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LIFE-THREATENING METHAEMOGLOBINAEMIA SECONDARY TO CETRIMIDE

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ABSTRACT

Methaemoglobinaemia is a rare but potentially life-threatening condition in which there is diminution of the oxygen-carrying capacity of the circulating haemoglobin. It can result from either congenital or acquired processes. Acquired methaemoglobinaemia is more prevalent than congenital methaemoglobinaemia, and notably it has a higher prevalence in infants and neonates than in adults; it results from exposure to oxidising agents. Methaemoglobin forms when haemoglobin is oxidised to contain iron in the ferric (Fe^{3+}) state rather than the normal ferrous (Fe^{2+}) state. Methaemoglobinaemia is a clinical diagnosis and is suspected in the presence of hypoxaemia refractory to supplemental oxygen and in the presence of chocolate-coloured blood. Symptoms are usually dependent on the methaemoglobin levels; at levels higher than 35%, systemic symptoms from tissue hypoxia may be fatal. We present a case of severe life-threatening methaemoglobinaemia following intra-abdominal use of cetrimide during hydatid cyst removal in a 60-year-old female.

KEYWORDS

Cetrimide, hypoxia, oxygen therapy, confusion, methaemoglobulinaemia

LEARNING POINTS

- Cetrimide can cause methaemoglobinaemia when used as a protoscolicidal agent during the surgical treatment of hydatid cysts.
- Severe methaemoglobinaemia has high mortality rate and is usually missed and not easily diagnosed.

INTRODUCTION

In normal physiology, haemoglobin holds and releases oxygen. Physiologically, a small part of iron in haemoglobin is oxidised slowly from the ferrous state (Fe^{2+}) to the ferric state (Fe^{3+}) to create methaemoglobin, which can hold but cannot release oxygen[1]. Daily methaemoglobin formation is about 3%. Methaemoglobinaemia is a rare blood condition in which the production of methaemoglobin is irregular (oxidisation

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of some or all the iron species from ferrous state (Fe^{2+}) to oxidised ferric state (Fe^{3+})[2]. Methaemoglobinaemia causes inadequate release of oxygen to body tissues and leads to functional anaemia. Acquired methaemoglobinaemia is a rare but potentially life-threatening condition, resulting from the exposure to specific medications or agents that cause methaemoglobin production to increase[2]. Nitroglycerin, nitric oxide, dapsone, sulfonamides, phenytoin, phenacetin and local anaesthetics are typical medicines with an oxidising impact[3]. The incidence is much higher in neonates and infants, and the clinical presentation and the course of the disease vary greatly between patients[4]. The diagnosis relies on methaemoglobin levels of 10% or higher causing peripheral cyanosis. Methaemoglobin levels higher than 35% cause generalised symptoms secondary to tissue hypoxia[4]; levels of 70% methaemoglobin are potentially fatal and may result in coma. At high levels, the condition is treated with hyperbaric oxygen, methylene blue and ascorbic acid in high doses[2]. Cases of severe methaemoglobinaemia after excision of hydatid cysts and liberal irrigation of the cysts in the liver with a 0.1% solution of cetrimide were rarely reported[5]. Here, we present a case of severe life-threatening methaemoglobinaemia following intra-abdominal use of cetrimide during hydatid cyst removal in a 60-year-old female.

Cetrimide is a quaternary ammonium that consists of trimethyltetradecylammonium bromide and dodecyltrimethylammonium. It is mainly used to sterilise the hydatid cyst and prevent intraoperative dissemination of the parasite[6].

CASE DESCRIPTION

A 60-year-old female patient presented to the hospital for surgical resection of a hepatic hydatid cyst that was unresponsive to albendazole treatment. The patient was known to have coronary artery disease, dyslipidaemia and a hepatic hydatid cyst, she was on albendazole 200 mg PO daily for 7 months then switched to 200 mg PO twice daily one week prior to surgery.

Intraoperatively, 0.1% solution of cetrimide was administered into the hydatid cyst. A few minutes later, the patient experienced hypoxia, metabolic acidosis and hypotension. Initially, anaphylactic shock was suspected, stemming from potential dissemination of hydatid vesicles. Despite multiple doses of adrenaline, hydrocortisone and IV hydration (6 l of IV crystalloids) there was a limited response, and the patient was commenced on continuous intravenous administration of adrenaline and noradrenaline. In spite of the administration of dual vasopressors (noradrenaline and adrenaline) along with hydrocortisone, the patient's blood pressure continued to decrease.

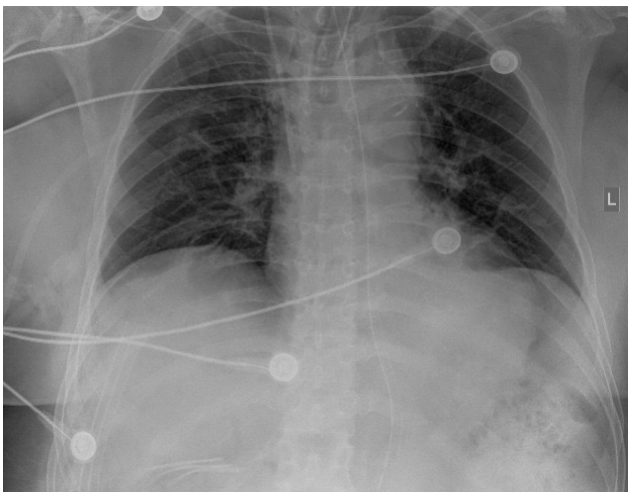


Figure 1. Chest X-ray showing clear lung fields with no pertinent abnormalities.

Upon arrival at the intensive care unit (ICU), the patient was hypotensive (mean arterial pressure 55 mmHg) on dual vasopressors at maximum doses (adrenaline 0.4 mcg/kg/min and noradrenaline 2 mcg/kg/min), tachycardiac in rapid atrial fibrillation, intubated with a low PaO_2 despite a FiO_2 of 100%. She exhibited cold extremities and bluish lips; there was no wheezing, hives or other signs suggestive of anaphylactic shock or distributive shock. The patient was not responsive to verbal or painful stimuli, her pupils were dilated, non-reactive, and the corneal reflexes were absent bilaterally. An urgent echocardiogram was performed to exclude the possibility of an acute cardiac event or obstructive shock, and showed a preserved ejection fraction, good contractility and a non-dilated inferior vena cava. There was no pericardial effusion, no pulmonary hypertension and no signs of right ventricular strain. A chest X-ray was normal (Fig. 1).

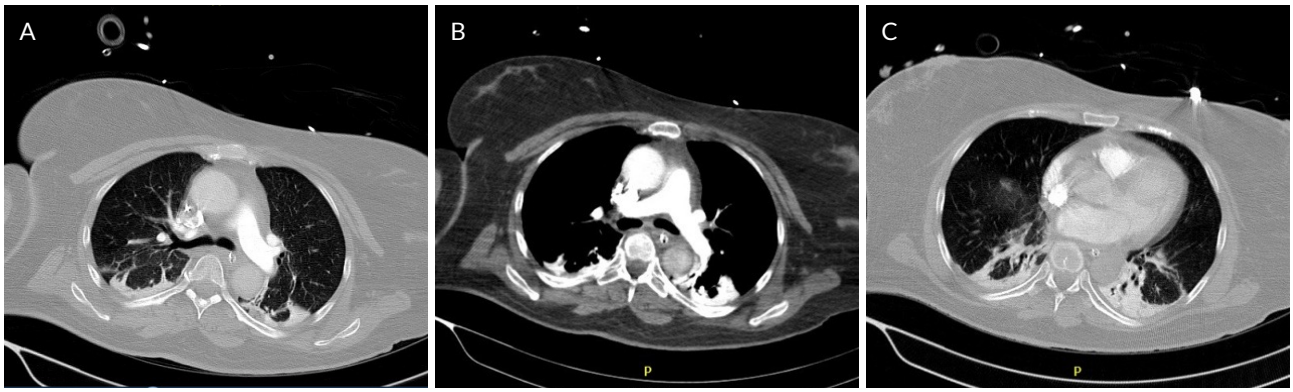


Figure 2. CT angiography showing A) bilateral pleural effusions with no evidence of pulmonary embolism; B) no signs of pulmonary embolism; C) no evidence of pericardial effusion.

A thorough blood workup revealed a decline in haemoglobin level from 14 g/dl (pre-operative) to 8 g/dl, severe lactic acidosis (lactic acid level = 98 mg/dl, normal range from 5 to 20 mg/dl) and notably low SpO_2 and $ScvO_2$ levels, with no other significant abnormalities. Notably, the patient received three units of packed red blood cells flush to improve oxygenation and cardiac output, in response to the diminished $ScvO_2$ levels. An urgent total body computed tomography (CT) scan angiography was performed.

Imaging showed a small bilateral pleural effusion (Fig. 2), oedema around the thyroid (Fig. 3) and a diffuse bowel oedema (Fig. 4). There was no evidence of pulmonary embolism, neither an intra-abdominal bleed nor pneumonia. Cardiac and pulmonary aetiologies that could explain hypoxaemia and shock were excluded. The only explanation left for the arterial and venous oxygen desaturation was decreased haemoglobin binding ability to oxygen, leading to functional anaemia. Consequently, our focus shifted to differential diagnoses encompassing methaemoglobinaemia, cyanide toxicity and carbon monoxide poisoning. The patient's cyanotic lips and markedly darkened blood favoured a diagnosis of methaemoglobinaemia. Furthermore, a swift review of pertinent literature revealed a single case report linking cetrimide to methaemoglobinaemia.

While in the ICU, the patient continued to have extremely high anion gap metabolic acidosis due to severe lactic acidosis, hypoxia despite FiO_2 of 100% and a positive end-expiratory pressure of 14, hypotension despite vasopressors and hyperglycaemia (HGT 432 mg/dl), necessitating initiation of intravenous insulin therapy. Subsequently, she experienced tonic-clonic seizure, prompting administration of anti-epileptic medication (valproic acid 1,500 mg IV loading dose then 1,500 mg as continuous infusion over 24 hours). In the absence of available methaemoglobin level confirmation, a therapeutic trial was initiated. The patient received 100 mg (1 mg/kg) of methylene blue administered over 15 minutes with partial clinical improvement. A second dose of methylene blue was given (1 mg/kg) after one hour. Following the second dose, the patient's partial pressure of oxygen (PO_2) increased significantly from 55 mmHg to 350 mmHg in less than 30 minutes, SpO_2 improved from 80 to 100%, vasopressors were gradually tapered and discontinued within 36 hours. The patient did not experience any further seizures and regained full consciousness within 12 hours. After 48 hours, the patient was successfully extubated.

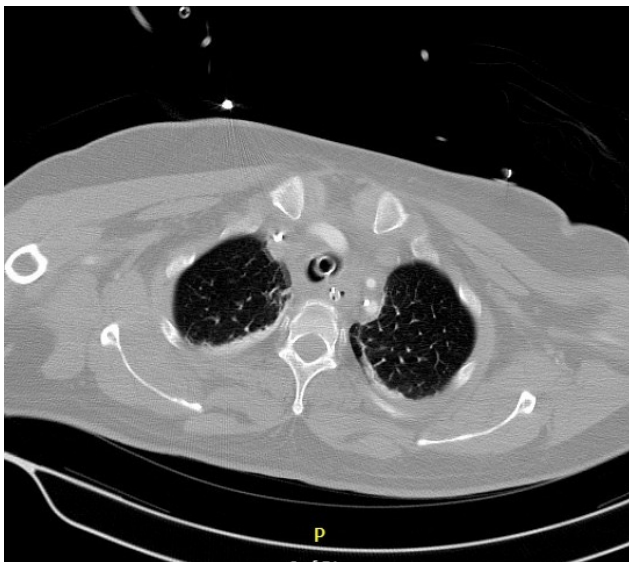


Figure 3. CT angiography showing mild oedema surrounding the thyroid gland.



Figure 4. CT angiography showing diffuse abdominal oedema with no signs of bleeding.

DISCUSSION

Methaemoglobinaemia is a potentially life-threatening condition. It can occur with the routine use of anaesthetics, such as benzocaine and lidocaine. To our knowledge, there are 71 case reports on benzocaine-induced methaemoglobinaemia. The earliest reference was made in 1947 by Ocklitz, reporting two infants treated with vaporised benzocaine powder for stomatitis. Methaemoglobinaemia has a higher prevalence in infants and neonates than in adults for several reasons. First, infants have a higher level of foetal haemoglobin, which is more easily oxidised to methaemoglobin[7]. Second, infants have a lower NADH-methaemoglobin reductase and glutathione peroxidase activity than adults. Third, they have a higher gastric pH, which favours the growth of bacteria such as *Escherichia coli* and *Pseudomonas aeruginosa*, which reduce nitrate to nitrite, resulting in methaemoglobinaemia[7].

The acquired form of methaemoglobinaemia can be triggered by various substances commonly found in households. These include laundry detergents, bathroom and kitchen cleaning agents, and nail polish removers[8]. Additionally, the analgesic acetaminophen, widely available over the counter, can also induce this condition[8]. Furthermore, nitrite-producing bacteria – most commonly *E. coli*, *Klebsiella* and *Proteus* – also cause methaemoglobinaemia. In addition, nitrite-containing well water and manure oil can cause methaemoglobinaemia[8]. Such exposure triggers

an overproduction of methaemoglobin, overwhelming the body's ability to convert the iron within haemoglobin back to its typical ferrous state.

Cetrimide is a quaternary ammonium that consists of trimethyltetradecylammonium bromide and dodecyltrimethylammonium. It is found in the antiseptic liquid known as Savlon® in 3% concentration, but no major side effect is mentioned or described. Cetrimide was used in 0.1% concentration to sterilise the hydatid cyst. The most commonly used protoscolicidal agents are 20% hypertonic saline, albendazole, ivermectin and praziquantel solutions. Cetrimide has been efficiently assessed against hydatid protoscolices as a protoscolicidal adjunct to hydatid surgery, to sterilise the hydatid cyst and prevent intraoperative dissemination of the parasite. It showed rapid mortality of the protoscolices after 5 minutes of exposure[6]. Cetrimide would not be expected to cross the membranes enveloping the hydatid cyst in sufficient amounts to produce clinically significant methaemoglobinaemia. At methaemoglobin levels below 15%, there are typically no symptoms[8]. The signs and symptoms of methaemoglobinaemia become prominent at methaemoglobin levels of 15–20% or higher[8]. Pulse oximetry is consistent with lower oxygen saturation levels and the appearance of blood may be dark brown[7]. At levels between 15 and 20% there may be cyanosis, with no response to supplemental oxygen. At methaemoglobin levels between 20 and 50% there may be dyspnoea and central nervous system involvement with headaches, dizziness, syncope, and generalised fatigue and weakness[7]. At even higher levels of 50–70% there may be tachypnoea, metabolic acidosis, dysrhythmia, seizure and coma, as was seen with our patient[7]. At levels above 70%, there may be death[7]. In our patient, life threatening aetiologies such as pulmonary embolism, myocardial infarction, cardiac tamponade, haemorrhagic shock and aortic dissection were excluded by echocardiography and by total body CT angiography. The improvement in clinical status of the patient after receiving the two doses of methylene blue is consistent with the medical diagnosis of cetrimide-induced methaemoglobinaemia.

Pulse oximetry is inaccurate in patients with methaemoglobinaemia, as the pulse oximeter reading is based on the assumption of only two varieties of haemoglobin present: oxyhaemoglobin and deoxyhaemoglobin[7]. CO-oximetry gives accurate concentrations because it can identify the absorptive characteristics of several haemoglobin species at different wavelengths, including methaemoglobin[7].

Methylthioninium chloride (methylene blue) is the treatment of choice for patients with symptomatic methaemoglobinaemia[8]. It acts as a substrate for NADPH methaemoglobin reductase, resulting in the formation of reduced methylthioninium chloride, reducing iron (Fe) to its ferrous state[8]. The recommended dosage is 1–2 mg/kg over 5 to 30 minutes, which may be repeated one hour later if the methaemoglobin level remains above 30%[8].

CONCLUSION

This was a case of life-threatening methaemoglobinaemia secondary to intraperitoneal irrigation of cetrimide, and to our knowledge only one previous similar case was reported in the literature previously[5]. A high index of suspicion for methaemoglobinaemia should be maintained in cases of refractory hypoxia or cyanosis despite treatment with supplemental oxygen, especially in the setting of exposure to a known oxidative agent. Diagnostic clues are the presence of chocolate-coloured blood and an oxygen saturation gap, to be confirmed by methaemoglobin level. Methylene blue remains the first-line treatment.

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