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# A Curious Case of Methaemoglobinemia

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## Abstract

The most frequent cause of raised methaemoglobin is from recreational drug use, with oxidation of the haem molecule leading to methaemoglobinaemia. Our case describes that of a man in his early thirties who presented with shortness of breath, hypoxia and methaemoglobinemia due to ingestion of impure cocaine mixed with local anaesthetic agents, a common cause of acquired methaemoglobinemia. This case report demonstrates the need for clinicians to consider methaemoglobinaemia as a differential diagnosis for patients presenting with hypoxia.

## Keywords

Methaemoglobinaemia, Hypoxia, Cocaine, Drug Induced

## 1. Introduction

Methaemoglobinemia can be either attributed to genetic causes or ingested substances such as local anaesthetic agents, nitrates or dapsone [1] [2]. Common and relatively inexpensive local anaesthetic agents such as lidocaine, benzocaine and prilocaine have been used to bulk up cocaine in order to increase profit [3]. These substances can create direct or indirect oxidative stress that converts ferrous iron ($Fe^{2+}$) to ferric iron ($Fe^{3+}$) within the haemoglobin molecule, leading to haem being converted to methaemoglobin, shifting the oxygen dissociation curve to the left; this results in significantly impaired oxygen delivery to tissues, resulting in hypoxia [4] [5]. From a genomic standpoint, a lack of cytochrome B5 or cytochrome B5 reductase can cause methaemoglobinemia; indeed, these are required to actively reduce methaemoglobin in normal physiology [6]. A methaemoglobin concentration of less than 1% is considered normal in adults [7]. Usually, symptoms occur at levels above 10% and include shortness of breath, altered cognition and cyanosis, with significantly raised levels above 50% resulting in seizures, coma and death; however, hypoxia can occur at levels below 10% [8]. We

present an interesting case of acquired methaemoglobinaemia secondary to drug misuse.

## 2. Case

A 31-year-old man presented to the hospital with shortness of breath and hypoxia four times within 5 months. He has a background of substance misuse, autoimmune haemolytic anaemia, autism and depression.

The patient's chest was clear on auscultation and there was no peripheral oedema or cyanosis. Arterial blood gases showed a Type 1 respiratory failure on each admission with raised methaemoglobin, which ranged from 2.4% to 5.5%, with normal adult values typically being <1% [7]. He was found to be profoundly hypoxic on all four occasions, with oxygen saturation dropping to 88% on air. Chest X-rays were normal (**Figure 1** and **Figure 2**) and CTPAs to exclude PE were also normal (**Figure 3** and **Figure 4**). Bloods were unremarkable except for a longstanding mildly raised bilirubin.

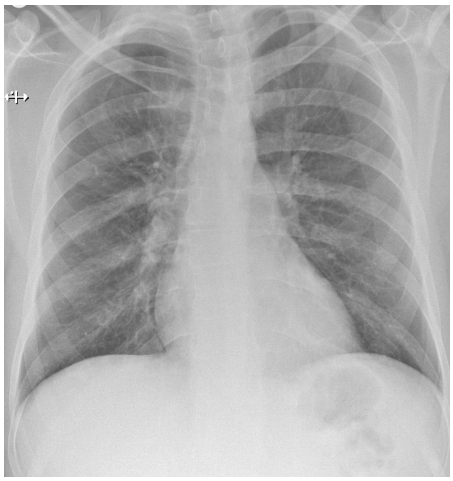

**Figure 1.** Showing clear chest X-rays on 2 separate admissions.

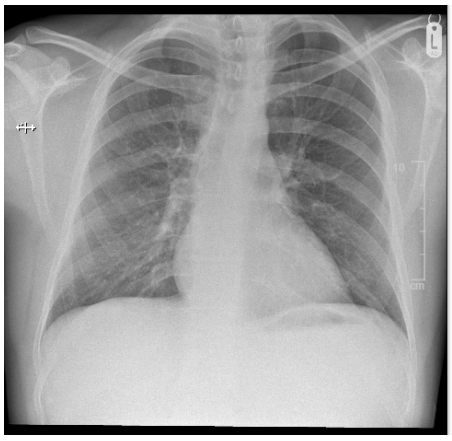

**Figure 2.** Showing clear chest X-rays on 2 separate admissions.

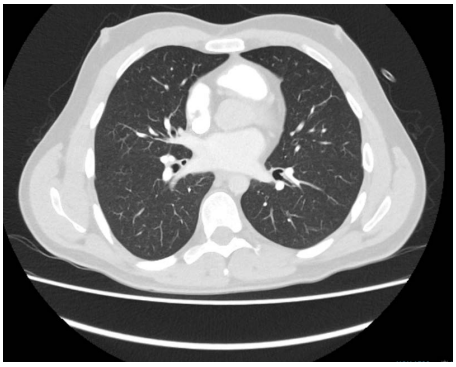

**Figure 3.** Showing clear CT Pulmonary Angiograms (CTPAs) on 2 separate admissions.

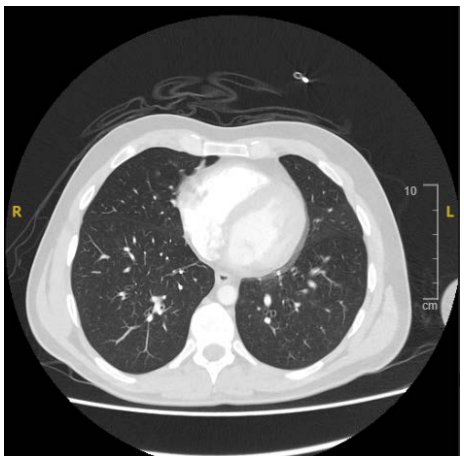


**Figure 4.** Showing clear CT Pulmonary Angiograms (CTPAs) on 2 separate admissions.

The patient was initially treated as a lower respiratory tract infection with broad spectrum intravenous antibiotics and high flow oxygen therapy that was gradually weaned down, in a stepwise manner, using venturi mask to control oxygen flow.

On the prior 3 admissions, the patient only admitted to use of cannabis and strongly denied the use of cocaine. However, after further probing during history taking, it was found that he had indeed been using cocaine. The patient admitted to using cocaine that was from a different supplier and likely impure, and this was correlated with all four of the admissions with shortness of breath.

His shortness of breath was deemed to be due to methaemoglobinemia caused by local anaesthetic agents commonly used when mixing cocaine.

## 3. Discussion

Congenital causes of methaemoglobinemia are extremely rare, and are typified by cytochrome B5 reductase deficiency, due to mutations in the CYB5R3 gene [9]. Type 1 occurs with a deficiency in red blood cells only, whilst Type 2 consists of deficiency in all cells; Type 2 is rarer than Type 1, exhibiting a higher mor-

bidity and mortality [6].

Drugs that cause methaemoglobinemia are multiple, including nitrites, sulfonamides and local anaesthetic agents such as benzocaine and lidocaine [9] [10] [11]. These oxidise ferric iron to ferrous iron within the haem molecule, impairing oxygen binding and thus oxygen delivery to tissues [4] [5]. Drug-induced methaemoglobinemia may cause haemolytic anaemia, especially with exposure to dapsone, sulfasalazine, or phenacetin; this is characterised by Heinz bodies and red cell fragmentation on blood film [12]. Methaemoglobinemia may be exacerbated in patients known to have anaemia [8]. Methaemoglobinemia due to drug exposure is treated with oxygen therapy or methylene blue 1% 1 - 2 mg/kg over 5 mins, or a combination of these two [13]. Methylene blue is given typically when methaemoglobin concentrations exceed 30% or when symptoms persist despite oxygen therapy [14]. Alternative second line treatments include ascorbic acid and N-acetylcysteine [6] [15] [16]; however, ascorbic acid acts much slower than methylene blue, often requiring greater than 24 hrs to have significant effect [6] [15], whilst the evidence for use of N-acetylcysteine is unclear [17]. Methylene blue is dependent on the availability of reduced NADP (NADPH), therefore may not work in patients known to have G6PD deficiency [18]. Dextrose is commonly given as it is required to form NADPH via the hexose monophosphate shunt [19]. Commonly after exposure to an oxidising agent, methaemoglobinemia is treated when <30% if asymptomatic and <20% if symptomatic; anaemic patients or those with known cardiorespiratory issues should have a low threshold for initiating treatment [20]. Local anaesthetic agents and dapsone may cause rebound methaemoglobinemia 4 - 12 hours after administration [21]; caution must be taken as toxic doses occur after >7 mg/kg [22] [23], which may manifest as cardiac arrhythmias, serotonin toxicity, pulmonary hypertension and renal hypoperfusion [24] [25]; therefore, care must be taken in patients taking concurrent SSRIs due to methylene blue acting as a monoamine oxidase inhibitor [26]. In our patient's case, their condition was resolved with simple oxygen therapy using a non-rebreather mask initially, which was gradually weaned down. They were discharged home with advice to avoid cocaine use.

## 4. Conclusion

Acquired methaemoglobinemia is an uncommon yet important differential in patients presenting with hypoxia that is recalcitrant to treatment. Workup for a patient with acquired methaemoglobinemia would be similar to other causes of hypoxia and shortness of breath, arterial blood gas sampling, chest X-ray and oxygen therapy. Therapy for an acquired methaemoglobinemia may include methylene blue, oxygen therapy and dextrose. However, this case report demonstrates the importance of a thorough social and recreational drug history in helping to aid the prompt diagnosis and management of these patients.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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