Why so blue? The blood gas has the clue…

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A 48-year-old female presented to the Emergency Department with a two-week history of increasing fatigue. On examination, she had blue-grey central and peripheral cyanosis with tachypnoea and an oxygen saturation of 85% on room air (Figure 1). She was placed on high-flow oxygen, but her oxygen saturation on the pulse oximeter only marginally improved to 90%. Arterial blood gas (ABG) on room air showed pH 7.66 (7.36–7.47), $PaCO_2$ 2.89

Figure 1 Picture of patient with peripheral cyanosis at presentation to hospital

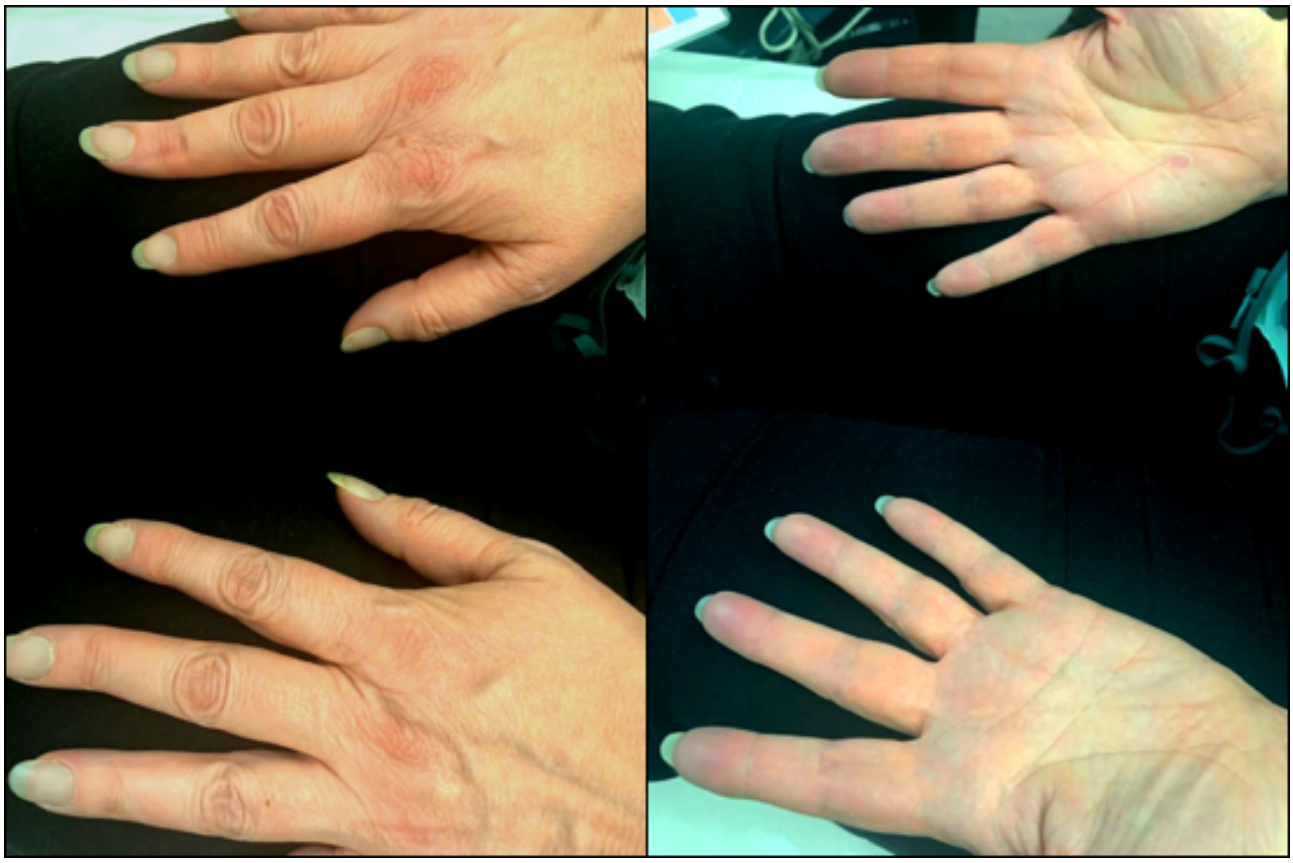

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Table 1 Drugs causing methaemoglobinaemia[2]

High risk agents	
Local anaesthetics	**Antimalarials**
Benzocaine	Quinine sulphate
Prilocaine	Primaquine
	Chloroquine
Antibiotics	
Sulphonamides	**Chemicals**
Dapsone	Aniline (dyes, ink)
Ciprofloxacin	Paraquat
Trimethoprim	Resorcinol
Nitrofurantoin	Chlorate
Nitrates/nitrites	**Aromatic hydrocarbons**
Nitroglycerine	Benzene derivatives
Nitric oxide	Naphthalene
Isosorbide dinitrate	
Amyl nitrate	**Hormones**
Nitroprusside	Flutamide
Antiepileptics	**Others**
Phenobarbital	Metoclopramide
	Phenelzine
Low–moderate risk agents	
Local anaesthetics	**General anaesthetics**
Lidocaine	Propofol
Bupivacaine	Thiopental
Mepivacaine	Succinylcholine
Articaine	Inhalational anaesthetics
Etidocaine	
	Analgesics
Sedatives	Fentanyl
Benzodiazepines	Meperidine
	Paracetamol
Antipsychotics	Aspirin
Phenothiazines	Phenazopyridine

kPa (4.60–6.40 kPa), PaO_2 13.7 kPa (10.6–14.6 kPa), HCO_{3-} 26.6 mmol/L (22–28 mmol/L), base excess 1.2 mmol/L (–2 to +1 mmol/L), SaO_2 96.4% (>94%), FO_2Hb 81.3% (>94%) and methaemoglobin 15.9% (<1%). She had a background history of hidradenitis suppurativa (HS) and asthma. She had been on dapsone for the last four years for HS and the dosage had been recently increased by her dermatologist from 100 mg to 200 mg once daily. Additionally, her records revealed a persistently elevated reticulocyte count for the past four years and unexpectedly high oxygen demands during a recent surgical procedure. These findings led to the diagnosis of dapsone-induced methaemoglobinaemia.

The patient was asked to stop dapsone and discharged the same day. She returned to the outpatient clinic one week later with resolution of both her symptoms and clinical signs of cyanosis. Her oxygen saturation was 98% on air and an ABG revealed normal arterial oxygen saturation (SaO_2), fractional oxyhaemoglobin (FO_2Hb) and methaemoglobin levels.

Table 2 Clinical findings in patients with methaemoglobinaemia[4]

Methaemoglobin concentration	**Clinical findings**
1–3%	None
3–15%	Possibly none, low oxygen saturations on pulse oximeter
15–20%	Cyanosis (central and peripheral) not improving with oxygen administration, slate-grey skin colour
20–50%	Dyspnoea, tachypnoea, headache, fatigue, dizziness, syncope, weakness, nausea
50–70%	Metabolic acidosis, dysrhythmia, seizures, central nervous system depression, coma
>70%	Grave hypoxic symptoms, death

Methaemoglobinaemia is defined as an abnormal increase in methaemoglobin levels, i.e. >1–2% of total haemoglobin.[1] It arises due to oxidation of one or more haem molecules within haemoglobin from the reduced ferrous state to the ferric state. High methaemoglobin levels cause left-shift of the oxygen–haemoglobin dissociation curve and impaired oxygen delivery to tissues. Whilst small amounts of methaemoglobin are produced constantly, the enzymes cytochrome-b5 reductase and NADPH methaemoglobin reductase maintain methaemoglobin levels below 1%.[2] When the rate of methaemoglobin formation exceeds that of reduction, tissue hypoxia occurs. This can arise due to congenital disorders, e.g. genetic defects in haemoglobin structure/metabolism, or acquired causes from exposure to external oxidising agents, e.g. food additives, workplace chemicals (e.g. aniline dyes) or drugs such as dapsone (Table 1).[2] Haemolysis is also well-documented with dapsone therapy and is associated with the presence of methaemoglobinaemia.[3]

At methaemoglobin concentrations below 20%, the patient is usually asymptomatic; however, as levels exceed 20%, blue-grey central cyanosis and chocolate-brown discolouration of the blood begin to manifest. Concentrations above 70% can be fatal (Table 2).[4]

As demonstrated in this case, ABG analysis can clinch the diagnosis.[4] The total FO_2Hb, i.e. the proportion of oxygenated haemoglobin in relation to total haemoglobin (including dyshaemoglobins such as methaemoglobin and carboxyhaemoglobin), will be low in these patients. However, it is important to note that they will have normal PaO_2 (partial pressure of oxygen in blood) and SaO_2. This is because the PaO_2 level relates to the fraction of oxygen that is dissolved in blood plasma rather than that bound to haemoglobin.[5] As methaemoglobinaemia does not affect oxygen diffusion from the alveoli to the blood plasma, arterial PaO_2 will remain normal. SaO_2 reflects the level of oxygen bound to haemoglobin but will be falsely normal as its calculation is based on the assumptions of a normal oxygen dissociation

curve and physiological levels of dyshaemoglobins, which do not hold true in methaemoglobinaemia.[6] However, oxygen saturation measured by pulse oximetry will be reduced because methaemoglobin absorbs the two wavelengths of light that are utilised to non-invasively estimate the percentage of oxyhaemoglobin in the blood.[6] Thus, administration of high-flow oxygen will not increase the FO_2Hb, SaO_2 or resolve blue-grey cyanosis, but it can improve blood gas PaO_2 and, to a lesser degree, oxygen saturation on the pulse oximeter.

Patients with methaemoglobin levels of <20% can be managed conservatively by discontinuing the offending agent, as methaemoglobin will be reduced over several hours by the intrinsic activity of methaemoglobin reductase enzymes.[4] Patients in respiratory distress should be given high-flow oxygen. Symptomatic patients or those with methaemoglobin levels >20% require treatment with methylene blue infusion (contraindicated in glucose-6-phosphate-dehydrogenase deficiency) which causes non-enzymatic reduction of methaemoglobin. Plasma exchange, haemodialysis, hyperbaric oxygen therapy and supplemental antioxidants (e.g. *N*-acetylcysteine) can be used as adjuvants or alternative strategies if initial treatment fails.[4]

In conclusion, methaemoglobinaemia is an uncommon but potentially fatal clinical encounter that is often not considered in patients presenting with hypoxia and cyanosis. It is important that patients on regular oxidising medications (e.g. dapsone) are monitored appropriately for methaemoglobinaemia. Early recognition of the condition and appropriate treatment can result in a favourable outcome for patients.

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