Dapsone Induced Methemoglobinemia in Pediatric Patient: A Case Report

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Abstract

Background: Acquired methemoglobinemia is significantly more common than the congenital form, though it remains a rare condition. Most cases arise from accidental chemical exposure or the use of topical and local anesthetics.

Case Description: We present a case of 14-year-old male presented with complaints of dark grayish discoloration of the skin on the face and hands, persisting for the past two months prior to admission. He was later diagnosed with dapsone induced methemoglobinemia. Patient was then discharged with oral therapy consisting of agents with antioxidant properties and instructed to discontinue dapsone consumption.

Conclusions: In pediatric patients undergoing dapsone therapy, the risk of dapsone induced methemoglobinemia should be carefully considered to ensure early identification and prompt management, thus minimizing the potential for severe complications.

Introduction

Acquired methemoglobinemia is much more frequently encountered than the congenital form; although, remains an unommon occurrence. Most cases are due to inadvertent exposure to a chemical or through the use of topical or local anesthetics.[1] Methemoglobin levels below 10% typically cause skin discoloration but are often asymptomatic.

As methemoglobin levels rise, clinical manifestations such as dyspnea, syncope, chest pain, and palpitations may progress to tachypnea, arrhythmias, seizures, delirium, altered consciousness, severe hypoxemia, and potentially coma.[2] Therefore, Accurate diagnosis of methemoglobinemia and timely administration of appropriate treatment are essential. Here we described a case of dapsone induced methemoglobinemia in pediatric patient

Case Description

A 14-year-old male presented at our hospital with dark grayish discoloration of the skin on the face and hands persisting for the past two months prior to admission. The patient had a medical history of leprosy diagnosed seven months prior to admission. The treatment regimen consisted of multi-drug therapy for multibacillary leprosy, including 600 mg of rifampicin once a month, 100 mg of dapsone once daily, 300 mg of clofazimine once a month, and 50 mg of clofazimine

once daily. The patient has consistently taken the medication daily and continues to attend monthly check-ups at the community health center.

Upon physical examination, consciousness and examination of the lungs and heart were within normal limits; however, peripheral arterial oxygen saturation showed mild hypoxia, measuring 88% on room air. On dermatological examination, dark grayish discoloration was observed in the facial region and on both the right and left hands. Blood evaluation revealed hemolytic anemia due to drug induced hemoglobinopathy and fully compensated metabolic acidosis. Investigations including chest X-ray, electrocardiogram, echocardiography were carried out, and the results were within normal limits.

Figure 1. Blood work evaluation

Date of laboratory results				
Hematology	**8/8/2024**	**14/8/2024**	**15/8/2024**	**Reference value**
Hemoglobin	11.0 g/dl	10.9 g/dl	-	13.20-17.30
Hematocrit	33.1 %	33.6 %	-	40.00-52.00
Red blood cell	3.5 10^6/uL	3.5 10^6/uL	-	4.40-5.90
Leucocyte	4.7 10^3/uL	4.3 10^3/uL	-	3.80-10.60
Platelet	202 10^3/uL	177 10^3/uL	-	150-440
MCV	94.8 fL	95.5 fl	-	80.0-100.0
MCH	31.5 pg	31.0 pg	-	26.0-34.0
MCHC	33.2 g/dL	32.4 g/dL	-	32.0-36.0
LED	-	3 mm/ hour	-	0-10
Differential count				
Basophil	1 %	1 %	-	0-1
Eosinophil	6 %	2 %	-	2-4
Band neutrophil	2 %	3 %	-	0-6
Segmented neutrophil	48 %	52 %	-	50-70
Lymphocyte	36 %	36 %	-	20-40
Monocyte	7 %	6 %	-	2-8
Bleeding time	1.00 minute	-	-	1-3
PT-INR				
Control	11.3 Seconds	-	-	
PT (Prothrombin time)	12.6 seconds	-	-	9.4-11.3
PT-INR	1.2 seconds	-	-	
APTT				
Control	24.7 seconds	-	-	
APTT	34.3 Seconds	-	-	23.4-31.5
Liver function tests				
SGOT	34 U/L	-	-	0-40
SGPT	18 U/L	-	-	0-41
De Ritis Ratio (SGOT/SGPT)	1.9	-	-	
Ureum	35 mg/dL	-	-	<50
Creatinine				
Creatinine	0.64 mg/dL	-	-	0.46-0.77
eGFR	90 mm/minute/1.73 m2	-	-	eGFR : > 90 Normal
Random blood glucose	130 mg/dL	-	-	60-100
Creatinine				
Creatinine	0.64 mg/dL	-	-	0.46-0.77
eGFR	90 mm/minute/1.73 m2	-	-	eGFR : > 90 Normal
Random blood glucose	130 mg/dL	-	-	60-100
Electrolytes				
Natrium	134 mmol/L	-	-	136-145
Kalium	4.0 mmol/L	-	-	3.5-5.1
Chloride	102 mmol/L	-	-	98-107
Chemistry				
LDH	-	-	451 U/L	135.0-225.0
Immunology/serology				
SARS-CoV-2 Antigen	-	-	Negative	Negative
Hematology				
D-dimer	-	-	0.24 ug/mL	< 0.5
G6PD	-	-	19.3 U/gr Hb	10-14.2
Blood gas analysis				
Temperature	-	37.3 Celsius	-	
PH	-	7.360	-	7.35-7.45
pO2	-	180 mmHg	-	83.0-108.0
pCO2	-	30.1 mmHg	-	35.0-48.0
HCO3 (-)	-	16.6 mmol/L	-	21.0-28.0
CO2 Total	-	17.5 mmol/L	-	24.0-30.0
Base excess	-	-7.4 mmol/L	-	-2.4-2.3
SaO2	-	H 99.6 %	-	
Natrium (Na)	-	144 mmol/L	-	
Kalium (K)	-	3.6 mmol/L	-	
Chloride (Cl)	-	104 mmol/L	-	
Calcium (Ca)	-	0.5 mg/dL	-	
Hematocrit	-	28 %	-	

Table 2. Peripheral blood smear examination

	Results
Peripheral blood smear	Normocytic normochromic anaemia with signs of haemolysis, suspected glucose-6-phosphate-dehydrogenase deficiency or drug-induced haemolytic anaemia, accompanied by relative eosinophilia, suggestive of an allergic response

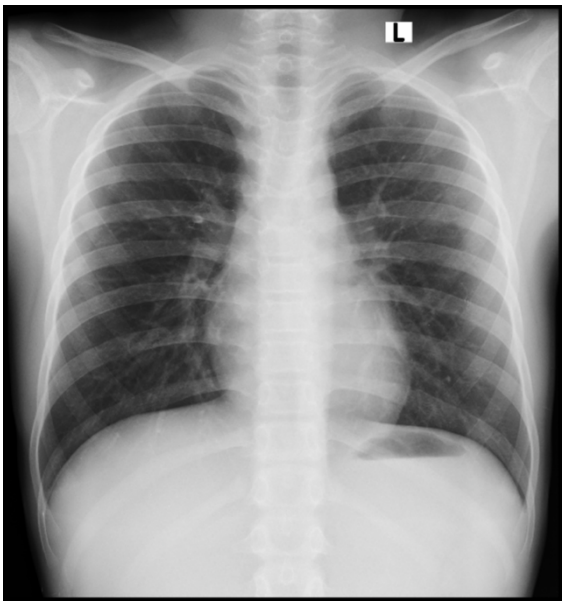

Figure 1. Chest X-ray posterioanterior view revealed no opacities or consolidation observed in both lungs, heart size and structure are within normal limits.

Intravenous therapy with 1 gram of vitamin C was administered once daily, alongside oral therapy with 600 mg of N-acetylcysteine, given twice daily. Initial peripheral arterial oxygen saturation measurement was 88% on room air, which

improved to 92% with the application of a simple mask at 7 L/min. Patient was instructed to discontinue dapsone consumption. By the second day of treatment, peripheral arterial oxygen saturation improved to 90% on room air and 93% with the application of a simple mask at 7 L/min.

On the third day, peripheral arterial oxygen saturation increased to 92% on room air and 94% with simple mask at 7 L/min, and by the fourth day, it further improved to 97% on room air. Therefore the patient was discharged and continues to be monitored at the outpatient clinic. Oral therapy of 500 mg vitamin C was given once daily, 600 mg of N-acetylcysteine given twice daily and the patient was instructed to discontinue dapsone.

Discussion

Dapsone is a common cause of acquired methemoglobinemia. Dapsone consumption results in its metabolism in the liver through the cytochrome P450 enzyme system, primarily via CYP2E1, while also acting as a substrate for CYP2C9 and CYP3A. The drug undergoes metabolism through N-acetylation and N-hydroxylation, processes that can lead to hematotoxicity associated with the formation of methemoglobin.[4] Methemoglobin is a metalloprotein characterised by the oxidation of heme iron from its ferrous form (Fe2+) to its ferric form (Fe3+). Various chemicals can facilitate the oxidation of Fe2+ to Fe3+, a form that is incapable to carry oxygen.[3]

The clinical manifestations associated with methemoglobinemia include decreased oxygen saturation accompanied by changes in skin color, such as pallor, grayish hues, or cyanosis. These changes may occur asymptomatically with methemoglobin levels below 10% in the blood. Clinical manifestations of cyanosis and dark brown blood typically emerge in patients with methemoglobin levels ranging from 10% to 30%, often without accompanying symptoms. In patients with methemoglobin levels between 30% and 50%, clinical findings such as dyspnea, dizziness, syncope, confusion, chest pain, palpitations, headache, and fatigue are commonly observed. Patients with methemoglobin levels between 50% and 70% may exhibit symptoms including fatigue, chest pain, palpitations, headache, and confusion, along with clinical signs of tachypnea, metabolic acidosis, arrhythmias, seizures, delirium, and potential coma. In cases where methemoglobin levels exceed 70%, severe clinical manifestations, including severe hypoxemia and the risk of death are frequently noted. In our patient, mild hypoxemia was observed with a peripheral arterial oxygen saturation of 88% on room air. A dark grayish discoloration of the skin on the face and hands, had been present for two months prior to admission without any accompanying systemic symptoms.

This presentation suggests an estimated methemoglobin level below 10% in the blood.[2]

Methemoglobinemia is a clinical diagnosis based on history and presenting symptoms, including hypoxemia refractory to supplemental oxygen and the likely presence of chocolate-colored blood. "Refractory hypoxemia" is a significant diagnostic clue. The diagnosis is confirmed by arterial or venous blood gas with advanced pulse oximetry devices such as the Masimo Pulse CO-oximeter, which will speciate hemoglobin to determine the methemoglobin concentration and percentage.[1]

Another modality for evaluating methemoglobinemia is the "oxygen saturation gap". Oxygen saturation gap refers to the discrepancy between oxygen saturation calculated by a standard blood gas analyzer and the value obtained from a pulse oximeter. This phenomenon may indicate an underlying hemoglobinopathy. If the gap exceeds 5%, it may suggest the presence of an abnormal hemoglobin variant, such as in cases of carbon monoxide poisoning, methemoglobinemia, or sulfhemoglobinemia. Additionaly metabolic acidosis may be associated with elevated methemoglobin levels in critical cases.

In our patient, there was evidence of refractory hypoxemia, as indicated by a peripheral arterial oxygen saturation of 88% on room air and a maximum increase to 92% on a simple mask at 7 L/Min. Additionally, the oxygen saturation gap exceeded 5%, suggesting the presence of a hemoglobinopathy.[5] The arterial blood gas analysis also revealed fully compensated metabolic acidosis. Unfortunately, we do not have access to pulse oximetry devices such as the Masimo Pulse CO-oximeter.

Methemoglobinemia does not directly cause hemolysis; however, many oxidizing agents that induce methemoglobinemia can also lead to hemolysis. Assessing glucose-6-phosphate-dehydrogenase levels is critical in excluding the possibility of hemolysis mediated by oxidative stress, including the formation of Heinz bodies or damage to cellular membranes. This evaluation is particularly important for patients with impaired oxidative stress tolerance, as seen in individuals with glucose-6-phosphate-dehydrogenase deficiency. [2]

Screening for glucose-6-phosphate-dehydrogenase deficiency is recommended due to patients with glucose-6-phosphate-dehydrogenase deficiency are less tolerant of pharmacologic oxidative stress and are at risk for substantial hemolysis. It is essential to rule out glucose-6-phosphate-dehydrogenase deficiency before initiating dapsone therapy in all patients. Another reason for evaluating glucose-6-phosphate-dehydrogenase deficiency is to assess the suitability of methylene blue therapy.

Patients with hereditary methemoglobin reductase deficiency or glucose-6-phosphate-dehydrogenase deficiency may not respond to methylene blue, and its use can significantly worsen methemoglobinemia and induce hemolysis.[6,7]

In our patient, glucose-6-phosphate-dehydrogenase deficiency was not found; however, the peripheral blood smear examination revealed hemolytic anemia due to drug-induced causes. To Minimize differential diagnosis, additional laboratory investigations such as electrolyte and glucose levels can be performed. If hemolysis is suspected, further testing should include a complete blood count, total and direct bilirubin levels, a peripheral blood smear, and a urinalysis dipstick to detect occult blood.

Therapeutic modalities ranged from Emergency and supportive measures, specific drugs and antidotes, decontamination, and enhanced elimination. Emergency and supportive measure include Maintaining an open air way, providing ventilatory support if necessary, and administering supplemental oxygen. Usually, mild methemoglobinemia (<15–20%) will resolve spontaneously and requires no intervention. In cases of dapsone-induced methemoglobinemia, supplemental oxygen is critical due to methemoglobin's reduced ability to transport oxygen, causing hypoxia despite normal respiratory function. Although oxygen alone cannot lower methemoglobin levels, it supports tissue oxygenation until definitive treatment, such as methylene blue, can be provided. This interim oxygen therapy is essential for managing hypoxic symptoms and avoiding complications from inadequate oxygen delivery.[11]

Specific drugs and antidotes, Methylene blue is indicated in symptomatic patients with methemoglobin levels higher than 20% or for those in whom even minimal compromise of oxygencarrying capacity is potentially harmful (eg, pre-existing anemia, congestive heart failure, lung disease, acute coronary syndrome). Administer methylene blue, 1–2 mg/kg (0.1–0.2 mL/kg of 1% solution), over several minutes. The dose may be repeated once in 15–20 minutes if necessary.[8]

Decontamination, consider activated charcoal Administer 60–100 g orally or via gastric tube, mixed in aqueous slurry for ingestions within 1 hour.[7] Enhanced elimination, If methylene blue is contraindicated (eg, glucose-6-phosphate-dehydrogenase deficiency) or has not been effective, red blood cell transfusion or exchange transfusion may be necessary in patients with severe methemoglobinemia. Hyperbaric oxygen is theoretically capable of supplying sufficient oxygen independently of hemoglobin and may be useful in extremely serious cases that do not respond rapidly to antidotal treatment.[2]

Ascorbic acid or Vitamin C is a natural water-soluble vitamin which reduces excessive oxidative stress. Ascorbic acid can directly reduce methemoglobinemia. Ascorbic acid is the treatment of choice when methylene blue is not available and in cases of methemoglobinemia and glucose-6-phosphate-dehydrogenase deficiency.[9] However, ascorbic acid has limited utility in acute settings due to its slow onset of acion, despite its ability to reverse methemoglobin via an alternative metabolic pathway.[8]

N-acetylcysteine has three main mechanisms of action: as a free radical scavenger; a precursor for glutathione biosynthesis; and a reducer of disulfide bonds[14]. A combination of both N-acetylcysteine's anti-oxidant properties and replenishment of glutathione is hypothesised to subdue the methemoglobinemia accumulation seen.[10] In our patient, methylene blue was not administered as the first-line antidote for methemoglobinemia due to its unavailability. we opted to initiate intravenous therapy with 1 gram of vitamin C once daily, in conjunction with oral therapy of 600 mg of N-acetylcysteine administered twice daily.

Conclusion

In pediatric patients undergoing dapsone therapy, the risk of dapsone-induced methemoglobinemia should be carefully considered to ensure early identification and prompt management, thus minimizing the potential for severe complications.

Acknowledgment

None.

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