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CASE REPORT

Methemoglobinemia Masquerading as Supraventricular Tachycardia: Unveiling the Hidden Danger of Chronic Nitrate Toxicity

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ABSTRACT

Methemoglobinemia, a condition characterized by the oxidation of hemoglobin to its ferric state, compromises oxygen delivery and can lead to life-threatening hypoxia. We present a case of a patient with refractory hypoxemia and cyanosis, ultimately diagnosed with methemoglobinemia and associated supraventricular tachycardia (SVT). While congenital cases are rare, acquired methemoglobinemia is frequently induced by medications and oxidant exposures. Our case underscores the importance of early recognition, as methemoglobinemia-induced hypoxia can precipitate severe cardiovascular complications. Prompt administration of methylene blue led to rapid clinical improvement, reinforcing its role as the first-line treatment. This case highlights the need for heightened clinical vigilance, thorough exposure history, and multidisciplinary management to optimize outcomes in methemoglobinemia-related emergencies.

Keywords

• Methemoglobinemia; • Supraventricular Tachycardia; • Methylene Blue; • Hypoxia • Emergency Medicine

INTRODUCTION

Methemoglobinemia is a hematologic disorder characterized by the oxidation of iron in hemoglobin from its ferrous state (Fe^{2+}) to the ferric state (Fe^{3+}), rendering it incapable of oxygen transport. The remaining functional hemoglobin exhibits increased oxygen affinity, impairing oxygen delivery to tissues.

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This pathological state may be congenital or acquired, with the latter being significantly more prevalent.[1]

Acquired methemoglobinemia arises from exposure to oxidizing agents, including nitrates, aniline dyes, pesticides, and a spectrum of medications such as nitroglycerin, nitroprusside, and silver nitrate. Additionally, sulfonamides, dapsone, and benzocaine contribute substantially, with dapsone and benzocaine alone accounting for nearly 45% of drug-induced cases.[2] The spectrum of potential causative agents continues to expand as novel triggers are identified.

The clinical manifestations of methemoglobinemia correlate with methemoglobin concentration, baseline hemoglobin levels, and cardiovascular reserve. While methemoglobin levels below 3% are clinically insignificant, levels between 3% and 15% are often asymptomatic. Cyanosis becomes apparent at concentrations exceeding 15%, while levels of 20–30% typically induce symptoms such as dyspnea, tachycardia, dizziness, and nausea. When methemoglobin levels surpass 40%, severe complications, including seizures, coma, arrhythmias, and lactic acidosis, can occur, with levels above 70% frequently proving fatal.[3]

Methylene blue remains the primary treatment for symptomatic methemoglobinemia, functioning as an electron donor to reduce methemoglobin back to its functional ferrous state. The standard intravenous dose is 1–2 mg/kg over five minutes, with rapid symptom resolution following administration.[4]

This case report presents a rare instance of methemoglobinemia occurring in conjunction with supraventricular tachycardia (SVT), underscoring the potential for hypoxia induced arrhythmias in affected patients. Early recognition and intervention are imperative to mitigate morbidity and prevent fatal outcomes.

CASE

A 62-year-old female, a known case of type 2 diabetes mellitus and coronary artery disease, presented to the Emergency Department with complaints of chest discomfort and palpitations persisting for two hours. On primary survey, her airway was patent, respiratory rate was 24 cycles per minute, and oxygen saturation was 82% on room air. Chest auscultation revealed clear lung fields with bilaterally equal air entry. Despite oxygen supplementation via a face mask at 7 L/min, her saturation remained unchanged at 82%. Her heart rate was 186 beats per minute, blood pressure was 110/60 mmHg, and capillary refill time was within normal limits (2 seconds), with warm peripheries.

Electrocardiography (ECG) showed supraventricular tachycardia (SVT). (Figure 1) Intravenous adenosine 6 mg was administered, followed by a saline flush, successfully converting the rhythm to normal sinus. Arterial blood gas (ABG) analysis revealed a saturation of 95%, with an oxygen saturation gap prompting further evaluation using co-oximetry, which showed methemoglobin levels of 20%. (Table 1) Notably, the patient's blood appeared darker and had a brownish discoloration compared to other patients' blood samples, further supporting the diagnosis of methemoglobinemia. (Figure 2)

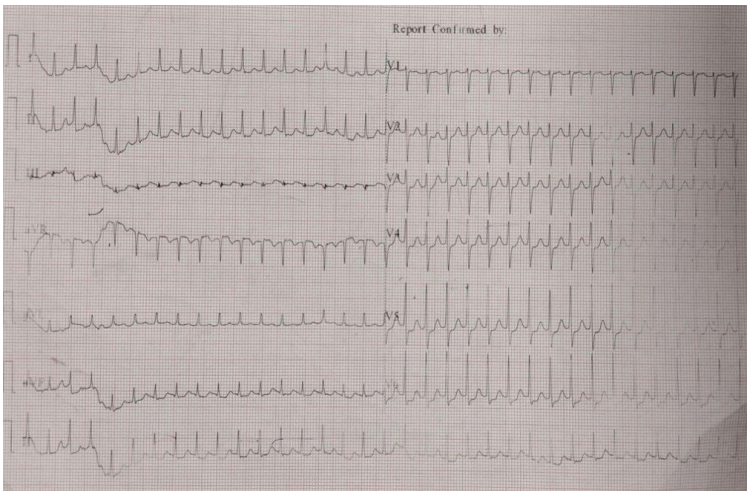


Figure 1: Electrocardiogram showing supraventricular tachycardia with narrow QRS complex and regular rhythm

Table 1: Lab Parameters of patient in ED

Parameter	Patient Value	Normal Range	Unit
pH	7.41	7.35 - 7.45	-
PCO_2	32	35 - 45	mmHg
PO_2	75	80 - 100	mmHg
HCO_3^-	21	22 - 26	mmol/L
SaO_2	95%	94 - 100%	%
Lactate	1.4	0.5 - 2.2	mmol/L
MetHb	20%	< 1.5%	%
CoHb	1.20%	< 3% (non-smokers)	%
Hemoglobin	12	16-18	g/dL
White Blood Cell Count	6,500	4,000 - 11,000	/mm³
Red Blood Cell Count	2.2	4.2 - 5.4	million/ mm³
Platelet Count	220,000	150,000 - 450,000	/mm³
Sodium	134	135 - 145	mEq/L
Potassium	4.5	3.5 - 5.0	mEq/L
Calcium	9	8.5 - 10.5	mg/dL
Magnesium	1.8	1.7 - 2.2	mg/dL
Troponin T	Negative	Negative	-





Figure 2: Brownish Discoloration of the Patient's Blood **(A)** Compared to Normal Blood **(B)** from a Control Sample

Neurologically, she was alert with a Glasgow Coma Scale (GCS) score of E4V5M6, pupils bilaterally equal and reactive, and no focal neurological deficits. Her random blood glucose was 118 mg/dL, and her body temperature was recorded at 98.5°F.

A repeat ECG post-cardioversion confirmed normal sinus rhythm. The patient reported that she had initially presented to a nearby clinic with chest discomfort and palpitations, where ECG abnormalities led to her referral to our facility. She denied symptoms of excessive sweating, radiation of pain, vomiting, or altered sensorium.

Her medication history included aspirin (75 mg), atorvastatin (10 mg), and nitroglycerin (5 mg) for 15 years with irregular compliance. She had been on metformin (500 mg) for eight years for type 2 diabetes mellitus. General physical and systemic examinations were within normal limits apart from tachycardia, which resolved post-cardioversion.

The patient was managed initially with intravenous adenosine and oxygen therapy via a face mask at 7 L/min, later escalated to a non-rebreather mask at 15 L/min. Despite these interventions, her oxygen saturation remained

unchanged. Due to the high suspicion of methemoglobinemia, intravenous methylene blue (50 mg) was administered. Within four hours, she demonstrated significant clinical improvement, and repeat ABG revealed a reduction in methemoglobin levels from 20% to 2%. She was then shifted to critical care for further monitoring.

After consultation from the cardiology, Nitroglycerin was discontinued, and after 24 hours she was transferred to the general ward. She remained hemodynamically stable throughout her hospital stay and was discharged in a stable condition after two days with advice on avoiding nitrate-containing medications and regular follow-up with the cardiology team.

DISCUSSION

Methemoglobinemia is a rare but potentially life-threatening condition that occurs when hemoglobin is oxidized from its ferrous (Fe^{2+}) to its ferric (Fe^{3+}) state, impairing oxygen transport and delivery despite adequate oxygenation. This result in functional anemia and tissue hypoxia, manifesting as cyanosis, dyspnea, neurological symptoms, and, in severe cases, arrhythmias.[5] The condition is frequently underdiagnosed due to the limitations of conventional pulse oximetry, which fails to differentiate between oxyhemoglobin and methemoglobin, often leading to falsely low or misleadingly stable oxygen saturation readings. A critical diagnostic clue is the presence of an oxygen saturation gap, where pulse oximetry-derived SpO_2 does not correlate with arterial blood gas (ABG)-derived oxygen saturation.[6] The definitive diagnosis requires co-oximetry, which directly measures methemoglobin levels and distinguishes it from other causes of hypoxia.

Medication-induced methemoglobinemia is well documented, particularly with oxidant drugs such as local anesthetics (benzocaine, prilocaine), nitrates (nitroglycerin, nitroprusside, oral nitrates), sulfonamides, dapsone, and certain antimalarial agents.[2] While nitrates are a well-recognized cause, clinicians must also consider other implicated medications. Fadah *et al*.[2] reported a case of a 64-year-old hypertensive female who developed methemoglobinemia (26%) following the initiation of hydrochlorothiazide-losartan therapy. Despite an extensive workup, no infectious or autoimmune cause was identified, and methemoglobin levels normalized within two weeks of hydrochlorothiazide discontinuation, implicating the drug as the likely etiology. This highlights the need to consider even widely used antihypertensive agents as potential contributors to methemoglobinemia. Another case, described by Mintoft et al.[7] involved two premature neonates receiving glyceryl trinitrate (GTN) patches for limb ischemia. Both infants exhibited increased oxygen requirements, which improved following patch removal, reinforcing the importance of routine methemoglobin monitoring in neonates receiving nitrate therapy due to their immature enzymatic pathways and increased susceptibility to oxidative stress. Additionally, a severe case was documented by Katabami et al.,[4] where a 28-year-old male presented with cyanosis and transient loss of consciousness following sodium nitrite ingestion. His methemoglobin level reached an alarming 92.5%, necessitating immediate intubation and methylene blue administration. Despite the severity, the patient recovered fully, demonstrating that rapid recognition and intervention can lead to complete reversal.

Cardiovascular manifestations of methemoglobinemia, though less frequently discussed, are clinically significant.[8] In the present case, supraventricular tachycardia (SVT) developed as a consequence of systemic hypoxia, likely triggered by a compensatory increase in heart rate due to inadequate oxygen delivery at the tissue level.[9] Hypoxia-induced catecholaminergic surge, autonomic dysregulation, and metabolic stress contribute to arrhythmogenesis. While methemoglobinemia is not a primary arrhythmogenic disorder, severe hypoxia can exacerbate underlying cardiac instability, necessitating consideration of metabolic and toxicological causes when evaluating unexplained arrhythmias. The successful termination of SVT with adenosine in this case was notable; however, the persistence of refractory hypoxia despite rhythm stabilization underscored the need for further investigation, ultimately leading to the diagnosis of methemoglobinemia. This highlights the necessity for clinicians to look beyond primary cardiac causes when assessing patients with tachyarrhythmias and unexplained hypoxia.[5]

The mainstay of treatment for methemoglobinemia is methylene blue, which functions as an electron acceptor, facilitating the enzymatic reduction of methemoglobin via the NADPH-dependent methemoglobin reductase pathway.[6] In the present case, a single intravenous dose of methylene blue resulted in a rapid decline in methemoglobin levels and significant clinical improvement. However, it is crucial to recognize that methylene blue is contraindicated in glucose-6-phosphate dehydrogenase (G6PD) deficiency, as it depends on NADPH for reduction and may induce hemolysis in affected individuals.[10] In such cases, alternative therapies such as ascorbic acid, hyperbaric oxygen, or exchange transfusion may be required. In addition to pharmacologic intervention, discontinuation of the offending agent is essential to preventing recurrence. Given that nitrate-induced methemoglobinemia is a dose-dependent phenomenon, clinicians should exercise caution in patients receiving prolonged or high-dose nitrate therapy, particularly those with predisposing enzymatic deficiencies.[3]

This case reinforces the importance of early recognition of methemoglobinemia in patients presenting with refractory hypoxia, particularly when there is a discrepancy between pulse oximetry and ABG-derived oxygen saturation.[7] Standard pulse oximetry is often misleading in these cases, making co-oximetry an essential diagnostic tool.[5] Furthermore, given the expanding indications for nitrate therapy, clinicians must maintain a high index of suspicion for this rare but serious adverse effect.[6] By integrating clinical vigilance, advanced diagnostic modalities, and timely therapeutic intervention, emergency physicians can effectively mitigate the morbidity and mortality associated with methemoglobinemia.

CONCLUSION

This case highlights the critical need for early recognition and prompt management of methemoglobinemia, particularly in patients presenting with unexplained cyanosis and refractory hypoxemia. While congenital forms are rare, acquired methemoglobinemia remains a significant clinical concern, often triggered by commonly used medications or industrial toxins. The association between methemoglobinemia and supraventricular tachycardia underscores the systemic impact of hypoxia, necessitating a high index of suspicion in at-risk patients.

Despite its rarity, severe methemoglobinemia can lead to life-threatening complications if left untreated. The efficacy of methylene blue in reversing methemoglobin accumulation highlights its role as the first-line therapy. However, cases secondary to prolonged drug exposure or high-dose ingestion may require alternative interventions, including exchange transfusion or hyperbaric oxygen therapy.

Furthermore, this case emphasizes the importance of medication review and exposure history in patients with unexplained hypoxemia. Given the wide range of potential oxidant triggers, clinicians must remain vigilant to prevent delayed diagnosis and adverse outcomes. A multidisciplinary approach involving emergency physicians, toxicologists, and hematologists is essential in optimizing patient outcomes and mitigating the risks associated with methemoglobinemia.

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