Once in a blue moon: Primaquine-induced methemoglobinemia - A case report

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ABSTRACT

Methemoglobinemia is a rare blood disorder that should be suspected in patients with cyanosis and low oxygen saturation of around 85%, especially when both do not improve despite supplemental oxygen. We describe the case of a 67-year-old lung transplant patient who was treated with primaquine and clindamycin because of a positive Pneumocystis jirovecii polymerase chain reaction on bronchoalveolar lavage fluid. Soon thereafter the patient developed increasing shortness of breath, central cyanosis and hypoxia, with an oxygen saturation of 86% on pulse oximetry despite supplemental oxygen. Arterial blood gas analysis showed a peculiar dark brown color and a significantly increased methemoglobin percentage. A diagnosis of methemoglobinemia due to primaquine was made. As treatment option, we preferred ascorbic acid over methylene blue because of concerns of possibly eliciting a serotonin syndrome. Our patient recovered rapidly after initiation of appropriate treatment. A high index of suspicion is crucial since this condition is potentially fatal.

1. Introduction

Methemoglobinemia is a rare blood disorder in which abnormal amounts of methemoglobin are produced. Methemoglobin is an oxidized form of hemoglobin in which the ferrous (Fe++) iron ions are oxidized to the ferric (Fe+++ ) state. As ferric heme is unable to reversibly bind oxygen and oxygen affinity of ferrous heme is increased when ferrous irons are present in the same hemoglobin tetramer, the oxygen-carrying and oxygen-delivering capacity of blood diminishes, resulting in hypoxia and related symptoms, such as shortness of breath, headache, lightheadedness and lethargy [1]. Methemoglobin-containing blood has a typical chocolate brown color resulting in a slight gray to blue skin color in methemoglobinemia patients, often mistaken for regular cyanosis [2].

Although inherited causes do exist, acquired methemoglobinemia is much more frequent and usually drug-induced [3]. Treatment usually consists of methylene blue, but severe hemolysis in glucose-6-phosphate dehydrogenase (G6PD) deficient patients and serotonin syndrome when other serotonergic drugs are co-administered, have been described [4,5]. We describe a case of primaquine-induced methemoglobinemia in a 67-year-old-male who was successfully treated with ascorbic acid.

2. Case presentation

A 67-year-old man was evaluated at the emergency department because of fever (up to 38,9 °C), general fatigue, rhinorrhea and dyspnea for four days, without cough, thoracic pain or sore throat.

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The patient had a history of severe chronic obstructive pulmonary disease (COPD) for which he underwent a bilateral lung transplantation eleven years ago. He also suffered from mild obstructive sleep apnea syndrome, type 2 diabetes mellitus and chronic renal insufficiency, with an estimated glomerular filtration rate (eGFR) of 30 mL/min/1.73m². The patient’s therapy consisted of azathioprine, everolimus and methylprednisolone, as well as thrice weekly azithromycin and twice weekly dapsone to prevent *Pneumocystis jirovecii* (PJP) infection. Other medications included spironolactone, bumetanide, bisoprolol, atorvastatin, enalapril, moxonidine, prazosin, omeproazole, trazodone, zolpidem, gliclazide, magnesium, calcium and vitamin D.

On physical examination, he appeared mildly ill, without fever. Oxygen saturation was 96% while breathing ambient air. Pulmonary auscultation revealed normal breath sounds and clinical examination was otherwise normal. Blood analysis showed mildly elevated inflammatory markers (C-reactive protein (CRP) 57.8 mg/L), stable chronic renal insufficiency (serum creatinine 2.49 mg/dL with an eGFR of 26 mL/min/1.73m²) and normal liver function. Chest radiography showed no abnormalities. A mild infectious bronchitis was diagnosed, moxifloxacin was initiated and the patient was admitted to the respiratory department.

Two days after admission the patient developed high fever (39.1 °C). Oxygen saturation was 93% while breathing ambient air. Clinical examination and pulmonary auscultation were normal. Blood cultures were taken and moxifloxacin was switched to piperacillin-tazobactam. Over the next four days the patient continued to develop daily fever. Blood cultures remained negative. Nevertheless, meropenem was started instead of piperacillin-tazobactam and a further work-up was performed.

Chest computed tomography (CT) scan revealed bilateral ground glass opacities scattered over both lung fields (Fig. 1). Everolimus was discontinued and replaced by tacrolimus, due to concerns of possible pulmonary toxicity. Transbronchial biopsies (TBB) revealed mild (grade A2B0) acute cellular rejection, which was treated with high-dose intravenous corticosteroids followed by tapering. Bronchoalveolar lavage (BAL) fluid showed a concurrent positive PJP polymerase chain reaction (PCR) despite adequate prophylaxis. Because of the patient’s underlying chronic renal failure primaquine and clindamycin were administered as first choice for PJP treatment, instead of trimethoprim-sulfamethoxazole.

Soon after starting treatment fever disappeared and the patient’s dyspnea improved significantly. Inflammatory markers returned to normal. Four days after initiation of therapy, however, dyspnea at rest reappeared. Oxygen saturation on pulse oximetry was 87% while breathing ambient air and chest auscultation revealed normal heart and breath sounds. The patient appeared mildly cyanotic, without signs of respiratory distress. Arterial blood gas analysis showed a pH of 7.49, a pO2 of 80.3 mmHg, a pCO2 of 29.5 mmHg, a bicarbonate of 22.4 mmol/L and a methemoglobin of 13.0%. Chest radiography did not show any new findings. A diagnosis of methemoglobinemia was made and a conservative approach was chosen. Supplemental oxygen through nasal cannula (2 L/min) was initiated. Three days later the patient appeared in moderate respiratory distress and seemed more cyanotic. Chest auscultation was clear, oxygen saturation on pulse oximetry was 86% with supplemental oxygen (3 L/min) and respiratory rate was 22 per minute. Repeated arterial blood gas analysis showed a dark brown color (Fig. 2), a pO2 of 100 mmHg, a pCO2 of 35.6 mmHg and a methemoglobin of 33.7%.

Treatment with primaquine was discontinued and replaced by trimethoprim-sulfamethoxazole, despite the reduced eGFR. Oxygen flow rate was increased to 5 L per minute through nasal cannula. The next day, however, the patient continued to experience moderate respiratory distress and methemoglobinemia had even increased to 36.0%. We preferred not to treat with methylene blue due to concerns of possible serotonin syndrome, since the patient was also taking trazodone once daily. Ascorbic acid intravenously at a dose of 1 g four times daily was administered. Over the next days, the patient’s shortness of breath disappeared completely, oxygen saturation on pulse oximetry improved and the patient’s skin color and methemoglobin levels returned to normal (Fig. 3). The patient recovered completely and was eventually discharged from the hospital after 35 days, without need for supplemental oxygen.

Fig. 1. CT of the lungs showing widespread scattered ground glass opacities.
3. Discussion

This case of methemoglobinemia in a patient to whom primaquine was administered illustrates the importance of determining methemoglobin levels in patients with apparent cyanosis or low oxygen saturation on pulse oximeter, especially when there is no improvement with supplemental oxygen. A high index of suspicion is crucial not to overlook this potentially life-threatening disorder.

In a normal physiologic state, a small amount of hemoglobin is daily auto-oxidized to methemoglobin. However, compensation mechanisms are present to reduce methemoglobin to hemoglobin resulting in a steady-state methemoglobin level of less than one percent (Fig. 4) [6]. These mechanisms include reduction of methemoglobin by the nicotinamide adenine dinucleotide (NADH) dependent cytochrome b5 reductase, which is the only physiologically active pathway, and reduction by the nicotinamide adenine dinucleotide phosphate (NADPH) methemoglobin reductase. The latter only becomes active when an additional electron carrier is present such as methylene blue or riboflavin, both of which are potential treatments for methemoglobinemia [7].

One of the hallmarks of methemoglobinemia is a stable diminished oxygen saturation on pulse oximetry of around 85% [8]. Pulse oximetry takes use of the absorption of red and infrared light by blood running through the ear or fingertip. The ratio of absorption of red and infrared light, which is different for hemoglobin and deoxygenated hemoglobin, is used to estimate the oxygen saturation of the blood by comparing it to different ratios of healthy volunteers. Methemoglobin absorbs red and infrared light almost equally well, resulting in an absorption ratio of close to 1 which happens to coincide with an oxygen saturation of 85%. This effect is uninfluenced by supplemental oxygen.

Methemoglobinemia can have different causes, both inherited and acquired. The most common inherited cause is cytochrome b5 reductase deficiency, of which two types are distinguished [9]. The first type results in isolated methemoglobinemia of 10–35% and is endemic in parts of Alaska and Siberia and amongst Navajo Indians and Puerto Ricans. Patients with this genetic disorder usually experience headaches and fatigue and have reactive polycythemia. Type 2 is much less common and results not only in methemoglobinemia but also in severe neurologic deficits and death at a young age [10]. Acquired methemoglobinemia on the other hand is much more frequent and usually caused by drugs or medication such as chloroquine, dapsone, topical lidocaine and benzocaine, inhaled nitric oxide (iNO), sulfonamides, primaquine and the so-called ‘poppers’ (drugs containing volatile nitrates) [3]. In children, cases of methemoglobinemia due to contaminated well water used for food or formula feeding are described [11]. Well water may...
contain a high level of nitrates or nitrites and intestinal bacteria can convert nitrate to nitrite, which oxidizes hemoglobin to methemoglobin.

Treatment of methemoglobinemia is aimed at improving the oxygen-carrying capacity of the blood. The cause of methemoglobinemia should be identified and discontinued. Since our patient had been taken dapsone for many years and methemoglobinemia only started after initiation of primaquine (methemoglobin level was 1.8% on admission), the latter was believed to be the culprit.

Supplemental oxygen should be given and titrated to improvement of respiratory distress and shortness of breath and not to oxygen saturation on pulse oximetry or the patient’s color. In patients with a methemoglobin count of more than 30%, or lower levels of 20–30% but severe symptoms, additional pharmaceutical interventions are warranted.

Methylene blue is the drug of choice due to its rapid onset of action and is usually administered at a dose of 1–2 mg/kg intravenously over 5 min [12,13]. Repeated doses may be necessary but can provoke hemolysis, which is especially an issue in patients suffering from G6PD deficiency [4]. Use of methylene blue in these patients should be avoided. Since our patient had been treated with dapsone for many years without problems of hemolysis, G6PD deficiency seemed very unlikely. Another concern in the use of methylene blue, however, is the possibility of serotonin syndrome if serotonergic drugs are co-administered [5]. Our patient was indeed taking trazodone which has an elimination half-life of 5–9 hours. Therefore, the risk of causing serotonin syndrome in our patient was believed to be too high and methylene blue was not the preferred treatment.

As an alternative, ascorbic acid (vitamin C) was administered because of its antioxidant effects. Prospective studies are lacking and doses administered in case reports vary greatly (from 1 to 2.5 g intravenously four times daily, to more than 40 g per day orally) [14,15]. However, severe hemolysis while using very high doses is described and should be avoided [16]. Another potential treatment for diminishing the blue color in patients with inherited methemoglobinemia is riboflavin (vitamin B2) but it plays no role in the treatment of acute methemoglobinemia [17].

4. Conclusion

Methemoglobinemia is a rare disorder that should be suspected in patients with cyanosis and low oxygen saturation of 85%. A high index of suspicion is crucial as this condition is potentially lethal. Additional treatment is necessary in patients with a serum methemoglobin of more than 30% and/or severe symptoms. Ascorbic acid can be used as an alternative to methylene blue in G6PD deficient patients or when serotonergic drugs are co-administered.

Contributors

NDC was responsible for the first draft of the manuscript. All authors revised subsequent versions and approved the final version.

Patient consent

Written informed consent was obtained and is available upon request.

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed.
Declaration of competing interest

None declared.

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