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Case Report

Naphthalene toxicity in a patient with G6PD deficiency

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Abstract

Naphthalene, an aromatic hydrocarbon prevalent in mothballs and deodorizers, poses significant health risks upon exposure, primarily through ingestion or dermal absorption. Herein, we report the case of a previously healthy 28-year-old male who presented with hemolysis, methemoglobinemia, and acute renal failure. The patient had a history of ingestion of mothballs, mistaking them for candy, prompting consideration of naphthalene intoxication as the clinical diagnosis, which was subsequently confirmed by laboratory findings. Given concurrent hepatic dysfunction and a diagnosis of glucose-6-phosphate dehydrogenase (G6PD) deficiency, N-acetyl cysteine was administered instead of methylene blue. The patient's condition improved after he was managed with aggressive fluid resuscitation, noninvasive ventilation, blood transfusions, and hemodialysis. Naphthalene ingestion can result in hemolysis, methemoglobinemia, and acute kidney injury, with heightened susceptibility observed in patients with G6PD deficiency.

Keywords: G6PD deficiency, intravascular hemolysis, methemoglobinemia, mothball, naphthalene

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Naphthalene, with the chemical formula C10H8, is a polycyclic aromatic hydrocarbon used in the formulation of moth repellents and toilet deodorizers. Absorption can occur through ingestion, dermal contact, or inhalation. Prolonged or excessive exposure to naphthalene commonly induces symptoms including headache, confusion, excitement, malaise, profuse sweating, nausea, vomiting, and abdominal pain [1]. Studies indicate that the lethal dose of acute naphthalene toxicity ranges from 5 to 15 grams for adults and 2 to 3 grams for children [2]. Ingestion of naphthalene leads to methemoglobinemia, characterized by a leftward shift of the oxygen-hemoglobin dissociation curve, resulting in decreased release of oxygen to the tissues. Naphthalene, being a potent oxidizing agent, initiates the generation of free oxygen radicals and triggers the depletion of glutathione, leading to intravascular hemolysis. This cascade of events further manifests as anemia, hematuria, leukocytosis with neutrophil predominance, jaundice, and dysfunction of the hepatic and renal systems [3].

Case Report

A 28-year-old male presented to the emergency department reporting ingestion of naphthalene balls (2 tablets of naphthalene balls—6 grams each) three days before admission. The patient subsequently experienced progressive dyspnea and yellowish discoloration of the skin and sclera over the following two days, which was accompanied by a 1-day history of fever. Initially managed at another facility, the patient underwent nasogastric lavage and received supplemental oxygen via a face mask because of low oxygen saturation. The following day, the patient was transferred to noninvasive ventilation because of persistent hypoxemia despite oxygen therapy. Jaundice developed two days before presentation, accompanied by one episode of dark-colored urine the day before. On examination, the patient had tachypnea (a respiratory rate of 26/26/min), a pulse rate of 122/min, normal blood pressure (110/70 mm Hg), and a temperature of 100.2°F. On admission, his oxygen saturation in room air was 64%, prompting the initiation of noninvasive ventilation

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with 100% oxygen. Despite this intervention, his saturation remained between 84% and 88%. The patient remained alert and oriented; however, he had evidence of jaundice and cyanosis of the lips and bilateral palms. Systemic examination revealed no other abnormalities. A urinary catheter was inserted, revealing dark-colored urine resembling cola (Fig. 1), while blood samples exhibited a dark brown to blackish hue (Fig. 2).

Results

Arterial blood gas (ABG) performed while the patient was on NIV showed a pH of 7.37, pCO_2 of 28 mm Hg, pO_2 of 145 mm Hg, and HCO_3 of 16 mmol/L, while peripheral oxygen saturation (SpO_2) ranged from 84% to 88%. The investigations of the patient are summarized in Table 1. The direct and indirect Coombs tests were negative, but the patient's urine tested positive for hemoglobin, with no red blood cells observed in urine cytology. The chest X-ray was normal. Methemoglobin was detected in his blood via spectrophotometry, with a recorded value of 15.3%. Methemoglobin levels on the day of admission or serial monitoring of methemoglobin could not be performed because it was not available at our center. The management of naphthalene toxicity typically involves the administration of N-acetyl cysteine. However, in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency, the administration of N-acetyl cysteine can intensify the condition. Hence, the patient's G6PD levels were examined, revealing a value of 2.2 units/gram of hemoglobin (normal range: 5.5 to 20.5 units/gram of hemoglobin) via the kinetic method. Management: The patient was started on intravenous fluids, injections of N-acetyl cysteine (1800 mg in 3 divided doses), and vitamin C tablets (1000 mg/day). However, because of low G6PD levels, injections of methylene blue could not be administered to the patient. The patient received 6 units of packed red blood cells and underwent 9 sessions of hemodialysis because of elevated creatinine levels and reduced urine output. NIV was gradually discontinued, and on the fifth day of hospitalization, the patient transitioned to oxygen via a face mask. Oxygen supplementation was discontinued on the eighth day after the patient's saturation level became normal. Urine color normalized by the ninth day (Fig. 3), with gradual improvement in urine output, and he was discharged on the thirteenth day. Follow-up at two months revealed normal hemoglobin, liver function, and renal profile.

Discussion

The prevalence of naphthalene mothball usage is rampant. A common method for identifying the composition of a mothball is to submerge it in water, where a naphthalene-based product will float. In addition to its role as a moth repellent, naphthalene is used as a toilet bowl deodorizer and soil fumigant, as well as a component in numerous other industrial products [2].

Naphthalene poisoning causes methemoglobinemia. Normally, red blood cells (RBC) contain iron in its reduced form (Fe^{2+}), which can combine with oxygen by sharing an electron, thus forming oxyhemoglobin. When oxyhemoglobin releases oxygen into the tissue, the iron molecule is restored to its original

Figure 1. Urobag of the patient.

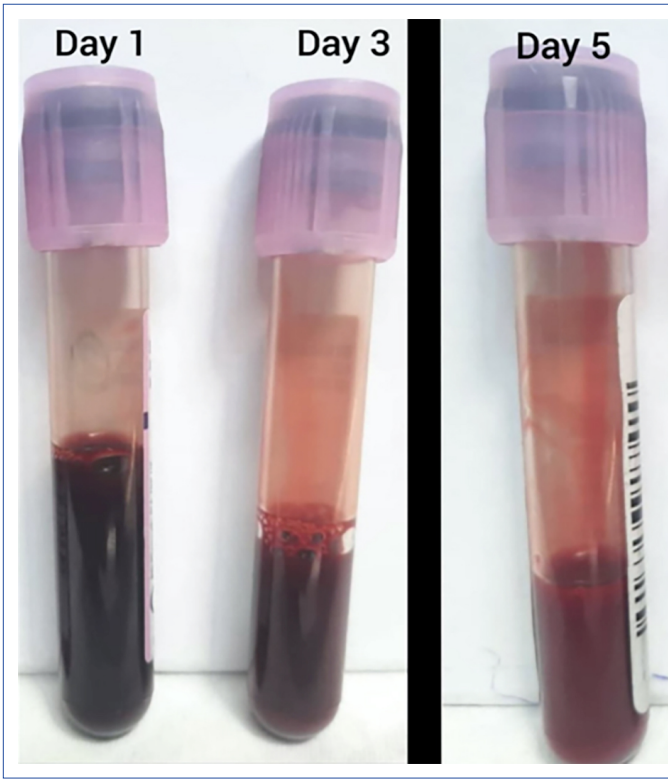
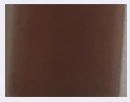
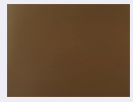
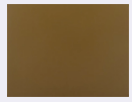
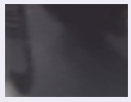
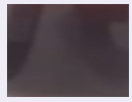
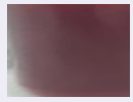


Figure 2. Colour of the patient's blood on day 1,3 and 5.

Table 1. Summary of patient investigations

Day of admission	Day 1 14/2/22	Day 2 15/2/22	Day 3 16/2/22	Day 4 17/2/22	Day 5 18/2/22	Day 7 20/2/22	Day 8 21/2/22	Day 9 22/2/22
Haemoglobin in (gm/dl)	4.4	5.5		9.7	11			9.4
Retics corrected	5.2							
Leucocyte count in cell/cu	32400	32400		23100	19800			12700
Platelets /cmm	320000	255000		227000				374000
Creatinine in (mg/dl)	3.48	7.02	7.65	7.3	6.5		7.9	
Blood Urea in mg/dl	139	240	205	160	143		192	
Urine colour								
LDH (U/L)	4028		3692					
T. bilirubin in (mg/dl)	6.1				6.1			
D. bilirubin in (mg/dl)	0.44				1.7			
AST in U/L	282				48			
ALT in U/L	42				183			
Blood colour								

LDH: Lactate dehydrogenase; AST: AST: Aspartate aminotransferase; ALT: Alanine aminotransferase

ferrous state. Hemoglobin can accept and transport oxygen only when the iron atom is in the ferrous state. Naphthalene causes the oxidation of hemoglobin to methemoglobin, i.e., oxidized iron is converted to the ferric state (Fe^{3+}), which lacks the electron needed to form a bond with oxygen and hence makes it incapable of transporting oxygen, resulting in hypoxia. Therefore, the measurement of oxygen saturation using a pulse oximeter is unreliable, as observed in this case, where the pulse oximeter saturation was less than 88% and the partial pressure of oxygen in arterial blood gas was 145 mm Hg. Co-oximetry is the gold standard for these patients [4]. Usually, methemoglobin levels are less than 1%, and levels greater than 20% cause anxiety, headaches, and dizziness. Methemoglobin ranges between 30% and 50% can cause fatigue, confusion, and tachypnea. At levels >50%, arrhythmias, acidosis, seizures, and coma can occur [1].

Naphthalene causes the depletion of glutathione, which is required for Nicotinamide Adenine Dinucleotide Phosphate (NADPH) production, resulting in the accumulation of methemoglobin as NADPH is responsible for approximately 5% reduction of methemoglobin. Also, depletion of glutathione decreases the tolerance of erythrocytes to oxidative stress, resulting in extensive hemolysis. Studies have also demonstrated naphthalene's role in the enhanced production of free

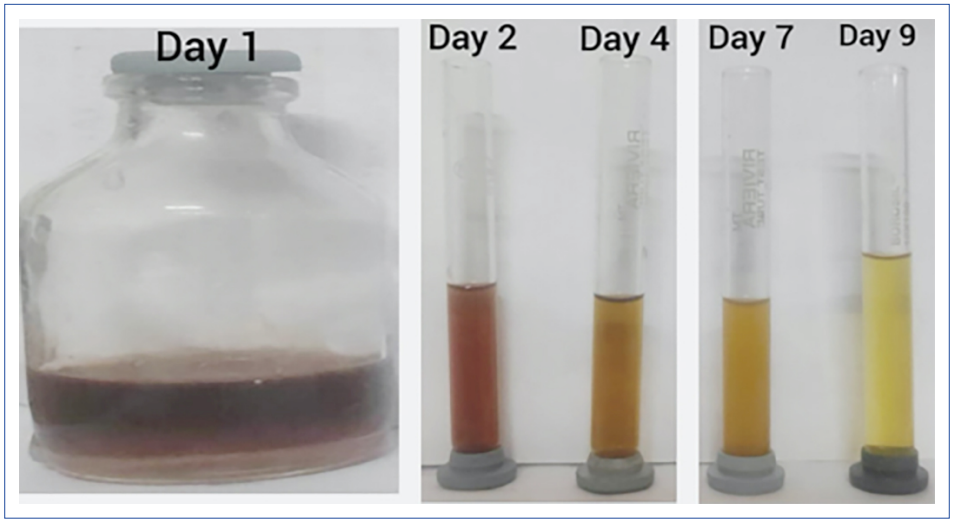


Figure 3. Colour of the urine of the patient on days 1, 2, 4, 7 and 9.

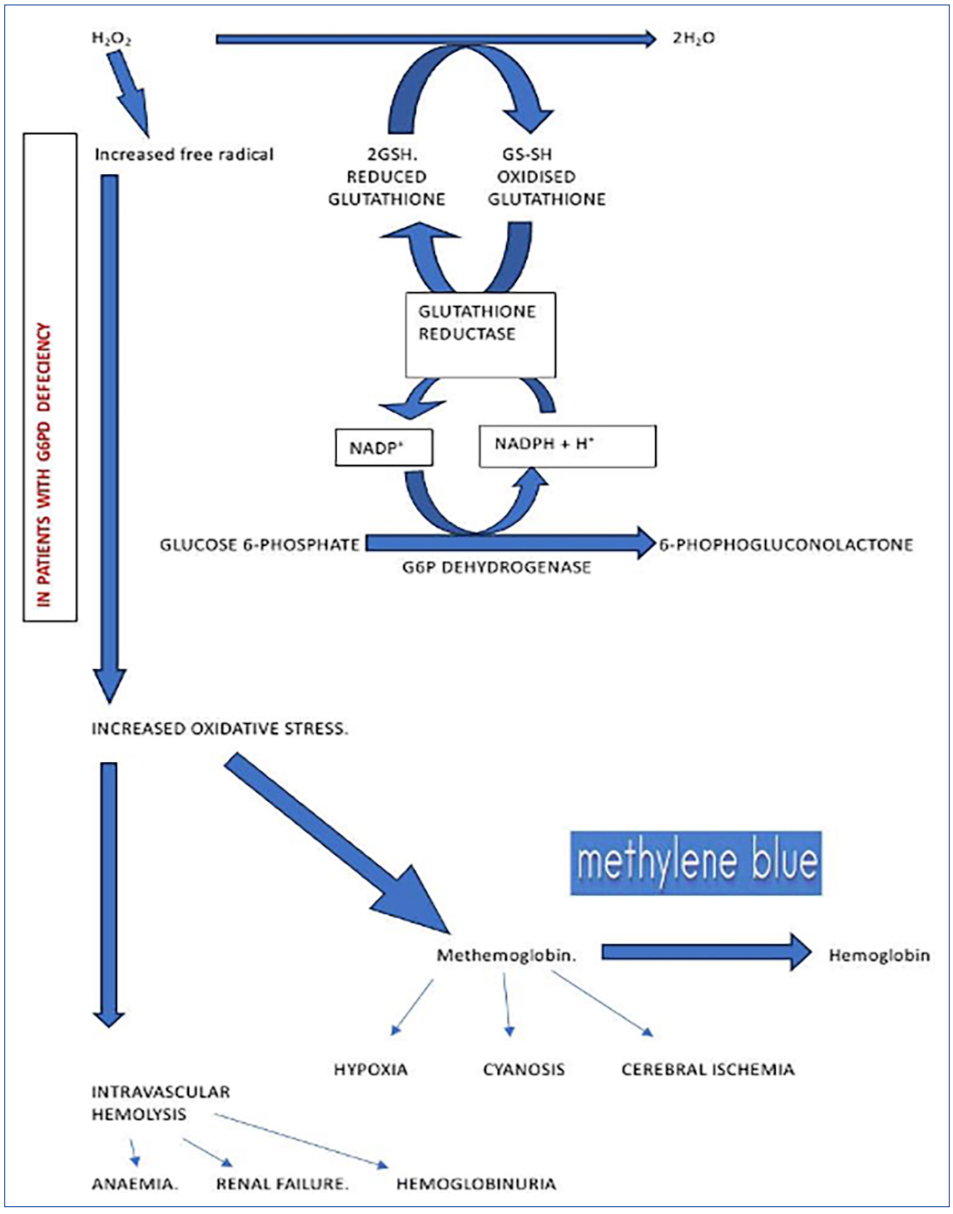


Figure 4. Flow chart explaining the pathophysiology of naphthalene toxicity.

oxygen radicals, which in turn increases methemoglobin levels and hemolysis [4]. NADPH production requires G6PD; thus, G6PD deficiency also augments methemoglobinemia and hemolysis [1], which is probably the cause of the disease severity in this case. Our patient had methemoglobinemia and G6PD deficiency, which was confirmed by elevated methemoglobin and low G6PD levels. His investigations also revealed elevated bilirubin levels, elevated LDH, and severe anemia with hemoglobinuria secondary to hemolysis. Hemoglobinuria and the direct renal toxicity of naphthalene resulted in acute kidney injury, with anuria requiring multiple hemodialysis sessions. Despite the potential risk, a heightened suspicion or a strong family history of G6PD deficiency should not entirely discourage the use of methylene blue; instead, its administration should be approached cautiously. Given the diverse manifestations and varying degrees of severity associated with G6PD enzyme deficiency, responses to different oxidative stressors can be unpredictable, making clinical outcomes challenging to anticipate. Therefore, the use of methylene blue should be considered judiciously, particularly when the potential benefits outweigh the perceived risks. If therapeutic doses of methylene blue fail to improve methemoglobin levels, further administration should be avoided to mitigate the elevated risk of hemolysis. Alternative treatment modalities should be explored, and personalized interventions can be tailored on the basis of individual patient presentations (Fig. 4).

Free radical scavengers such as ascorbic acid [5, 6], N-acetyl cysteine (a reducing agent) [7], and exchange transfusion have been found to be useful in treatment. Methylene blue augments methemoglobin's reduction to hemoglobin. A dose of 1 mg/kg body weight in adults is administered as an intravenous slow infusion in a 1% sterile aqueous solution. However, methylene blue was

not used in this case because it may induce hemolysis in cases of G6PD deficiency and may result in paradoxical methemoglobinemia. Hemolysis and hemolysis-induced acute kidney injury are managed by PRBC transfusion and hemodialysis [8].

Conclusion

Naphthalene exposure typically presents with mild symptoms; however, patients with G6PD deficiency may experience severe toxicity. Potential complications, such as methemoglobinemia and hemolytic anemia, should be anticipated and managed promptly. While there is limited evidence to direct the treatment of complex naphthalene toxicity, understanding its underlying mechanisms can facilitate appropriate management and supportive measures, leading to improved patient outcomes.

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

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