Methaemoglobinaemia: an explosive case

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ABSTRACT

Methaemoglobinaemia is an important perturbation to recognise, as untreated it may cause severe tissue hypoxia and cell death. We describe a case of methaemoglobinaemia acquired in an unusual manner, during an explosion at an explosives manufacturing plant.

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Methaemoglobin is produced by the oxidation of the ferrous (Fe^{2+}) iron within the haem moiety of the haemoglobin molecule to its ferric (Fe^{3+}) form. Supraphysiological accumulation of this dyshaemoglobin (methaemoglobinaemia) results in functional anaemia, with the potential for severe tissue hypoxia. While aetiologies are diverse, occupational exposure is rare and usually relates to chronic, low-level exposure.[1] We report a case of methaemoglobinaemia thought secondary to percutaneous exposure and absorption of 2,4,6-trinitrotoluene (TNT) following an explosion.

Clinical record

In May 2006, a massive explosion occurred at an isolated explosives manufacturing plant, 200 km north of Adelaide, South Australia. The shock was felt by observers 45 km away, with debris propelled over a kilometre radius. Three of five workers at the site were killed immediately by the blast.

A 25-year-old man with no significant past medical history was working outside the factory walls during the blast, its force throwing him to the ground. He was initially transferred to a district hospital before helicopter retrieval to a tertiary referral trauma centre. During this period, he received supplemental oxygen as well as intravenous benzylpenicillin, metronidazole, aliquots of fentanyl, and 2 L compound sodium lactate solution.

On arrival at the trauma centre, the patient was alert and oriented, with a heart rate of 70 beats per minute and blood pressure of 170/90 mmHg. He was not in respiratory distress; however, oxygen saturation by pulse oximetry (Spo_2) was only 92% while receiving high-flow oxygen by non-rebreathing mask. Acral cyanosis was present. No abnormality was found on chest auscultation. A pale, solidified, very hard material was noted to be adherent to the skin and hair, and was associated with superficial burn injury to the head, neck, arms and legs (Figure 1). There were also superficial lacerations and shrapnel wounds to the same areas. Otoscopy revealed bilateral tympanic membrane rupture.

No abnormality was found on laboratory testing of routine haematological and biochemical indices. There was no radiological evidence of more disseminated blast-overpressure or penetrating injury to the pulmonary parenchyma and hollow organs.

Management of these injuries necessitated removal of the foreign material, debridement and closure of lacerations, and dressing of burns. However, before surgery, concern was raised as to whether the material adherent to the skin contained TNT in a form that was potentially explosive if exposed to heat or spark, as no formal decontamination measures had as yet been undertaken.

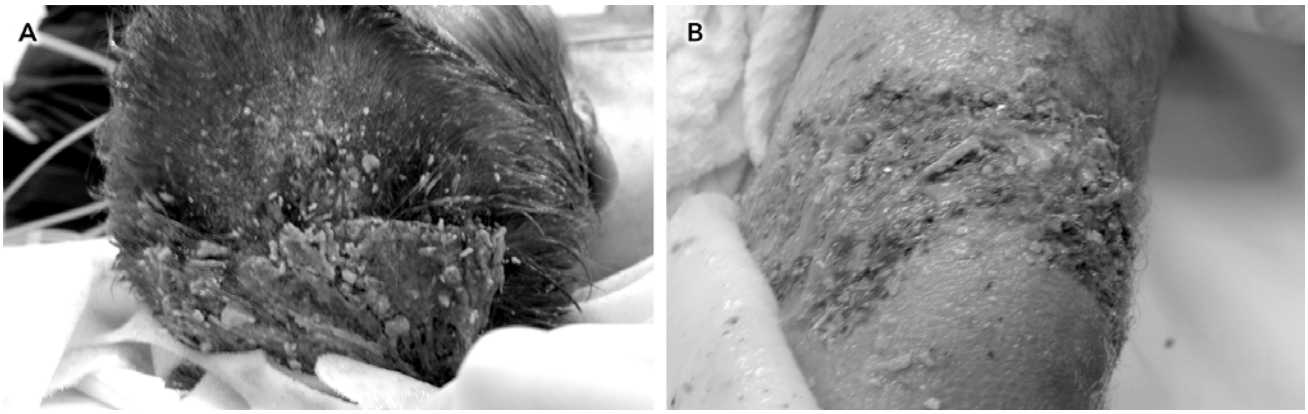
Under general anaesthesia, the foreign material was carefully separated from the patient with a scalpel and removed with soap and water. The lacerations were debrided and dressed, while the burns were treated with a biosynthetic skin substitute and antimicrobial barrier dressings. Throughout the operative period, given the potential hazards to patient and staff, active heating of the patient and electrical diathermy were not used.

During this time, a progressive decline in oxygen saturation was noted. Despite undergoing mechanical ventilation with fraction of inspired oxygen (FIO_2) of 1.0, the Spo_2 ranged from 89% to 90%. However, simultaneous arterial blood gas analysis revealed a Po_2 of 344 mmHg, with a calculated saturation of 99%. About 2 hours earlier, at the scene of the accident, the Spo_2 had been 100%. It had fallen to 92% by the time the patient arrived in the emergency department (despite a corresponding Po_2 of 171 mmHg) (Table 1). This discordance flagged the possibility of dyshaemoglobinaemia; this was confirmed by co-oximetry, which detected methaemoglobinaemia with a fraction of 18.4%. However, this level did not require specific treatment, and the patient was discharged home after an otherwise uneventful 10-day hospital admission.

Discussion

Within the haem moiety of haemoglobin, the oxidation of the ferrous iron to its ferric configuration disassembles its oxygen-carrying facility. The dyshaemoglobin created — methaemoglobin — perturbs physiological oxygen storage, delivery and transfer. The ferric form of haem is unable to bind oxygen and furthermore influences the remaining unaltered haem groups to bind oxygen with greater affinity, with leftward shift of the oxygen-dissociation curve.

Figure 1. Foreign material contaminating a patient after a trinitrotoluene (TNT) exposion



A. *Foreign material firmly adherent to scalp.* **B.** *Material adherent to forearm and underlying burn. (Images taken with patient permission.)* ◆

Table 1. Patient's oxygen saturation, FIO_2, Po_2 and methaemoglobin fraction over time after exposure to trinitrotoluene (TNT)

Hours after explosion	FIO_2	Oxygen saturation (%)*	PO_2 (mmHg)	Methaemoglobin fraction (%)†
0	0.8	100%	na	na
2	0.8	92%	171	na
4	1.0	89%	344	18.4%
8	0.6	91%	111	15.3%
48	0.21	97%	na	1.3%
72	0.21	97%	na	0.2%

* By pulse oximetry. † By co-oximetry.
FIO_2 = fraction inspired oxygen. na = not assessed. ◆

The cytochrome b5–methaemoglobin reductase system is the main apparatus for reducing the physiological production of methaemoglobin, maintaining levels at about 1% of total haemoglobin. This enzyme system can be congenitally deficient, but methaemoglobinaemia more commonly results when homoeostatic mechanisms are overwhelmed by oxidative stress incurred through exposure to various oxidising agents and chemicals. These include agents implicated in occupational exposures, such as aniline dye derivatives, chlorates, nitrites and nitrates.[1] In addition, numerous pharmaceuticals are well established iatrogenic causes of methaemoglobinaemia, including local anaesthetic agents, nitroglycerine, nitroprusside, phenytoin, chloroquine, primaquine, dapsone and sulfonamide antibiotics.

The high explosives manufactured at the plant were intended for use in the mining industry. Typically, these explosives are mixtures of TNT, ammonium nitrate, aluminium powder, water and gelatinising agents. Of these, at least TNT was known to have been present at the blast site.[2] Although the material adherent to our patient was not analysed, the probability that it contained TNT was sufficient to raise the concerns both of the authorities managing the incident and the staff managing the patient.

TNT is a nitroaromatic compound created by the combination of toluene with a mixture of nitric and sulfuric acids. Commonly referred to as 2,4,6-trinitrotoluene, it is also known as 2-methyl-1,3,5-trinitrobenzene. First synthesised in 1863, TNT is now used extensively in the manufacture of explosives for military and industrial purposes.

From an occupational health perspective, TNT was initially thought to be harmless, but high levels of exposure in the ammunition industry of two world wars revealed otherwise.[3] TNT is now a well established cause of methaemoglobinaemia in humans, especially in the context of chronic, low-level exposure. TNT and its metabolites have been implicated in the causation of methaemoglobinaemia in workers at ammunition factories, mining sites, and in disposal of military waste.[4] Such exposure has been associated with a variety of health effects in addition to methaemoglobinaemia, including cataracts, dermatitis, anaemia, hepatitis, splenomegaly, and mutagenic effects including leukaemiagenesis.[5] Employees in such environments should be provided with impervious clothing, gloves and face shields,[5] and possibly biological surveillance[4] (with urinary screening for TNT metabolites) to prevent such complications — none of which were features in our patient, and would not be expected in the context of acute exposure.

TNT has been shown to be an efficient methaemoglobin-forming agent *in vitro*.[6] Moreover, these nitroaromatic compounds are readily transmitted via dermal or inhalational exposure due to their high lipophilicity and volatility.[1] Conceivably, methaemoglobinaemia observed in our patient was brought about by transdermal absorption of the adherent

explosive compound TNT. The inhalational route is considered less likely in the light of the progressive desaturation noted in our patient, implying ongoing absorption of the culprit substance until removal under anaesthesia. Although methaemoglobinaemia resulting from acute (less than 24-hour) occupational inhalational or dermal exposure to TNT has been described, only one other report has documented a similar mechanism of exposure, whereby an explosion during the manipulation of a bomb containing TNT sparked methaemoglobinaemia.[7]

The bedside determination of oxygen saturation by pulse oximetry can be dangerously misleading in the presence of significant methaemoglobinaemia as, even when saturation is near normal, the oxygen-carrying capacity of the blood may be markedly reduced. The absorbance ratio of methaemoglobin for the two wavelengths of light transmitted by pulse oximetry (660 nm and 940 nm) is unity, corresponding to an oxygen saturation of ~85%. As methaemoglobin concentration increases, the saturation by pulse oximetry trends towards this value.

Arterial blood gas analysis may be similarly misleading, as a normal P_{O_2} value does not always imply adequate oxygen-carrying capacity. In this method, arterial oxygen saturation is calculated by the manipulation of the Henderson–Hasselbach equation after the measurement of pH, P_{CO_2} and P_{O_2} by high-impedance electrodes. The absence of dyshaemoglobinaemia is assumed.

Co-oximetry can differentiate and quantify the haemoglobin fractions: oxyhaemoglobin (O_2Hb), deoxyhaemoglobin (HHb), carboxyhaemoglobin (COHb), sulfhaemoglobin (SHb), and methaemoglobin. Together with determination of the P_{O_2} and haemoglobin concentration, the true oxygen-carrying capacity of the blood can be ascertained, even in the presence of dyshaemoglobinaemia.

The spectrum of clinical signs and symptoms of methaemoglobinaemia ranges from headache and anxiety at low levels (< 20%); fatigue and confusion at moderate levels (30%–50%); acidosis, coma, seizures and cardiac arrhythmia at high levels (50%–70%); to death with levels > 70%.[1] However, the severity of the clinical sequelae induced by methaemoglobin depends not only on its fractional concentration, but also on patient comorbidity and functional reserve.

As a general rule, treatment should be initiated in all patients with methaemoglobin levels greater than 30%, and for symptomatic patients in the range 10%–20%. In most cases, this involves intravenous administration of methylene blue. It is typically given at a dose of 1–2 mg/kg over 5 minutes, producing an expected response within 30 minutes. Although generally not required, this dose can be repeated after 1 hour. Methylene blue is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency. Rare, severe cases may necessitate exchange transfusion or hyperbaric oxygen therapy. In our case, no specific management was required apart from the prevention of ongoing absorption of the offending substance, as the patient was otherwise well, had no apparent symptoms, and had a methaemoglobin fraction less than 20%. The decline in methaemoglobin fraction seen in Table 1 is in keeping with the natural history of most cases of acquired methaemoglobinaemia, with levels usually returning to normal within 36 hours once exposure to the agent is eliminated.[7]

Adequate decontamination for percutaneous TNT exposure mandates removing all soiled clothing and jewellery, then washing the affected areas with soap or mild detergent, with ongoing irrigation until all contaminant is removed.[5] This should have occurred at the scene before transport or on arrival at hospital. Unfortunately, it was delayed until the patient was in the operating theatre, where conditions may have posed a significant fire hazard had precautions not been taken.

Conclusions

Our patient developed methaemoglobinaemia as a complication of blast injury. Although putative, the most likely culprit agent was TNT, based on the known exposure, recognised method of absorption, plausible mechanism of methaemoglobin formation, and lack of any other apparent endogenous or exogenous source. This case illustrates the diverse causes, diagnostic difficulties, and management options related to methaemoglobinaemia.

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