Mothball Ingestion in the Setting of G6PD Deficiency Causing Severe Hemolytic Anemia, Methemoglobinemia, and Multiple Organ Failure in a Toddler

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Abstract

Mothballs containing naphthalene or paradichlorobenzene are known to cause hemolysis and methemoglobinemia. They can also affect the other organs, including the kidneys, liver, lungs, and skeletal muscles. The involvement of 1 or 2 organs at a time has been commonly reported. However, more than 2 organ dysfunction in mothball intoxication is rare and usually indicates severe illness. The intoxication can have more pronounced symptoms in children with glucose-6-phosphate dehydrogenase (G6PD) deficiency. We report this case of a previously healthy 13-month-old patient who presented with severe hemolysis, lactic acidosis, methemoglobinemia, acute renal failure, hepatic dysfunction, and rhabdomyolysis. He required aggressive fluid resuscitation, blood transfusions, and mechanical ventilation. The underlying etiology of his illness was initially unclear; however, upon repeated questioning, the father recalled the patient chewing on a mothball 3–4 days before admission. Hence, mothball intoxication was considered the most plausible clinical diagnosis in this patient. He was given N-acetylcysteine, instead of methylene blue, because of hepatic dysfunction and the fact that G6PD deficiency could not be ruled out in the presence of acute hemolysis. The patient made a full recovery after 2 weeks of intensive care unit management. G6PD testing after 3 months confirmed the deficiency. These mothballs are available in Hawai'i, but this is the first report of such a severe presentation to our knowledge. The presence of methemoglobinemia, severe hemolysis, and thorough history-taking helped us determine the diagnosis of mothball intoxication and enabled definitive treatment.

Keywords

hemolysis, anemia, methemoglobinemia, multiple organ failure, mothball, naphthalene

Abbreviations and Acronyms

ALT = alanine aminotransferase
AST = aspartate aminotransferase
BUN = blood urea nitrogen
DIC = disseminated intravascular coagulation
ED = emergency department
G6PD = glucose-6-phosphate dehydrogenase
HUS = hemolytic uremic syndrome
LDH = lactate dehydrogenase
NAC = N-acetylcysteine
NADPH = nicotinamide adenine dinucleotide phosphate
PRBC = packed red blood cell
PICU = pediatric intensive care unit
RBC = red blood cells
TTP = thrombotic thrombocytopenic purpura
WBC = white blood cells
UA = urinalysis

Introduction

Naphthalene is an aromatic hydrocarbon used in mothballs and some insecticides. Paradichlorobenzene has also been used in mothballs and is less toxic than naphthalene.[1,2] These toxins are known to cause hemolysis by oxidative stress. A little over 1000 cases of mothball intoxication were reported in the United States in 2018. A majority of these cases occurred in children younger than 5 years of age, and 95.8% of the cases were accidental.[1] Intoxication occurs upon ingestion, inhalation, or dermal exposure. The symptoms are proportionate to the degree of exposure. Clinical course after intoxication can be self-limiting in otherwise healthy individuals.[2-4] Mild symptoms include nausea, vomiting, diarrhea, fever, abdominal pain, and headache.

Intoxication can have more pronounced symptoms in children with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Severe hemolysis and the need for multiple transfusions have been reported in this population.[4] G6PD is an enzyme that protects against oxidative stress by providing a source of nicotinamide adenine dinucleotide phosphate (NADPH) through the pentose phosphate pathway. Red blood cells (RBC) rely on the pentose phosphate pathway to provide the protective effects of NADPH, especially in times of oxidative stress.[5] Severe complications like renal failure, hepatic dysfunction, cerebral edema, rhabdomyolysis, respiratory depression, and methemoglobinemia have been reported in mothball intoxication.[2-4,6-10] The degree of organ involvement varies according to the severity of illness. While the involvement of 1 or 2 organ systems is commonly reported, more than 2 organ system dysfunction is less frequent and indicates severe illness.[2-4,6-7] Hemolysis and methemoglobinemia can be prolonged without intervention and can lead to severe complications, such as renal failure requiring dialysis or even death.[6-12] Therefore, prompt recognition and a high index of suspicion are critical in these cases to administer appropriate interventions, including ascorbic acid or N-acetylcysteine (NAC). Methylene blue is commonly used to treat methemoglobinemia but is contraindicated in patients with G6PD deficiency because of the risk of worsening hemolysis.[2,3]

We report this case of a 13-month-old patient who presented with severe hemolytic anemia, methemoglobinemia, lactic acidosis, and multiple organ failure after exposure to mothballs.

Case Report

A previously healthy 13-month-old male developed a cough, runny nose, and fever. Four days later, this progressed to lethargy, pallor, jaundice, vomiting, and diarrhea. He presented to the emergency department (ED) with tachypnea and decreased urine output. His vital signs in the ED included a temperature of 100.8° Fahrenheit, heart rate 170/min, respiratory rate 70/min with severe distress, and hypoxemia to 80% on room air, which improved to 85% on supplemental oxygen via a non-rebreather face mask. His initial workup showed hemoglobin of 2.7 g/dL, absolute and corrected reticulocyte counts were 0.047 x 10^{12} and 1.2%, respectively, with a peripheral blood smear showing evidence of hemolysis, white blood cells (WBC) 46.8 x 10^9/L, platelets 351 x 10^9/L, indirect bilirubin 4.4 mg/dL, blood urea nitrogen (BUN) 36 mg/dL, creatinine 1.07 mg/dL, anion gap 22 mEq/L, aspartate aminotransferase (AST) 120 U/L, and urinalysis (UA) with large blood by dipstick but only 5–10 RBC per high power field and elevated urobilinogen. His blood gas showed metabolic acidosis with pH 6.75, PCO_2 of 26.5 mm Hg, bicarbonate 3.6 mmol/L, lactate 15.47 mmol/L, methemoglobin 6.4% (normal range, 0.4% to 1.1%). The remainder of his initial workup was unremarkable.

He required intubation, mechanical ventilation, intravenous fluid resuscitation, and 3 units of packed red blood cell (PRBC) transfusion in the ED. After initial stabilization, he was admitted to the pediatric intensive care unit (PICU) for further management.

Critical care was continued, and a thorough history was obtained in the PICU. The history included diet and other occurrences spanning the days before hospitalization to identify potential triggers for his presentation. Upon repeated and thorough questioning, the father recalled the patient chewing on a mothball 3-4 days before admission. An uncertain portion of the mothball appeared to have been ingested. Medical attention was not pursued at that time because of an apparent lack of symptoms.

The patient developed multiple organ system dysfunction including hemolytic anemia with peak values of haptoglobin 17 mg/dL, lactate dehydrogenase (LDH) 5439 U/L, methemoglobinemia 6.4%, creatine kinase (CK) 3412 U/L (indicating myolysis), creatinine 3.7 mg/dL, BUN 93 mg/dL, alanine aminotransferase (ALT) 1431 U/L, and respiratory failure. The patient required multiple blood products, including PRBC, fresh frozen plasma, and platelet transfusions. He exhibited signs of fluid overload from ongoing fluid resuscitation and blood transfusions in the setting of acute renal failure. Renal replacement therapy was considered but was avoided with medical management. A respiratory viral panel was positive for rhinovirus/enterovirus, which was suspected of contributing to his respiratory failure. Blood, urine, respiratory, and stool cultures were all negative. Abdominal and renal ultrasounds found hepatomegaly and increased renal parenchymal echogenicity, respectively. NAC was administered per recommendations by the Hawai‘i Poison Center.

His organ dysfunction gradually improved and normalized during approximately 24 days of hospitalization, although he continued to have mild hemolysis with elevated LDH. Following extubation, he was deconditioned with muscle weakness, hypotonia, and dysphagia, which returned nearly to baseline by the time of discharge following 10 days of extensive rehabilitation. Magnetic resonance imaging of the brain showed no evidence of hypoxic injury. He required hydralazine and clonidine for hypertension, most likely due to renal injury, which was weaned over 3 months following discharge. Renal function and blood pressure were normal at his last nephrology follow-up, 18 months after the hospital discharge.

Although initial testing was negative for G6PD deficiency, a follow-up outpatient testing revealed a deficiency with levels at 3 u/gHgb@37 dg (normal value, 7.0 to 20.5).

Discussion

This case report describes rare and severe manifestations of multiple organ system failure after mothball ingestion.

The differential diagnosis in our patient included hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), sepsis with disseminated intravascular coagulation (DIC), and mothball intoxication. Lack of thrombocytopenia excluded HUS, TTP, and DIC. Negative blood, urine, and respiratory cultures made sepsis less likely. Our patient's initial cough and runny nose can be attributed to rhinovirus infection. However, severe hemolysis, methemoglobinemia, and extreme multiple organ failure have not been described in this context. Conversely, respiratory tract involvement with congestion, fever, and acute respiratory distress syndrome have been reported from mothball intoxication.[11] Congenital methemoglobinemia usually presents within the first few hours to days of life.[15,16] A new-onset methemoglobinemia at 13 months in our patient resolved with treatment, making an acquired etiology more likely. Certain medications, dietary, environmental substances can cause acquired methemoglobinemia.[5] These etiologies were ruled out by detailed history-taking. Therefore, mothball intoxication was the most plausible clinical diagnosis in our patient. In our literature review, a history of mothball exposure followed by hemolysis, methemoglobinemia, with or without organ failure, was considered diagnostic of mothball intoxication.[2,3,6,9,11-14] In some case reports, there was a definite history of mothball exposure followed by the development of hemolysis or methemoglobinemia, with or without organ failure.[6,8,10,11,13,14] In other cases, the patients had a similar presentation, and the mothball exposure was identified in retrospect due to a high index of suspicion.[3,9,12] The latter was similar to our case. Naphthalene levels were not obtained in those other reported cases.[2,3,6,9,11-14]

Naphthalene and paradichlorobenzene can cause hemolysis by oxidative stress. Methemoglobinemia occurs because of the inability of heme to be reduced from the ferric (3+) state back to the ferrous (2+) state, and therefore, the oxygen-carrying capacity

is severely compromised.[2] A methemoglobin level of more than 1.5% can be associated with cyanosis.[15] Rhabdomyolysis is likely due to very high amounts of oxidative stress leading directly to muscle breakdown.[12]Skeletal muscles can be the source of AST and ALT,[17] though direct hepatic dysfunction and death have been reported from naphthalene toxicity.[18] Our patient's AST and ALT elevation could be related to rhabdomyolysis or from direct hepatic injury from the mothball intoxication. Renal failure is usually associated with direct damage by the free filtering of hemoglobin following hemolysis and myoglobin following rhabdomyolysis.[2,3,6,9,14] Respiratory failure may occur due to methemoglobinemia-induced endothelial dysfunction.[19]

The diagnosis of G6PD deficiency is based on enzymatic activity. The activity can be falsely elevated in the presence of hemolysis, reticulocytosis, or after blood transfusion.[2,3,5] We repeated the assay after 3 months, which confirmed the diagnosis of G6PD deficiency. The rationale of repeating the test after 3 months was based on the expectation of hemolysis resolution and the anticipation of transfused RBC replacement by native RBC.

Decontamination with activated charcoal has been recommended within the first 4 hours of ingestion, and further decontamination with whole-bowel irrigation with polyethylene glycol can be considered.[2] This treatment was not indicated in our patient because he presented after 3-4 days of exposure. The toxic dose of mothballs is unknown in the pediatric population, but any amount of ingestion should warrant thorough workup and close monitoring. More than 1 mothball (0.5 g) can be potentially toxic in an adult patient. [2] Naphthalene toxicity is treated with supportive care, hydration, and blood transfusion.[2,3,11,13] Ascorbic acid or NAC may be used in these situations to reduce oxidative stress.[2,3,11] NAC is also a source of glutathione and supports hepatic recovery.[2,3,11,15,16] Our patient had both methemoglobinemia and hepatic dysfunction. Therefore, NAC was the treatment of choice in our case. Since G6PD deficiency could not be ruled out in our patient during the acute hemolytic phase, he did not receive methylene blue. Renal replacement therapy and hemodialysis have been described in other cases; however, we avoided this with medical management.[9,11,14] Rhabdomyolysis has been rarely reported, and our patient had a more severe presentation than the existing literature.[12] To our knowledge, our patient represents 1 of the more severe cases of mothball intoxication described, made even more noteworthy by his complete recovery.

Conclusion

Our case report revealed the following recommendations: (1) Intoxication from mothball containing naphthalene or paradichlorobenzene should be considered in cases presenting with severe hemolysis and methemoglobinemia with or without organ dysfunction.[2-4,6-11] This clinical diagnosis can be supported by quantitative serum or urine analysis for naphthalene levels but not required;[2,3,6,9,11-14] (2) Hemolysis and methemoglobinemia can be prolonged without intervention[10], leading to severe complications such as renal failure requiring dialysis or even death.[2,6,8,9,11,14] Therefore, prompt recognition and treatment are pivotal. Diagnosis of such intoxication is also essential for the family's education to prevent such recurrences and seek early medical attention; (3) Supportive care with fluid resuscitation and blood transfusion is the mainstay of the treatment of mothball-induced hemolysis. Methylene blue is commonly used for the treatment of methemoglobinemia but is contraindicated in patients with G6PD deficiency. Ascorbic acid or NAC can be considered in such cases[2,3,11]; (4) Diagnosis of G6PD in the acute phase may not be possible; therefore, it should be repeated approximately 3 months after the acute phase is over.

Conflict of Interest

None of the authors identify any conflict of interest.

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