.x. PMID: 20055829.
5. **Hansen DG, Challoner KR, Smith DE.** Dapsone intoxication: two case reports. *J Emerg Med*. 1994 May-Jun;12(3):347-51. doi: 10.1016/0736-4679(94)90277-1. PMID: 8040592.
6. **Asakuma M, Yokoba M, Katono K, Takakura A, Katagiri M, Masuda N.** A case of diaphenylsulfone-induced methemoglobinemia concurred with bronchial asthma. *Nihon Kokyuki Gakkai Zasshi (Annals of the Japanese Respiratory Society*). 2014;3:98-102. (Article in Japanese, abstract in English.)