A Boy with Nephrotic Syndrome and Methemoglobinemia: A Diagnostic Challenge

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Abstract
Methemoglobinemia is a rare disease characterized by the elevated levels of methemoglobin in the blood. It may be congenital or acquired. Co-trimoxazole is an antibiotic that belongs to the sulfone group. Sulfone group drugs may produce drug-induced acquired methemoglobinemia. Methemoglobin is an oxidized form of hemoglobin that has an increased affinity to oxygen and a reduced ability to release oxygen to tissues. High levels of methemoglobin in red blood cells cause tissue hypoxia. This disorder may present with several symptoms such as cyanosis, fatigue, dyspnea, and headache. Because it is a rare cause of cyanosis and hypoxemia, the diagnosis of methemoglobinemia is often delayed. We herein discuss a five-year-old boy with steroid-resistant nephrotic syndrome who presented with exertional dyspnea and cyanosis and was later diagnosed as a case of co-trimoxazole-induced methemoglobinemia.

Keywords: Methemoglobinemia; Co-trimoxazole; Nephrotic Syndrome; Child.

Introduction

Co-trimoxazole is an antibiotic containing sulfamethoxazole and trimethoprim. Sulfamethoxazole is a sulfonamide anti-microbial agent that works against various bacterial infections (1). It is an inexpensive drug that is generally used in many diseases like respiratory, ear, GI, and urinary tract infections as well as for prophylaxis against pneumocystis carinii (2).
Co-trimoxazole rarely causes dose-independent methemoglobinemia (meth Hb). This drug is metabolized in the liver through the cytochrome P-450 pathway. Its metabolites, which are potent oxidants, are responsible for some adverse hematological impacts such as methemoglobinemia (3). Here, we report a case of methemoglobinemia due to the use of co-trimoxazole for the prophylaxis of pneumocystis carinii after Rituximab infusion and discuss the relevant pathophysiology, clinical presentation, and management of drug-induced methemoglobinemia.

The parents agreed to the non-anonymized reporting of the case.
Since the occurrence of co-trimoxazole-induced methemoglobinemia is uncommon, our point here is to improve mindfulness about this condition. The key to diagnosis and management of such cases is clinical suspicion and immediate discontinuation of the agent. Methylene blue is the best antidote, and other options include high dose vitamin C and N–acetylcysteine. The serious and life-threatening complications of methemoglobinemia may necessitate exchange transfusion.

Case report

A 5-year-old boy was brought to the hospital with cyanosis, exertional dyspnea, and chest tightness for 14 days. He was diagnosed as a case of steroid-resistant nephrotic syndrome at three years of age. A biopsy was done, which revealed focal segmental glomerulosclerosis (FSGS). He received CNI and

was in remission for two years, but he developed proteinuria again.

He received two doses of rituximab infusion in 2020 followed by mycophenolate mofetil. He also received co-trimoxazole for pneumocystis carinii prophylaxis. He had no family history of a similar illness. On examination, he was cyanotic (Figure 1) with a saturation level of 60-65%. There were no obvious lung and heart issues confirmed by a normal chest X-ray and echocardiography. Bedside filter paper test was immediately done, which showed a positive result for methemoglobin. The patient's blood turned dark chocolate in the air while normal control's blood remained bright red (Figure 2). There was also a saturation gap (the difference between ABG O2 saturation of 95.5% versus pulse oximeter O2 saturation of 60%) (Figure 3 & Figure 4). His methemoglobin level measured by co-oximetry was 48%, which was elevated.

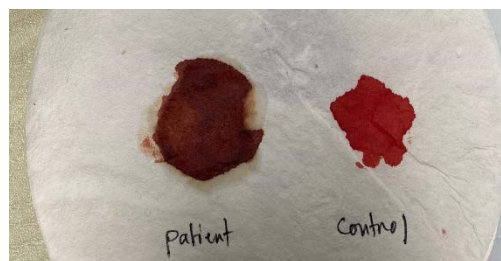

Figure 3. Blood gas of the patient

Figure 1. Feature of the patient

Figure 4. Pulse oximeter O2 saturation of the patient

Figure 2. The patient's blood turned dark chocolate in the air while normal control's blood remained bright red

His detailed investigations are given in table 1. Although methylene blue is an effective antidote for methemoglobinemia, as since was not available, high dose vitamin C-1000 mg I/V every 6 hours and N-acetyl cysteine (NAC) 600 mg I/V every 6 hours started immediately and continued for seven days. Repeat co-oximetry showed a methemoglobin level of 11 %. The patient was discharged and followed up after 14 days, and the methemoglobin level was normal.

Table 1. Paraclinical parameters of the patient

Paraclinics	Results
Complete blood count	Hb 16.3 g/dl TLC 11500/cu mm Plts 241000/cu mm
Peripheral smear	Neutrophilic leucocytosis
Liver function	normal
Renal function	normal
Chest X-ray	normal
Pulse oximetry	60% O2
ABG	Ph 7.5 PO2 68.8 Torr PCO2 18.3 Torr HCO3 14.2 mmol/L
Echocardiography	normal
Serum electrolytes	Na134, K3.7, CL103 mEq/L TCO2 14.6 mm of Hg

Discussion

Hemoglobin is a major component of red blood cells responsible for carrying oxygen to all organs in the body. Methemoglobin is hemoglobin in the form of metalloprotein in which iron in the heme group has been oxidized into Fe^{3+} (ferric) instead of Fe^{2+} (ferrous) in normal hemoglobin. Methemoglobin cannot bind to oxygen, which suggests it cannot carry oxygen to tissues. Besides, the binding of oxygen to methemoglobin leads to an increased affinity for oxygen in the remaining heme sites, which are in normal ferrous state within the same tetrameric hemoglobin unit. This results in an overall reduced ability of the red blood cells to release oxygen to tissues, with the associated oxygen–hemoglobin dissociation curve therefore shifting to the left (4). High levels of methemoglobin concentration in red blood cells cause tissue hypoxia. This disorder may present with several symptoms such as cyanosis, dyspnea, and headache (5). Our patient also presented with cyanosis, exertional dyspnea, and fatigue.

There are two types of methemoglobinemia including acquired and congenital. At least two forms of congenital cytochrome b5 reductase deficiency exist in an autosomal recessive pattern. Cyanosis is usually the first presenting symptom and appears since birth but it is usually otherwise asymptomatic (6,7). Other congenital conditions include glucose-6-phosphodiesterase deficiency, nicotinamide adenine dinucleotide phosphate

(NADPH) dependent methemoglobin reductase deficiency, and NADH-dependent methemoglobin reductase deficiency. Such defects are quite rare, so most reported cases are acquired methemoglobinemia and involve an excessive production of methemoglobin, which is often related to the utilization of or exposure to oxidant drugs, chemicals, or toxins, including sulfamethoxazole, dapsone, and native anesthetic agents (8). Our patient presented at five years of age after taking oral co-trimoxazole for prophylaxis against pneumocystis carinii. Therefore, it is acquired sulfamethoxazole induced methemoglobinemia. There is a report of methemoglobinemia in a six-year-old male patient following treatment with co-trimoxazole as prophylaxis against pneumocystis carinii after rituximab infusion, which is similar to our case (9). Methemoglobinemia is extremely rare following therapeutic doses of TMP/SMX (1,2). No other drugs causing methemoglobinemia were found in our patient. There are two case reports of co-trimoxazole induced methemoglobinemia in 14-year-old and 6-year-old boys who were receiving co-trimoxazole at a prophylaxis dose for pneumocystis carinii (9,10).

Pulse oximetry that can estimate methemoglobin levels is now commonly known as co-oximetry. Patients with methemoglobinemia may present with a low Sao2 measured by co-oximeter. Pulse oximeters only measure two ultraviolet wavelengths: oxyhemoglobin (940 nm) and deoxyhemoglobin (660 nm). Methemoglobin is detected mainly by the pulse oximeter's deoxyhemoglobin sensor only at a low level of methemoglobin (<20%), causing falsely low oxygen saturation values. At high levels of methemoglobin (>70%), methemoglobinemia is only detected by the oxyhemoglobin sensor (11). If methemoglobinemia is suspected, it is much more prudent to look at the saturation gap instead of the oxygen saturation on the pulse oximeter.

An oxygen saturation gap is defined as the difference between the ABG's oxygen saturation and the oxygen saturation measured by the pulse oximeter. This gap is usually greater than 5% in patients with methemoglobinemia. Unlike the pulse oximeter, a co-oximeter measures numerous ultraviolet wavelengths, and can detect carboxyhemoglobin, oxyhemoglobin, deoxyhemoglobin, and hemoglobin. Thus, it is a

more accurate method to assess the oxygen saturation status in patients with methemoglobinemia (6, 11).

In our patient, we also detected a saturation gap (ABG saturation of 95.3% vs. pulse oximeter saturation of 62%) of more than 33%. We also measured the methemoglobin level, which as high as 46% and confirmed the diagnosis.

The initial treatment of methemoglobinemia includes discontinuation of the inciting agent whenever possible. The first-line treatment of moderate to severe cases is methylene blue, which should be infused in asymptomatic patients with methemoglobin levels greater than 30% and in symptomatic patients with levels greater than 20%. Methylene blue is administered intravenously at a dose of 1-2 mg/kg (12). Ascorbic acid (vitamin C) is an effective alternative if methylene blue is not available; it acts as a potent reducing agent in various oxidative-reductive reactions. It requires doses as high as 300 mg /kg. In this case, since methylene blue was not available, vitamin C 1000 mg was administered every 6 hours from the beginning. N-acetyl cysteine (NAC) was also given to the patient, which is an antidote for the treatment of methemoglobinemia. It can reduce MetHb through glutathione production. NAC reacts with glutamate and glycine in the presence of ATP to form glutathione. Glutathione detoxifies oxidative agents or directly reduces MetHb (13,14).

If symptoms of methemoglobinemia do not resolve after this initial treatment with oxygen and the antidote, a prompt decision should be taken for secondary options like exchange transfusion, plasma exchange, and/or dialysis as prolonged methemoglobinemia can be lethal (15).

Conclusion

Sulfamethoxazole can seldom cause methemoglobinemia. As it is a rare cause of cyanosis and hypoxemia, the diagnosis of methemoglobinemia is often delayed. Another reason for delayed diagnosis is that the disease often remains asymptomatic unless the methemoglobin level exceeds 40%. N-acetyl cysteine (NAC) and a high dose Vitamin C seem to be effective treatments for methemoglobinemia.

Conflict of Interest

The authors declare no conflicts of interest.

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