Methemoglobinemia in an Infant After Sclerotherapy With High-Dose Doxycycline

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Methemoglobinemia occurs when the heme moiety of hemoglobin (Hb) is oxidized from the ferrous to ferric state, leading to impairments in oxygen transport and delivery. Methemoglobinemia is rare in pediatric patients but has been described in the setting of congenital abnormalities in the Hb structure, inherited enzyme deficiencies, oxidative Hb injury in response to illness, and oxidative Hb injury due to toxicants. We present a 1-week-old infant born with a cervical lymphangioma who developed persistent desaturations that were unresponsive to oxygen after sclerotherapy with doxycycline. Arterial blood gas revealed a high Pao_2 despite low saturations being found on pulse oximetry and a methemoglobin level that was found to be elevated. Further sclerotherapy was discontinued, the saturations eventually normalized, and the methemoglobin level decreased. This is a novel report of sclerotherapy with doxycycline associated with the development of methemoglobinemia.

Methemoglobinemia is a rare diagnosis but should be considered in patients with persistent, unexplained desaturations that are unresponsive to increases in the fraction of inspired oxygen (Fio_2), particularly in the setting of normal or elevated arterial oxygen concentrations. Because the heme moiety of the hemoglobin (Hb) molecule is altered, Hb cannot adequately bind oxygen. Oxygen delivery is impaired, and tissue hypoxia may result. In pediatrics, methemoglobinemia is most commonly seen in the setting of exposure to a known predisposing chemical; local anesthetics are a common cause, although many drugs have been implicated (Table 1).[1] Patients with methemoglobinemia typically present with a normal or elevated Pao_2 but a low pulse oximeter reading that does not change with increased Fio_2. In patients with end-organ sequelae of hypoxia, treatment with methylene blue may be indicated, but milder cases may be self-limited and safely observed.

CASE REPORT

A male infant was admitted to our unit on day of life (DOL) 0 for the management of a prenatally diagnosed large cervical lymphangioma. Conception was natural and the pregnancy was otherwise uncomplicated. Labor began spontaneously at 37 weeks' gestation, and delivery was via cesarean because of a previous cesarean delivery. He was endotracheally intubated at birth for airway protection, but he required minimal ventilator settings and no supplemental oxygen.

With an MRI of the neck, providers confirmed the clinical diagnosis of a large left cervical lymphatic malformation without the involvement

abstract

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Dr Coughlin participated in the patient's care, drafted the initial manuscript, and reviewed and revised the manuscript; Dr Vrecenak made the correct diagnosis and reviewed and revised the manuscript; Drs Flibotte, Cahill, Osterhoudt, and Hedrick participated in the patient's care and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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of major neck vessels (Fig 1). He remained intubated given the size of the mass pending the initiation of treatment. His remaining needs were minimal; he tolerated full enteral feeds, and his serum bilirubin levels never crossed the threshold for treatment. Of note, his newborn screen results included a new diagnosis of glucose-6-phosphate dehydrogenase (G6PD) deficiency. Primary surgical resection and sclerotherapy were considered to be the 2 options for management. Given the size and cystic nature of this patient's neck lesion, sclerotherapy was chosen.

Sclerotherapy commenced on DOL 8. An interventional radiologist placed a drain in the lymphangioma, fluid was aspirated, and when the lesion was decompressed, it was injected with 500 mg of doxycycline (~150 mg/kg) mixed with 10 mL of iohexol, a water-soluble contrast agent (iohexol also contains 1.21 mg/mL tromethamine and 0.1 mg/mL edetate calcium disodium; pH 6.8–7.7). That evening the patient's Hb-oxygen saturation, as measured by using transcutaneous pulse oximetry, appeared to be 85% to 92%. The clinical care team increased the F_{IO_2} to 50% with no improvement in oxygen saturations. Venous blood gases revealed intact ventilation. Additional diagnostic testing, including serial blood gases and chest radiography, did not reveal further impairments of respiratory function or pathologic changes. Attempts to alter ventilator settings and vary the F_{IO_2} did not improve the patient's saturations (Fig 2). The only additional abnormalities that evolved were a mild metabolic acidosis and darkened urine; he did not have any diarrhea or evidence of enteritis.

On the following day (DOL 9), the infant received his second sclerotherapy injection at the bedside. The etiology of the abnormal saturations remained unclear; therefore, only 300 mg of doxycycline was injected and left to dwell for 4 hours. A morning complete blood count revealed new anemia (Fig 3). At that point, arterial blood gas revealed a Pa_{O_2} of 185 mm Hg, and subsequent testing results for methemoglobin were abnormal at 8.8% of an Hb of 10.2 g/dL. The methemoglobin level peaked at 14.2% of an Hb of 7.6 g/dL on DOL 10. The patient had no further sclerotherapy; the level returned to normal and was 0.7% on DOL 11. The oxygen saturation on pulse oximetry improved without any interventions. Methylene blue was not indicated as a treatment because the infant had no evidence of tissue hypoxia. In addition, the patient was G6PD-deficient on his newborn screen. This was confirmed with a low G6PD quantitative level of 2.5 U/g Hb, which we considered a relative contraindication to the use of methylene blue.

TABLE 1 Examples of Some Common Drugs Associated With Methemoglobinemia in Pediatrics

Common	Less Common
Benzocaine (topical)	Sulfonamides
Prilocaine	Amethocaine
Nitrites	Cetacaine
Dapsone	Tetracaine
Primaquine	Nitrates
Phenacetin	Methylene blue
Phenazopyridine	Metodopramide

DISCUSSION

Doxycycline is not typically identified as an agent that induces methemoglobinemia. We searched PubMed with the search terms "doxycycline" and "methemoglobinemia." We found only 1 publication in which an agent consisting of doxycycline and benzocaine (much more commonly associated with methemoglobinemia) was identified as the inciting exposure.[2] However, the doses of doxycycline used for sclerotherapy are substantially higher than those used for the treatment of antimicrobial infections. In older children, the intravenous dose rarely exceeds 4.4 mg/kg or 200 mg, whereas our patient weighed 3.3 kg and had 500 mg initially injected into his lymphangioma. Sclerotherapy has been successful in treating head and neck lymphatic malformations in children, and noted side effects include metabolic acidosis, hypoglycemia, and hemolytic anemia.[3] All of these side effects were noted in our patient. Sclerotherapy has also been associated with fever, pain, swelling, skin breakdown, cellulitis, and intracystic hemorrhage; however, methemoglobinemia has not previously been associated with this treatment.[4] Iohexol was administered in a small amount and has never been associated with acidosis or methemoglobinemia.

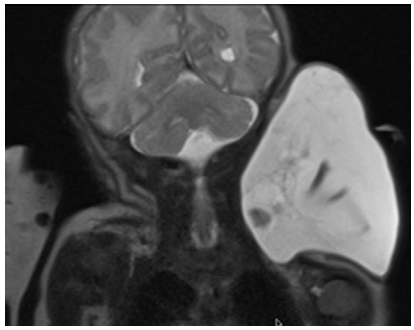

FIGURE 1
MRI of the neck, with contrast revealing a large cervical lymphangioma without impingement or involvement of the airway.

Doxycycline has been used extensively as a therapeutic agent during sclerotherapy[5] and was not known to cause methemoglobinemia in this setting, but it was a new medication administered to our patient before he developed the condition. The mechanism of methemoglobinemia formation with doxycycline is not clear; however, it is known that its degradation products are detoxified by a Fenton reaction and ferrous iron. In the setting of this Fenton reaction, superoxides, hydrogen peroxide, and hydroxyl radicals are formed.[6] Researchers in previous literature looking at the mechanism of methemoglobinemia with local anesthetic use theorized that the oxidation of Hb to superoxide

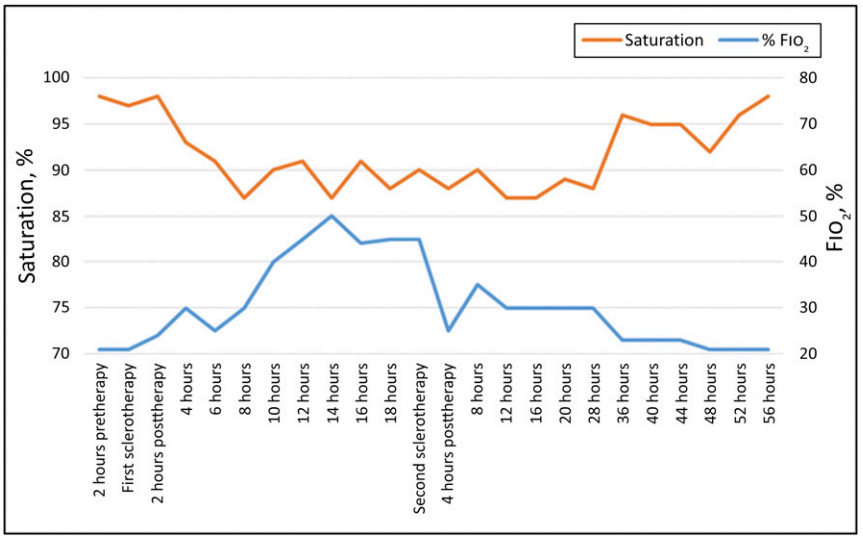

FIGURE 2
Patient FIO_2 and Hb-oxygen saturation on transcutaneous pulse-oximetry over time postsclerotherapy.

anions, hydroperoxy radicals, and hydrogen peroxide lead to increased methemoglobin formation.[7] General exposure to exogenous oxidizing drugs and their metabolites can overwhelm the reducing system and accelerate methemoglobin formation by >100-fold.[8] Although the role of oxidative injury induced by degradation products of doxycycline cannot be definitively linked to the development of methemoglobinemia, this represents a plausible mechanism in our patient and other infants with physiologically low nicotinamide adenine dinucleotide-methemoglobin reductase (NADH-MR) activity and it may warrant further exploration.

The deoxygenated heme moiety of Hb normally exists in the ferrous state, and when it is oxidized to the ferric state, methemoglobin is formed. Methemoglobin is minimally present under normal conditions because it is constantly reduced. However, when the level of methemoglobin increases, it becomes pathologic. Deoxygenated Hb must be in the ferrous state to allow for oxygen transport. Additionally, methemoglobin has an increased affinity for oxygen in the remaining unaffected heme moieties, shifting the oxy-Hb dissociation curve to the left. Thus, there is a decreased efficiency of oxygen delivery to the tissues in the setting of elevated methemoglobin.[9]

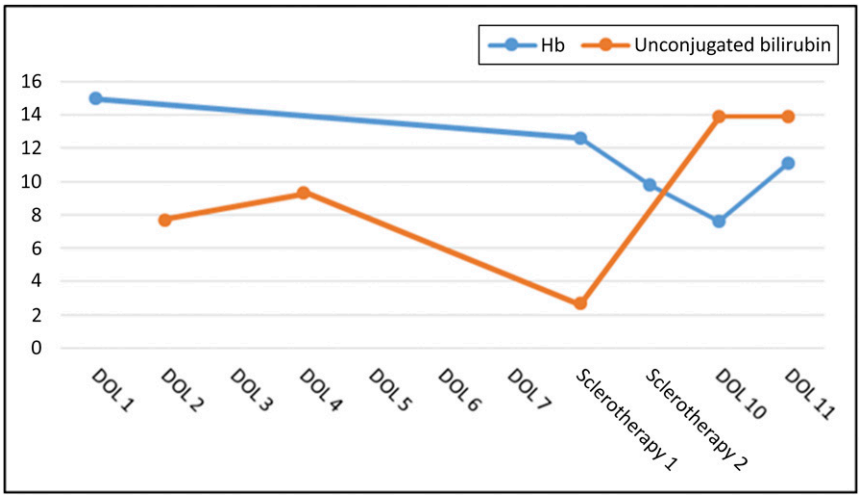

FIGURE 3
Patient Hb and unconjugated bilirubin trends over time.

Methemoglobinemia can occur because of a variety of causes, both congenital and acquired. Patients may have a congenital abnormality in their Hb structure, an inherited deficiency in methemoglobin-reducing enzymes, an oxidative Hb injury in response to illness (seen in infancy), or an oxidative Hb injury due to a chemical or toxicant exposure. Infants are thought to be more susceptible to methemoglobinemia because of a variety of reasons. They have a lower tolerance for oxidative stress as well as decreased levels of the previously mentioned reduction enzyme NADH-MR, which in some is less than half the adult level and does not normalize until between 7 weeks and 6 months of age.[10] Additionally, with fetal Hb possessing a greater affinity for oxygen than adult Hb, the neonate's oxy-Hb dissociation curve is already shifted to the left and would shift even further in the setting of methemoglobin.[11] In our patient, it is possible that the stress and acidosis associated with sclerotherapy was enough to cause excess methemoglobin formation in a neonate at high risk.

Endogenous (acquired) methemoglobinemia of infancy is a phenomenon seen most commonly in infants who have enteritis and acidosis. In this particular scenario, the enteral inflammation provides oxidant stress, and it is thought that the acidemia may inhibit already low levels of reducing enzymes. Although our patient did develop mild acidosis, this was thought to be a side effect of sclerotherapy, and there was no

evidence of enteritis. Chemical exposure is the most commonly cited cause of methemoglobinemia; although many drugs have been implicated, the presence or absence of an actual pathophysiology depends on the rate of entry of the compound into the circulation, the rate of metabolism, and the effectiveness of the methemoglobin-reduction systems.[10,12]

Patients with methemoglobinemia present with cyanosis that is unresponsive to oxygen despite normal arterial oxygen tension. As the methemoglobin level rises, the pulse oximeter will narrow to ~85% to 90% because methemoglobin has a spectrum of light absorption that is distinct from that of deoxygenated Hb, and this interferes with pulse oximetry. We saw this with our patient as the pulse oximeter narrowed to 88% and was unchanged regardless of the F_{IO_2}. Clinical signs become apparent when there is 1.5 g/dL of methemoglobin, and a rapid accumulation appears to be more clinically significant than a more gradual accumulation. Neonates can present with nonspecific findings, such as tachycardia, poor feeding, emesis, and excessive crying or sleeping. The arterial blood also becomes a chocolate-brown color with levels as low as 10% to 15%.[10]

The diagnosis can be presumptively made by noting the "saturation gap" (a discrepancy between the oxygen saturation of Hb as estimated by using the pulse oximeter when compared with the calculation derived from the blood gas measurement of Pa_{O_2}). It can be confirmed by sending a co-oximetry along with arterial blood gas. The methemoglobin level will be elevated on the co-oximetry, and the blood gas should reveal a normal or elevated Pa_{O_2}. A normal methemoglobin level is 0% to 3%, with signs and symptoms being possible at any level above that. Because this assumes a normal Hb level, lower percentages may still cause symptoms in the setting of anemia (which we saw). Symptoms are typically proportional to the methemoglobin level, and a level of 70% is usually fatal. Testing for heterozygous variability in enzymatic expression is typically unnecessary because it is unlikely to alter management and usually becomes clinically insignificant later in life.

Management is most often supportive. Indications for treatment with intravenous methylene blue include evidence of tissue hypoxia, central nervous system depression, cardiovascular instability, or comorbidities that would limit a patient's ability to tolerate decreased oxygen delivery. It should be strongly considered when a child who is not anemic develops a level >~30%. Of note, when given in excess, methylene blue can be a source of oxidative stress. In patients with G6PD deficiency, methylene blue is relatively contraindicated because the patient may have insufficient nicotinamide adenine dinucleotide phosphate hydrogen to serve as a cofactor for methemoglobin reduction, and methylene blue can instead induce hemolysis.[10] Ascorbic acid has been used when methylene blue was unavailable. It is an antioxidant that reduces methemoglobin at a much slower rate; however, it is affordable, widely available, and safe for patients who are G6PD-deficient.[13] Exchange transfusion has been described in severe cases.

In our patient, there were several factors that could have contributed to his doxycycline-associated methemoglobinemia; infants are at high risk because of low NADH-MR activity, the acidosis and hemolytic anemia secondary to his sclerotherapy likely further predisposed him, and it is possible that the high dose of doxycycline acted as a toxicant, causing oxidative stress. Clinicians practicing in environments where sclerotherapy is performed in this way or where doxycycline is used in high doses should consider methemoglobinemia in the differential for patients with new-onset desaturations without another obvious etiology.

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ABBREVIATIONS

DOL: day of life
F_{IO_2}: fraction of inspired oxygen
G6PD: glucose-6-phosphate dehydrogenase
Hb: hemoglobin

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
2. Kaczorowska-Hac B, Stefanowicz J, Stachowicz-Stencel T, Kozlowska M, Adamkiewicz-Drozynska E, Balcerska A. Methemoglobinemia in postchemotherapy stomatitis topical treatment: 2 pediatric cases. *J Pediatr Hematol Oncol*. 2012; 34(2):137–139
3. Cahill AM, Nijs E, Ballah D, et al. Percutaneous sclerotherapy in neonatal and infant head and neck lymphatic malformations: a single center experience. *J Pediatr Surg*. 2011;46(11): 2083–2095
4. Churchill P, Otal D, Pemberton J, Ali A, Flageole H, Walton JM. Sclerotherapy for lymphatic malformations in children: a scoping review. *J Pediatr Surg*. 2011;46(5):912–922
5. Cheng J. Doxycycline sclerotherapy in children with head and neck lymphatic

malformations. *J Pediatr Surg*. 2015; 50(12):2143–2146

6. Borghi AA, Oliveira-Nascimento L, Stephano MA, de Souza PM, Converti A, Palma MS. Cytotoxicity of doxycycline effluent generated by the Fenton process. *Sci World J*. 2014;2014: 439461
7. Nilsson A, Engberg G, Henneberg S, Danielson K, De Verdier CH. Inverse relationship between age-dependent erythrocyte activity of methaemoglobin reductase and prilocaine-induced methaemoglobinaemia during infancy. *Br J Anaesth*. 1990;64(1):72–76
8. Mansouri A, Lurie AA. Concise review: methemoglobinemia. *Am J Hematol*. 1993;42(1):7–12
9. Umbreit J. Methemoglobin–it's not just blue: a concise review. *Am J Hematol*. 2007;82(2):134–144
10. Erickson TB, ed. *Pediatric Toxicology: Diagnosis and Management of the Poisoned Child*. New York, NY: McGraw-Hill, Medical Pub. Division; 2005
11. Mutlu M, Erduran E, Aslan Y. Acquired methemoglobinemia in infants. *Turk J Haematol*. 2011;28(2): 131–134
12. Gunter JB. Benefit and risks of local anesthetics in infants and children. *Paediatr Drugs*. 2002;4(10):649–672
13. Waller HD, Benöhr HC, Tigges FJ. On the mechanism of ascorbic acid induced methemoglobin reduction of human erythrocytes (author's transl) [in German]. *Klin Wochenschr*. 1977;55(19): 955–964

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