

CASE REPORT

Do all patients with acquired methemoglobinemia need treatment? A lesson learnt

Raju Khanal, MD*, Paras Karmacharya, MD, Ranjan Pathak, MD,
Dilli Ram Poudel, MD, Sushil Ghimire, MD and Richard Alweis, MD

Department of Internal Medicine, Reading Health System, West Reading, PA, USA

Acquired methemoglobinemia is a medical emergency, and its prompt recognition and treatment can avoid catastrophic complications including death. However, in mild asymptomatic cases without any comorbid conditions, it would be reasonable to simply observe and treat symptomatically to avoid severe treatment-related complications, especially in patients with suspected glucose-6-phosphate dehydrogenase (G6PD) deficiency. We present a case of mild methemoglobinemia in occult G6PD deficiency in which the patient developed hemolysis after treatment with intravenous methylene blue, requiring transfusion.

Keywords: *methemoglobin; methemoglobinemia; G6PD deficiency; hemolysis*

*Correspondence to: Raju Khanal, Department of Internal Medicine, Reading Health System, 6th Avenue, Spruce Street, West Reading, PA 19611, USA, Email: dranju34@gmail.com

Received: 7 July 2015; Revised: 1 September 2015; Accepted: 3 September 2015; Published: 19 October 2015

Acquired methemoglobinemia is a rare, acquired disorder of oxygen-carrying capacity of hemoglobin, caused by hemoglobin oxidation from exposure to chemicals or medications, resulting in functional anemia, tissue hypoxia, and death. Its prompt recognition and treatment can avoid catastrophic complications. However, unnecessary treatment may lead to complications, including severe hemolysis, especially if the patient has occult glucose-6-phosphate dehydrogenase (G6PD) deficiency (1, 2). We present a case of mild methemoglobinemia in occult G6PD deficiency in which the patient developed hemolysis after treatment with intravenous methylene blue, requiring transfusion.

Case presentation

A 56-year-old Hispanic male presented to the emergency department for gradually progressive shortness of breath and chest tightness of 4-hour duration. He was recently diagnosed with stage IV mantle cell lymphoma and had received his first cycle of R-CHOP (rituximab, cyclophosphamide, doxorubicin, hydrochloride (hydroxydaunomycin), vincristine sulfate (Oncovin), and prednisone) chemotherapy 2 days prior to presentation. Rituximab infusion was postponed by 1 day due to inclement weather, and he received this 1 day prior to presentation. He also received one dose of intravenous (IV) rasburicase 2 days prior to presentation. He had been using EMLA (eutectic mixture of topical 2.5% lidocaine and 2.5% prilocaine) cream, 30 gm topically, around his port to minimize pain

during infusions, the last application being 1 day prior to the presentation. He denied any cough, fever, chills, sputum production, headache, or dizziness. Significant past medical history included corneal dystrophy, hyperlipidemia, hypertension, and gastro-esophageal reflux disease. He did not have any history of lung or heart disease. He was not a smoker. His medications included lisinopril and rosuvastatin.

On physical examination, blood pressure was 146/81 mmHg, pulse rate was 92/min, respiratory rate was 24/min, and temperature was 98.4F. Oxygen saturation by pulse oximetry was 86% on 100% oxygen through face mask. He was alert and oriented to time, place, and person, and not in respiratory distress. He did not have any cyanosis or lower extremity edema. He had a PORT-A-CATH in the right anterior chest with no erythema or discharge around the catheter entry site. His cardi thoracic examination was clear to auscultation bilaterally with normal heart sounds.

Laboratory investigation showed a white cell count of 77,900/mm³ (with differential count of neutrophils – 85.9%, lymphocytes – 0.8%, monocytes – 1.8%), platelet count of 394,000/mm³, and Hb of 9.3 g/dL. Leukocytosis was thought to be secondary to the dexamethasone and pegfilgrastim received 2 days ago. Serum uric acid was 0.6 mg/dL (3.4–7.8 mg/dL), creatinine 0.77 mg/dL (0.5–1.5 mg/dL), and potassium 3.9 mEq/L.

The patient was placed on non-invasive, positive pressure ventilation because of persistent hypoxia *via* face-mask, but his pulse oximetry remained at 86% with 100%

fractional inspiration of oxygen (FiO₂). Arterial blood gas (ABG) on 100% FiO₂ revealed PaO₂ 215.6 (normal 75–90 mmHg), pH 7.45 (normal 7.36–7.46), PCO₂ 42.6 (normal 34–46 mmHg), bicarbonate 29.5 (normal 22–27 mEq/L), base excess 5 (normal –2 to 2 mEq/L), and oxygen saturation 99.8% (normal 94.3–96.2%). Electrocardiogram showed normal sinus rhythm with no significant ST–T changes and cardiac enzymes were within normal range. Computed tomography scan of the chest was negative for pulmonary embolism and other abnormalities. Saturation gap between the oxygen saturation in pulse oximetry and arterial blood gas analysis led to a high suspicion of acquired methemoglobinemia. Methemoglobin level (MetHb) was 8.4% (normal 0.4–1.5%) and carboxyhemoglobin level was 3% (normal 1–2%). Although his symptoms were improved with oxygen therapy, he was given one dose of 100 mg (1 mg/kg) of intravenous methylene blue in the emergency department due to persistent hypoxia, and transferred to intensive care unit. Repeat MetHb level was still significantly elevated at 7.3% 2 hours later; hence, a repeat dose of methylene blue was given. However, the level of MetHb paradoxically increased to 7.6%. Although a third dose was planned, his hemoglobin (Hb) level dropped to 6.6 g% from 9.3 g%. LDH was 864 (normal 94–208 IU/L), haptoglobin < 1.0 (normal 36–195 mg/dL), total bilirubin 2.4 mg/dL (normal 0.2–1.1 mg/dL), and direct bilirubin 0.5 mg/dL (normal 0–0.4 mg/dL). Immune hemolysis was unlikely as direct Coomb's test was negative.

The third dose of methylene blue was held and he was transfused with four units of packed red blood cells. Given the clinical situation of methemoglobinemia, unresponsive to IV methylene blue, and hemolysis after IV methylene blue in the background of recent use of rasburicase, occult G6PD deficiency was suspected. Peripheral smear showed bite cells and few Heinz bodies. G6PD level was low (1.5 μg Hb) (normal 8.8–13.4 μg Hb), which is diagnostic for G6PD deficiency. Hb level stabilized at 9.3 g/dL. MetHb level normalized the next day and he was transferred out of the intensive care unit and then discharged from the hospital.

Discussion

Methemoglobin (MetHb) is constantly produced in the red blood cells by autoxidation of hemoglobin. Its level is maintained in a steady state of less than 2% of total hemoglobin (3). There are two mechanisms in the body that act to reduce MetHb to hemoglobin. The major pathway is cytochrome *b5* reductase pathway (also called nicotinamide adenine dinucleotide-dependent MetHb reductase). The second one is nicotinamide adenine dinucleotide phosphate (NADPH)-dependent MetHb reductase, which requires a cofactor such as methylene blue or riboflavin for activation. The latter is clinically important for the treatment of methemoglobinemia by intravenous methylene blue (4).

Exposure to oxidizing agents can result in excessive formation of MetHb, which can lead to clinically significant methemoglobinemia, resulting in tissue hypoxia and death (4, 5). Clinical manifestations of methemoglobinemia may not always correlate with blood MetHb level. Patients usually develop cyanosis without any symptoms in levels of 10–20%, with confusion starting above these levels and progressively worsening symptoms as the level increases resulting in coma, cardiovascular collapse, and death in levels above 70% (1, 6). The most common oxidizing agents are dapsone, topical anesthetic agents (benzocaine, lidocaine, and prilocaine), nitrites, and aniline dyes (7). Rasburicase is a recombinant uric acid oxidase and converts uric acid to water-soluble allantoin, and hydrogen peroxide, which is responsible for methemoglobinemia and hemolysis, especially with concurrent G6PD deficiency (8). Rasburicase-induced methemoglobinemia usually occurs within 24 hours of its use. Onset can be as early as 90 min from administration of rasburicase to beyond 6 hours (9). As our patient did not have any evidence of tumor lysis syndrome, and as Rituximab is not listed as an oxidizing agent, a combination of application of EMLA and recent use of rasburicase might have precipitated MetHb.

The diagnosis of methemoglobinemia requires high index of clinical suspicion. The lack of improvement in oxygen saturation with high-flow oxygen without any apparent causes and the gap in oxygen saturation > 5% between ABG and pulse oximetry (saturation gap) are considered to be the diagnostic clues. The diagnosis is confirmed by the level of methemoglobin in blood (1, 6).

The treatment with specific antidote is usually recommended in patients with blood methemoglobin level of > 20% in symptomatic patients and > 30% in asymptomatic patients. Patients with significant other comorbid conditions, including severe anemia, heart disease, lung disease, or carbon monoxide poisoning, should be treated even if the blood methemoglobin level is as low as 10%. However, symptoms may not always correlate with the level and clinical judgment is important for decision making (1, 2).

Our case had occult G6PD deficiency and developed hemolysis after a second dose of IV methylene blue. Although the patient had received rasburicase almost 60 hours prior to the hemolytic episode, the long half-life of rasburicase might have played a role in the setting of occult G6PD deficiency. Screening for G6PD deficiency before rasburicase therapy would have cautioned against the use of methylene blue and subsequently prevented hemolysis. It could have encouraged physicians to use an alternative therapy such as high-dose vitamin C, especially in the setting of methemoglobinemia. In fact, it is the drug of choice in G6PD deficiency, acting independent of the NADPH pathway (9). The diagnosis of G6PD deficiency in the suspected patient would require repeat testing in

2–3 months after the acute hemolysis episode resolves, if initial test is normal or borderline (10).

The Food and Drug Administration has a black box warning for both hemolysis and methemoglobinemia as contraindications to the use of rasburicase. It is suggested that high-risk ethnicity for G6PD deficiency, including people of African American, African, Mediterranean, and South Asian descent, should be screened for G6PD deficiency before the administration of rasburicase (10). However, it may not be practical in an emergency situation, such as severe tumor lysis syndrome and severe methemoglobinemia, because it takes 24–48 hours for test results to be available (8).

As our patient's symptoms were improved on oxygen even before the first dose of IV methylene blue, he could have been simply observed with oxygen. The decision was based on the basis of pulse oximetry, even though he did not have any tissue hypoxia and did not have any symptoms. This would have avoided the treatment-related complications, including hemolysis and blood transfusion, which can be devastating.

Conclusions

Acquired methemoglobinemia may be life threatening if not recognized and treated promptly. Non-improvement in oxygenation with high-flow oxygen without apparent causes and the saturation gap of $> 5\%$ between ABG and pulse oximetry are considered to be the diagnostic clues. The diagnosis is made by blood methemoglobin level. In patients with mild asymptomatic methemoglobinemia without any comorbid conditions, it would be reasonable to simply observe and treat symptomatically to avoid severe treatment-related complications, especially in patients with suspected G6PD deficiency. If we opt to treat these patients, treating with vitamin C would be a better choice.

Conflict of interest and funding

The authors have not received any funding or benefits from industry or elsewhere to conduct this study.

References

1. El-Husseini A, Azarov N. Is threshold for treatment of methemoglobinemia the same for all? A case report and literature review. *Am J Emerg Med* 2010; 28(6): 748.e5–748.e10. doi: <http://dx.doi.org/10.1016/j.ajem.2009.10.014>
2. Wright RO, Lewander WJ, Woolf AD. Methemoglobinemia: Etiology, pharmacology, and clinical management. *Ann Emerg Med* 1999; 34(5): 646–56. doi: [http://dx.doi.org/10.1016/S0196-0644\(99\)70167-8](http://dx.doi.org/10.1016/S0196-0644(99)70167-8)
3. Tran AN, Koo JY. Risk of systemic toxicity with topical lidocaine/prilocaine: A review. *J Drugs Dermatol* 2014; 13(9): 1118–22.
4. Cortazzo JA, Lichtman AD. Methemoglobinemia: A review and recommendations for management. *J Cardiothorac Vasc Anesth* 2014; 28(4): 1055–9. doi: <http://dx.doi.org/10.1053/j.jvca.2013.02.005>
5. Coleman MD, Coleman NA. Drug-induced methaemoglobinemia. Treatment issues. *Drug Saf Int J Med Toxicol Drug Exp* 1996; 14(6): 394–405.
6. Aryal MR, Gupta S, Giri S, Fraga JD. Benzocaine-induced methaemoglobinaemia: A life-threatening complication after a transoesophageal echocardiogram (TEE). *BMJ Case Rep* 2013; 2013. doi: <http://dx.doi.org/10.1136/bcr-2013-009398>
7. Kane GC, Hoehn SM, Behrenbeck TR, Mulvagh SL. Benzocaine-induced methemoglobinemia based on the Mayo Clinic experience from 28 478 transesophageal echocardiograms: Incidence, outcomes, and predisposing factors. *Arch Intern Med* 2007; 167(18): 1977–82. doi: <http://dx.doi.org/10.1001/archinte.167.18.1977>
8. Sonbol MB, Yadav H, Vaidya R, Rana V, Witzig TE. Methemoglobinemia and hemolysis in a patient with G6PD deficiency treated with rasburicase. *Am J Hematol* 2013; 88(2): 152–4. doi: <http://dx.doi.org/10.1002/ajh.23182>
9. Cheah CY, Lew TE, Seymour JF, Burbury K. Rasburicase causing severe oxidative hemolysis and methemoglobinemia in a patient with previously unrecognized glucose-6-phosphate dehydrogenase deficiency. *Acta Haematol* 2013; 130(4): 254–9. doi: <http://dx.doi.org/10.1159/000351048>
10. Roberts DA, Freed JA. Rasburicase-induced methemoglobinemia in two African–American female patients: An under-recognized and continued problem. *Eur J Haematol* 2014; 94(1): 83–5. doi: <http://dx.doi.org/10.1111/ejh.12350>