Case Report

Acute hemolytic anaemia following naphthalene poisoning in a G6PD deficient patient

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ABSTRACT:

Naphthalene is a widely used industrial and household chemical in the form of mothballs. They are potentially hazardous and rare agents of poisoning. We present a case of ingestional naphthalene poisoning in a G6PD deficient 20 years old male patient with a good outcome after proper management. He presented with abdominal pain, vomiting, fever, passage of dark cola colored urine and jaundice after deliberate ingestion of few mothballs. Features of severe intravascular hemolysis with methemoglobinemia were detected. His G6PD activity was found below normal and was diagnosed as G6PD deficiency disorder. He was treated with IV saline infusion, multiple blood transfusions, IV ascorbic acid and N-acetyl cysteine. He was discharged after 10 days of hospital stay with full recovery.

Key words: *Naphthalene, Hemolysis, Methemoglobinemia, G6PD deficiency disorder.*

Introduction:

Naphthalene is an aromatic hydrocarbon that may be found in mothballs, deodorizers, or insecticides[1, 2]. It is a commonly used household pesticide to protect clothes from moths[3] and widely available in all grocery shops, street shops and supermarkets. The lethal dose of acute naphthalene toxicity is 5–15 g for adults and 2–3 g for children[4]. Overdose, either accidental or deliberate ingestion, can lead to a myriad of clinical manifestations, including hemolysis [5].This is especially true in patients particularly susceptible to hemolysis and methemoglobinemia, such as individuals diagnosed with glucose-6-phosphate dehydrogenase (G6PD) deficiency [6].We present a case of acute hemolytic anaemia requiring multiple blood transfusions in a 20 years old male after deliberate ingestion of few naphthalene containing mothballs who was later on diagnosed as a case of G6PD deficiency disorder after evaluation.

Case presentation:

A 20 years old male patient with no other known co-morbidities was admitted in ICU in early December 2021 with the complaints of low grade intermittent fever, nausea, vomiting and passage of dark cola coloured urine for 1 day. He also noticed generalized body ache, mild upper abdominal pain and yellowish discolouration of skin and eyes. He felt severe fatigue and generalized weakness. Being frightened with these symptoms his parents took him to the emergency department where his SPO2 was found to be 75% in room air without having any shortness of breath. With these suspicious symptoms he was admitted in ICU for further management.

On further query he told that he self-ingested few mothballs (naphthalene) 4 days prior admission. This was an impulsive attempt after a heated conversation with his friend. He denied co ingestion of any other substances including pharmaceuticals. On exploration of personal history, he also admitted of having depressed mood for several years for some of his personal issues. He was a heavy smoker and occasional weed abuser.

On examination he was found to be conscious and oriented, having no neurological deficit. He was anaemic, icteric and cyanosed (peripheral). His pulse was 110/min (regular), BP: 110/70 mmhg, temperature: 100^0 F and respiratory rate: 20 breaths/min. His SPO2 was 70% in room air and 78% with 15 lit /min oxygen by NRM. Abdominal examination revealed no tenderness or organomegaly and examination of the respiratory system was normal. His urine was dark red coloured.

On initial bedside test ABG revealed: Ph -7.45; PCO_2 – 30.9; PO_2– 276, urine strip test showed trace blood and ECG revealed sinus tachycardia. On laboratory investigation: Hb% - 8.7 gm/dl, platelet count –1, 35,000/cumm, s. bilirubin- 7.51 mg/dl, indirect bilirubin-7.01 mg/dl. All liver enzymes were normal. His renal function and s. electrolytes were normal. Reticulocyte count was raised to 2.71% and LDH was raised. PBF revealed anisochromic and anisocytic RBC with a few spherocytic and occasional polychromatic and nucleated red cells with reduced platelets. Features were suggestive of hemolytic anaemia with thrombocytopenia. USG of whole

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abdomen was normal. His urine routine examination was normal and urine test for drugs of abuse were negative. Whereas his urine for hemoglobin test came positive.G6PD enzyme level was sent which came 5.45 U/gHb where the normal value was 7-20.5 U/gHb that means the patient was G6PD deficient.

Progression of the biochemical parameters of the patient is shown in Table -1

Table 1

Parameters	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Hb%(gm/dl)	8.7	7.1	7.3	9.4	10.3	10.5
S. bilirubin (mg/dl)	7.51	7.3	7	2	1.44	.86
Indirect S. bilirubin (mg/dl)	7.01	6.9	6.6	1.7	1.17	.50
Reticulocyte count	2.7%	-	4.11%	-	4.07%	4.5%
Urine colour	Dark	Dark	Red	Red	Normal	Normal
Urine for haemoglobin	(+) ve	(+) ve	(+) ve	Not done	Not done	(-) ve

He was been treated with 5 units of PRBC transfusion to keep his Hb% in desired level. He was also given Inj. N- acetyl cysteine 1.2 gm daily and IV ascorbic acid 500 mg daily. His hydration was maintained properly by giving 3.5 - 4 litres of fluids daily from day 1, hence his renal function remained adequate ensuring >50 ml/hr urine output. After second unit of PRBC transfusion patient's SPO_2 was maintaining around 95-96% with improvement of cyanosis. From day 5 he started improving having static haemoglobin level needing no further PRBC transfusion. His S.bilirubin dropped and urine colour became normal. SPO_2 was consistently > 95% in room air with stable vitals and ABG parameters.

On day 7 he was stepped down to ward and on day 10 he was discharged home as he was totally asymptomatic. He was discharged with the advice of further F/U with hematologist for G6PD deficiency and also to psychiatrist for counselling.

Discussion

Mothballs historically contained camphor but are currently more commonly comprised of para-dichlorobenzene or naphthalene[1].Naphthalene mothballs are commonly used in households. It has rarely been an agent of poisoning worldwide [7]. Acute hemolysis due to exposure of naphthalene mothball has been reported worldwide [8, 9]. But from Bangladesh naphthalene toxicity in adult following deliberate ingestion is rarely reported. In 2012 for the 1st time Rahman et al.[7] reported a 22 years Bangladeshi woman having hemolytic anaemia after accidental ingestion of coconut oil containing naphthalene. But the woman had normal G6PD level. But in our current reported case, acute hemolytic anaemia occurred in a 20 years old G6PD deficient Bangladeshi male after deliberate naphthalene mothball ingestion. Interestingly, this G6PD deficient male was undiagnosed at the time of presentation; even he had no past history of hemolytic episode. The diagnosis of G6PD deficiency was disclosed after laboratory confirmation.

Naphthalene (C10H8) is a volatile polycyclic hydrocarbon[10] with a molecular weight of 128 (C10H8)[8]. Toxic effects of naphthalene had been reported through various modes of exposure, including inhalation, external skin contact, and ingestion[10]. After ingestion, naphthalene is readily absorbed and metabolized by cytochrome P450 oxidation and later is excreted in the urine as mercapturic acids, methyl-thio derivatives and glucuronide conjugates[7]. Alpha- naphthol, a potent metabolite of naphthalene, causes oxidative stress[1] which induces enhanced production of free oxygen radicals, resulting in lipid per oxidation and deoxyribonucleic acid damage [8] which cause acute hemolysis, jaundice and anemia[1].

In addition to hemolysis, due to its potent oxidizing property, it converts hemoglobin to methemoglobin, leading to methemoglobinemia[11]. Methaemoglobin is abnormal haemoglobin in which the iron moiety of unoxygenated haemoglobin is in the ferric state rather than the ferrous state. Thus, methaemoglobin is the oxidized form of haemoglobin, which does not bind oxygen and increases the affinity of oxygen for the partially oxidized portion of haemoglobin[12]. Pulse oximetry is unreliable in the setting of methaemoglobinaemia[13]. If the oxygen saturation is 100%, the methaemoglobin spuriously decreases the pulse oximeter reading to around 85%[13]. Co-oximetry is the gold standard in these patients[12]. When the concentration of methaemoglobin in the blood is above 1.5%, the patient develops cyanosis[12]. Therefore, the presence of cyanosis and reduced SPO_2 with normal PO_2 in arterial blood gas should raise the suspicion of methemoglobinemia which actually happened in our case.

Apart from hemolysis and methemoglobinemia naphthalene exposure can cause myriads of systemic features which are listed in Table -2[14]

Table 2

Gastrointestinal Effects
Nausea, vomiting, abdominal pain, diarrhoea
Renal Effects
Increased creatinine level, increased serum urea nitrogen level, hematuria, renal tubular acidosis
Respiratory Effects
Acute Respiratory Distress Syndrome
Neurologic Effects
Confusion, lethargy, vertigo, fasciculations, convulsions, anesthesia, cerebral oedema, coma (coma is noted at 0.05mg/kg body weight per day)
Hepatic Effects
Jaundice, hepatomegaly, elevated liver enzyme levels (noted at 0.02mg/kg per day)
Ocular Effects
Ocular nerve atrophy, bilateral cataracts with chronic exposure

Following naphthalene exposure hemolysis occurs through either hemoglobin or cell membrane effects, particularly in patients with a low tolerance to oxidative stress, like G6PD deficiency [8]. G6PD deficiency is an X-linked recessive disorder, with male predominance, and has an incidence of about 400 million individuals globally[15].G6PD deficiency is the second most common human enzyme defect[15]. It is an inborn error of metabolism that predisposes to red blood cell breakdown[15].Triggers of hemolysis in G6PD deficiency include infection, fava beans, naphthalene and some antimalarial medications [15]. G6PD enzyme is essential in red cell metabolism through the pentose phosphate pathway, providing protection against oxidative stress on the cell [15]. G6PD deficient patients have decreased resistance to oxidative stress due to decreased production of the reduced form of NADPH [15].

After exposure to naphthalene hemolysis usually starts by the second day and can be protracted up until a week[16]. Therefore, screening for hemolysis should continue until a week of post-exposure [16]; however, in our case, the patient presented with features of hemolysis on the third day of ingestion. A fall in hemoglobin and hematocrit levels with a high reticulocyte index, as well as spherocytosis and Heinz bodies in blood picture denote hemolysis. Unconjugated hyperbilirubinemia as well as high lactate dehydrogenase would also be found. Significant intravascular hemolysis gives rise to hemoglobinuria due to over saturation of hemoglobin scavengers such as haptoglobin[12]. This may lead to acute kidney injury due to tubular precipitation of free hemoglobin [12], which was not seen in our patient. In our case pigment nephropathy and acute kidney injury were prevented by adequate hydration and urine alkalinization.

Treatment of naphthalene toxicity is mainly supportive which involves blood transfusion to restore normal hemoglobin level[5]. Other supportive treatment includes oxygen therapy, monitoring of adequate fluid balance to prevent renal failure and electrolyte correction, administration of alkalis in case of hemoglobinuria, and renal replacement therapy in case of AKI[3].

Specific treatment includes the use of methylene blue and exchange transfusion. Methylene blue increases the rate of conversion of methaemoglobin to haemoglobin by accepting an electron (in the presence of NADPH and methaemoglobin reductase), to form leucomethylene blue, which can then donate this electron to reduce methaemoglobin[17]. Exchange transfusion is the treatment of choice in patients with G6PD deficiency as methylene blue itself may induce haemolysis and cause paradoxical methaemoglobinaemia in these patients[18]. Ascorbic acid is used to treat methemoglobinemia when methylene blue is not available to restore normal hemoglobin levels[5]. N-acetyl cysteine may also be used as a reducing agent especially in G6PD deficient patients[5]. In mild cases, if the offending agent is removed, methemoglobin may return to normal hemoglobin within a few days[7].

This case describes the effect of oxidative stress and subsequent hemolytic anemia secondary to ingestion of naphthalene-containing mothballs in a patient who was later on diagnosed with G6PD deficiency. The patient was successfully treated with blood transfusion and supportive care. The patient was discharged with all biochemical parameters including the hemoglobin and hematocrit within normal limits. The patient's parents and patient himself were educated regarding the avoidance of foods and substances that may trigger hemolysis in G6PD deficiency.

Conclusion

Naphthalene overdose can be dangerous as it can lead to severe intravascular hemolysis as well as methemoglobinemia. Both are potentially treatable when diagnosed promptly and if managed properly, the patient can have good outcome. Complications such as acute kidney injury could be prevented by meticulous fluid management and urinary alkalization. As naphthalene is extremely common in households, physicians should be aware of the toxidrome of naphthalene poisoning.

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