CASE REPORT

Acquired Methemoglobinemia in Adults. When and how to treat?

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SUMMARY

Acquired methemoglobinemia (MH) is a rare but potentially life-threatening condition in which exposure to certain medications, chemicals or toxins causes an excessive amount of methaemoglobin (metHb) to be present in the blood, resulting in reduced oxygen delivery to tissues. Dapsone and primaquine are often used for prophylaxis and treatment of Pneumocystis jirovecii pneumonia. Primaquine is also a common anti-malarial therapy. We report 3 cases of acquired MH recently encountered in our centre. The three patients had different pre-existing conditions, posed different diagnostic challenges, and received different treatment modalities, but fortunately, all had favourable outcomes. We aim to raise awareness among clinicians to consider acquired MH as a differential diagnosis of a patient with unexplained hypoxia and to re-visit the treatment approaches.

INTRODUCTION

MH develops when haemoglobin (Hb) is oxidised to contain iron in the ferric (Fe^{3+}) rather than the normal ferrous (Fe^{2+}) state.[1] Oxidised iron molecules are unable to bind and transport oxygen, leading to decreased oxygen delivery and eventual tissue hypoxia.[1] MH may be congenital or acquired.[1] Acquired MH is caused by exposure to substances that oxidise Hb either directly or indirectly, producing excess metHb that exceeds the body's capacity to convert the iron within Hb back to the Fe^{2+} state.[1] Individuals with congenital MH tend to be asymptomatic.[2] On the contrary, manifestations of acquired MH can be severe or even fatal.[2] Symptoms, which include cyanosis, pallor and fatigue, develop when metHb level reaches 1.5g/dL (approximately 10% total Hb).[3] Clinical severity is multifactorial and depends on the percentage of metHb.[1] We aim to discuss the pros and cons of each treatment option to guide clinicians in decision-making.

CASE PRESENTATION

Case 1

A 35-year-old woman with Systemic Lupus Erythematosus (SLE) and antiphospholipid syndrome presented with symptoms of an upper respiratory tract infection (URTI) of one week. Additionally, she complained of breathlessness and reduced effort tolerance. She received cyclophosphamide for active lupus nephritis, but due to inadequate response, this was replaced with rituximab. She was prescribed dapsone for prophylaxis against Pneumocystis jirovecii pneumonia as she had a hypersensitivity reaction to trimethoprim/sulfamethoxazole (Bactrim).

At the Emergency Department (ED), pulse oximetry recorded an oxygen saturation on room air of 83%, which increased to 95% with supplemental O_2 8L/min via face mask. She had mild tachypnoea with peripheral and central cyanosis. However, arterial blood gas (ABG) indicated good oxygenation with a partial pressure of oxygen (PaO_2) 194mmHg. Chest radiography (CXR) showed normal heart size and clear lung fields. In view of a preexisting diagnosis of concomitant APS, echocardiogram and computed tomography pulmonary angiogram (CTPA) were performed to exclude both pulmonary hypertension and pulmonary embolism (PE). Both tests were reported as normal. A diagnosis of MH was considered, and review of an earlier ABG result revealed a metHb level of 11.6%. This finding was initially missed, as not all ABG analysers measure metHb levels, and it was therefore not specifically sought.

Diaminodiphenyl sulfone (DDS) (Dapsone) was identified as the cause and was immediately stopped. The toxicologist advised administering intravenous Methylene Blue at a 1mg/kg dose, after excluding Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency. MetHb level decreased to 1.9% after a single MB dose an hour later, with complete resolution of symptoms and cyanosis. She was discharged from the hospital the next day. A follow-up metHb level at two weeks showed a metHb of 0.6%.

Case 2

A 19-year-old international student with no prior health issues presented to the ED with five days of fever, myalgia, headache, vomiting and diarrhoea. She had a history of jungle trekking in Kashmir during a recent family vacation.

She was febrile with mild splenomegaly, but other vital signs were normal. Given her travel history, blood films for *malaria parasites* (BFMP) were performed, confirming a diagnosis of Plasmodium falciparum malaria. She was started on Artemether/Lumefantrine (Riamet) and a single dose of primaquine (after excluding G6PD deficiency) as per local treatment guidelines for malaria.

Three days later, oxygen saturation on room air recorded an oxygen desaturation to 85% but she remained clinically well. She was able to speak and ambulate fully without any breathlessness. MH secondary to primaquine was suspected and subsequently confirmed by ABG results of PaO_2 124mmHg with metHb level of 10.5%. As she was asymptomatic, Methylene Blue was not given. She was monitored and discharged from the hospital three days later when her metHb level reduced to 7.2%. Outpatient review 10

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Table I: Summary of patients' characteristics and management

Characteristic/Case	Case 1	Case 2	Case 3
Age (years)	35	19	32
Gender	Female	Female	Male
Race	Chinese	Indian	Malay
Primary Disease	SLE and APS with URTI	Malaria	Severe PJP in advanced RVD
Inciting Drug	Dapsone	Primaquine	Primaquine
Clinical severity (O2 requirement)	8L/min (FM)	None	15L/min (HFNC)
Hb level (g/L) on admission	8.0	10.0	12.0
Initial metHb level (%)	11.6	10.5	10.5
Treatment prescribed	MB	Supportive	ascorbic acid
Time to recovery	1 hour	10 days	7 days

Note: SLE-Systemic Lupus Erythematosus, PJP-Pneumocystis jirovecii pneumonia, APS-antiphospholipid syndrome, URTI-upper respiratory infection, RVD-Retroviral Disease, HFNC-High-flow nasal canula, FM-face mask, MB-Methylene Blue

Table II: Incidence of common drugs that cause methemoglobinemia

Medical Group	Common	Uncommon	Rarely
Analgesic-Antipyretic	Phenazopyridine Phenacetin		Acetaminophen Fentanyl
Anticonvulsant			Phenobarbital
Anti-Infective	Dapsone Primaquine	Sulphonamides	Chloroquine Nitrofurantoin
Local or Topical Anaesthetic (Topical)	Benzocaine Amethocaine Prilocaine	Lidocaine Cetacaine Tetracaine	
Vasodilator	Nitrates derivatives	Nitrates derivatives	
Miscellaneous		Methylene Blue Metochlopramide	

Source: Alanazi MQ[7]

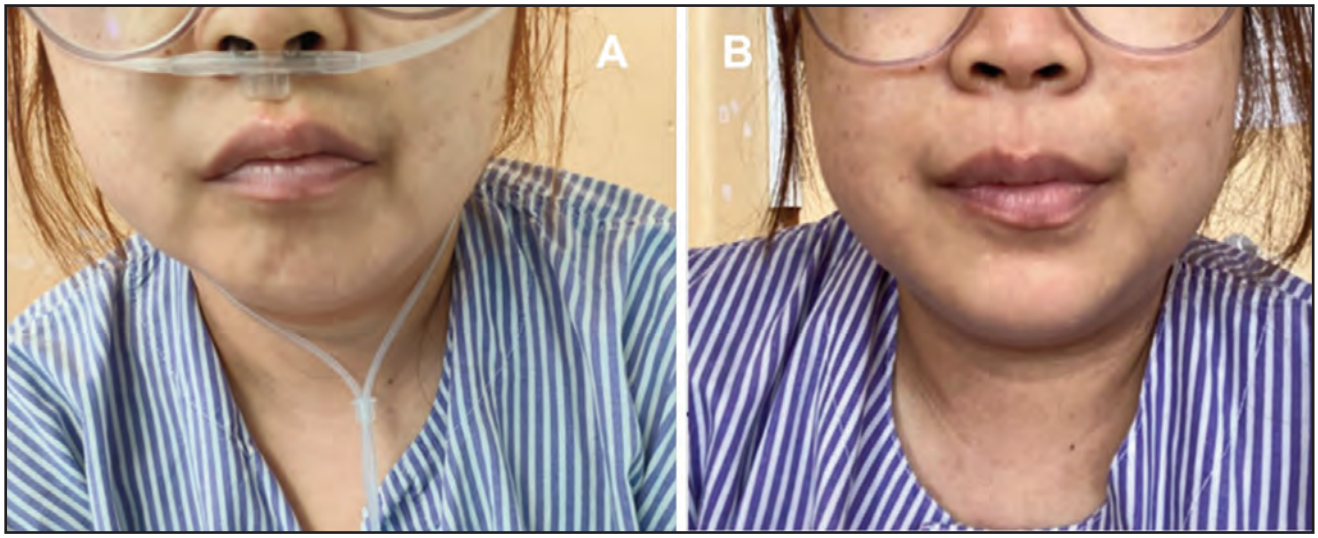

Fig. 1: Photos of patient in case 1 (Photo consented for publication purposes). Image on the left (A) showing pre-Methylene Blue, which patient having central cyanosis and required oxygen support, while image on the right (B) was post-Methylene Blue that cyanosis resolved and weaned off oxygen support.

days after discharge showed metHb had further decreased to 1.8%.

Case 3

A 32-year-old man with Retroviral Disease (RVD) but non-compliant to therapy, presented with fever, cough and exertional dyspnoea for two weeks. At ED, SaO2 at room air was 88% and improved to 97% on O_2 10L/min via face mask. CXR showed changes typical of Pneumocystis jirovecii pneumonia, and sputum examination later confirmed this diagnosis. He received trimethoprim/sulfamethoxazole and prednisolone as treatment for Pneumocystis jirovecii

pneumonia, but developed transaminitis. Hence, treatment was transitioned to second-line therapy of primaquine and clindamycin. Investigations for other opportunistic infections, including tuberculosis, were negative.

He had favourable clinical and radiologic responses to PJP treatment and was weaned off supplemental oxygen. Unfortunately, 10 days later, he developed tachypnoea and cyanosis. He had hypoxia requiring high-flow nasal cannula (HFNC) oxygen support. CTPA excluded PE. Having encountered two prior cases of unexplained hypoxia, the patient was checked for MH. Indeed, ABG showed PaO_2 on room air of 131mmHg and a metHb level of 10.5%. This patient developed acquired MH from primaquine, which was immediately discontinued.

He was prescribed high-dose oral vitamin C (1g TDS) for a week. Intravenous pentamidine replaced the combined therapy of primaquine and clindamycin. He gradually recovered and was discharged well. In retrospect, Methylene Blue should have been the treatment of choice in this patient, as Methylene Blue was clinically more severe in him compared to Case 1.

DISCUSSION

Literature search did not yield any known predisposition nor association of SLE, RVD and malaria with MH, except in the drugs used. SLE and RVD are immunocompromised states which place patients at increased risk of opportunistic infections. Bactrim, dapsone and primaquine are commonly prescribed as prophylaxis and treatment for Pneumocystis jirovecii pneumonia. A retrospective review of 138 patients with acquired MH by Ash-Bernal et al., revealed that the majority (42%) of cases were caused by dapsone.[4] This study reported that these patients, while on therapeutic doses of dapsone, had a mean metHb concentration of 7.6% but did not exhibit any effects.[4] Thus, the authors postulated that patients with chronic low-grade MH required a 'second-hit' event, most commonly anaemia, to further compromise oxygen tissue delivery and cause symptomatic hypoxia.[4]

The interval between time of exposure to the inciting drug and the onset of symptoms varied among our three cases - 8 months, 3 days and 10 days, respectively.

We suspect patient (Case 1) had asymptomatic chronic low-grade MH after initiation of dapsone. However, it was then aggravated by anaemia, which she required a blood transfusion from recurrent hemorrhoidal bleeds prior to the current admission.

Based on recommendations by Iolascon et al., no added treatment or oxygen supplementation is necessary for minimally symptomatic or asymptomatic patients.[3] Conversely, treatment should be initiated for symptomatic patients with a high metHb level of 10%-30%.[3] The recommended first-line treatment is intravenous MB.[3]

MB acts by accepting an electron from nicotinamide adenine dinucleotide phosphate (NADPH) to become leucomethylene blue. Leucomethylene blue acts to reduce ferric (3+) to the ferrous (2+) state, which binds oxygen in the erythrocytes. Significant reduction in metHb level is expected within an hour of MB,[3] as seen in Case 1, where the patient achieved a normal metHb level with the fastest recovery time among the three cases.

On the other hand, methylene blue may induce haemolytic anaemia in populations with G6PD deficiency.[3] G6PD, as the first enzyme in the hexose monophosphate shunt, is the sole source of NADPH in the erythrocyte, and methylene blue reduction to leucomethylene blue is a NADPH-dependent process.[5] Individuals with G6PD deficiency may not produce sufficient NADPH to reduce MB to LMB. Thus, methylene blue as an oxidant may induce haemolysis and paradoxically, worsen MH in a G6PD-deficient patient.[3]

Ascorbic acid is a natural water-soluble vitamin which reduces excessive oxidative stress. Whilst ascorbic acid can directly reduce metHb, the reaction rate is too slow to be effective when used alone, as it may take 24 hours or longer to lower the metHb level.[3] This explained the length of time (7 days) taken to normalise metHb level with high-dose oral ascorbic acid in Case 3. Intravenous ascorbic acid was not available in our centre. MB would be the preferred treatment according to Iolascon et al., recommendation.[3] Furthermore, there is no standardised dose for ascorbic acid used to treat MH.[3] Doses for adults are highly varied and range from 0.5g orally every 12 hours for 16 doses, to 6g to 30g intravenously given as a single dose or in divided doses.[6] Hence, ascorbic acid serves as an adjunct or alternative therapy when MB is not available.[3]

Although metHb levels in all three cases were similar, manifestations were more significant in Cases 1 and 3. It has been reported by Ludlow et al., that any pathology that impairs oxygen delivery, such as anaemia, congestive heart failure, chronic obstructive pulmonary disease, may worsen symptoms of MH.[1] Anaemia with Hb 8g/L reduced from a baseline of 11g/L was likely the precipitating cause in Case 1 and chest infection as the exacerbating factor in Case 3.

We aim to raise awareness amongst clinicians to consider MH as a differential diagnosis for hypoxia, especially when SaO_2 and PaO_2 results in ABG are discrepant. The presence of central cyanosis clinically is probably the most important clue when considering MH. All patients prescribed medications commonly associated with MH should be monitored closely for such a potential complication. Strong oxidising drugs produce more MH than weak oxidising drugs (Table II).[7] These are not uncommon medications used in daily clinical practice, hence noteworthy to keep in mind.

In addition, quantifying metHb level aids in the assessment of disease severity to guide therapeutic decisions. Once MH is diagnosed, the offending drug must be withheld immediately. Subsequently, treatment choice will depend on the stratification of its severity.

CONCLUSION

This case series highlights the importance of early recognition of MH to reduce morbidity and prevent mortality. Outcomes

of all three patients were good, but time to recovery differed amongst them. The threshold for initiating therapy and the choice of treatment should be individualised. Although providing supportive care and administering intravenous ascorbic acid were effective in reducing metHb levels in our patients, early intervention with MB could potentially hasten their recovery, enabling earlier discharge from hospitals.

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