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Hemodialysis in Methemoglobinemia, a friend or foe? A Case Report

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Abstract— *Methemoglobinemia is a potentially fatal illness in which circulating levels of methemoglobin in the blood surpasses the usual physiological level decreases hemoglobin's ability to transport oxygen by shifting the oxygen-dissociation curve to the left, limiting oxygen unloading to tissue and contributing to functional hypoxia.[1] Acquired causes are more prevalent as compared to congenital and arises from exposure to chemicals that oxidizes hemoglobin either directly or indirectly.[2] Most reports of adult methemoglobinemia are related to medication overdoses from local anesthetics. Hemodialysis is one of the researched causes of methemoglobinemia, even though it is not often reported.[3] Removing the causative substances and providing supportive care are the cornerstones of methemoglobinemia treatment. Although it is uncommon these days, physicians should be aware of the risks of methemoglobinemia during prolonged hemodialysis as well as the complications that can result from contamination of the dialysis water.[4]*

Keywords— *Acquired methemoglobinemia, hemodialysis, disinfectant agents, hemolysis, methylene blue, exchange transfusion*.

I. INTRODUCTION

Methemoglobinemia is a potentially fatal illness in which circulating levels of methemoglobin in the blood surpass the usual physiological level of 1-2%. Methemoglobin is a kind of hemoglobin in which the ferrous iron (Fe2+) in heme is oxidized to ferric (Fe3+).[1] Methemoglobin decreases hemoglobin's ability to transport oxygen by shifting the oxygen-dissociation curve to the left, limiting oxygen unloading to tissue and contributing to functional hypoxia.[5] Patients with high methemoglobin levels may have moderate symptoms such as dyspnea, headache, lethargy, and weariness. At higher methemoglobin levels, significant cyanosis may develop with symptoms progressing to respiratory distress, abnormal mental status, seizure, dysrhythmias, and death. Patients with comorbidities such as cardiovascular illness, lung disease, sepsis, or the presence of additional aberrant hemoglobin species may experience moderate to severe symptoms at far lower levels of methemoglobin.[6] Methemoglobinemia should be suspected when three clinical features are present: refractory hypoxia, a "cyanosis-saturation gap," and dark brown blood.[7] This report describes a case of acquired methemoglobinemia with unknown triggers in a ventilated patient.

II. CASE PRESENTATION

A 41-year-old male with no underlying medical illness with a history of kratom abuse for 11 years, otherwise his wife denied other high-risk behaviors. He was taken to the emergency department (ED) for several episodes of fits and postictal drowsiness. Methamphetamine and amphetamine were detected in his urine sample. He was intubated and admitted to intensive care unit (ICU) with the diagnosis of status epilepticus secondary to drug intoxication complicated with oliguric acute kidney injury and rhabdomyolysis (serum creatinine kinase: 2640 U/L). During his stay in the ICU, his consciousness level recovered and no new fitting episode was observed. However, his kidney function test result was further deranged with a significant increase of serum creatinine kinase (CK) of 22338 U/L despite hydration. Thus, warrant for hemodialysis on day three of admission. He was dialyzed for 2 hours and completed uneventfully.

On the next day, he had a desaturation episode despite being ventilated on FiO2 1.0, his pulse oximeter reading ranged from 80 to 86% with peripheral cyanosis.

TABLE I. Serial ABG with co-oximetry monitoring.

	Admission	**Post Dialysis (12hours)**	**Post Methylene Blue**	**Prior to CRRT**	**48 hours on CRRT**
FiO2	0.4	0.7	0.6	0.6	0.5
pH	7.3	7.35	7.296	7.276	7.3
pCO2 (mmHg)	45.3	39.7	61.7	52.3	59.1
pO2 (mmHg)	138.7	195.2	148.6	210.9	164.8
HCO3 (mmol/L)	20.7	21.3	26.7	22.1	26
BE (mmol/L)	-4.7	-3.8	2.4	-2.8	1.7
Total Hb (g/dL)	14.3	8.5	8.0	6.6	6.8
OxyHb(%)	98.1	95.2	83.1	82.2	94.6
MetHb(%)	0.3	3.3	14	15.5	2.1
COHb(%)	0.6	0.9	1.8	1.5	2.8

His repeated chest radiograph showed clear lung fields. His serial arterial blood gas (ABG) showed normal PaO2 in spite of his low SpO2 (Table 1) meanwhile while his co-oximetry reading showed an increasing trend of methemoglobin level. Otherwise, the patient was not given any new prescriptions prior to this event. His urine and serum

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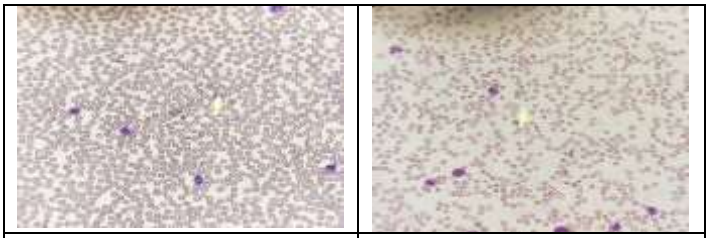
toxicology reported traces of mitragynine and propofol. Hemolytic work up sent after suspicious drop in hemoglobin level with concurrent increase of LDH and bilirubin level. Coomb's test was negative and he tested normal for G6PD. He was given 1 mg/kg of methylene blue.

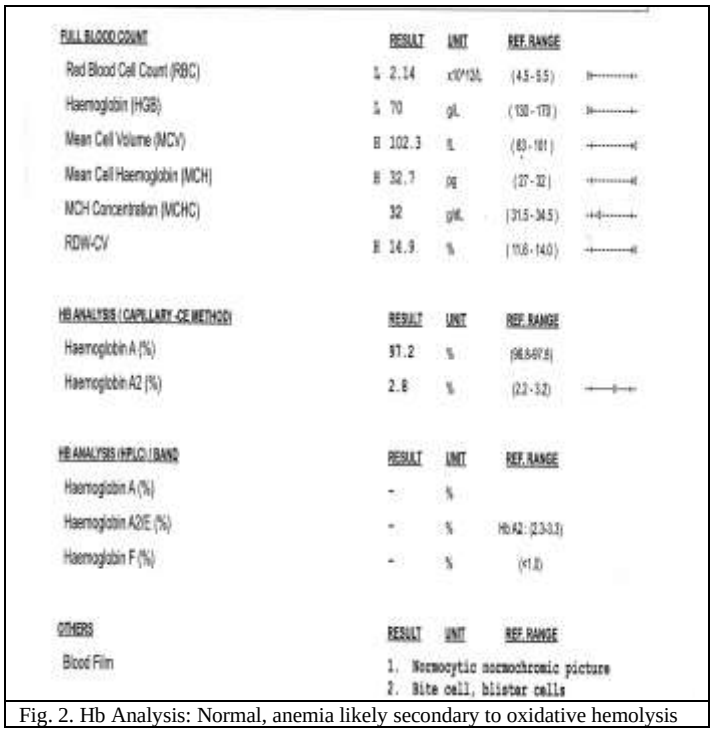


a) Admission: normal RBC morphology, leukocytosis with neutrophilia and monocytosis, reactive lymphocytes

b) During the event: numerous blister cells, Heinz body, Basophillic stippling and spherocytes. Irregularly contracted cells with polychromatic cells

Fig. 1. Peripheral blood film.

However, his peripheral blood film features were consistent with acute oxidative hemolysis evidence by presence of numerous blister cells, bite cells and spherocytes (Figure 1b). Hb analysis also reported normal findings with Hemoglobin A content of 97.2% (Figure 2).



FULL BLOOD COUNT	RESULT	UNIT	REF. RANGE
Red Blood Cell Count (RBC)	L 2.14	x10^12/L	(4.5 - 5.5)
Haemoglobin (HGB)	L 70	g/L	(130 - 170)
Mean Cell Volume (MCV)	H 102.3	fL	(83 - 101)
Mean Cell Haemoglobin (MCH)	H 32.7	pg	(27 - 32)
MCH Concentration (MCHC)	32	g/dL	(31.5 - 34.5)
RDW-CV	H 14.9	%	(11.6 - 14.0)
HB ANALYSIS (CAPILLARY -CE METHOD)	**RESULT**	**UNIT**	**REF. RANGE**
Haemoglobin A (%)	97.2	%	(96.8-97.8)
Haemoglobin A2 (%)	2.8	%	(2.2 - 3.2)
HB ANALYSIS (HPLC) / BAND	**RESULT**	**UNIT**	**REF. RANGE**
Haemoglobin A (%)	-	%	
Haemoglobin A2/E (%)	-	%	Hb A2: (2.3-3.2)
Haemoglobin F (%)	-	%	(<1.0)
OTHERS	**RESULT**	**UNIT**	**REF. RANGE**
Blood Film	1. Normocytic normochromic picture 2. Bite cell, blister cells		

Fig. 2. Hb Analysis: Normal, anemia likely secondary to oxidative hemolysis

His kidney function further worsened (uremia, hyperkalemia, anuric) with a significant increment of serum CK (531644 U/L), thus the patient was started on continuous renal replacement therapy (CRRT). As suggested by the hematologist, he was given a total transfusion of 3-pint packed cells during 48 hours of CRRT. His condition subsequently improved and the patient was successfully extubated. His further hospital course was uneventful and the patient was discharged home after 5 days of stay in the ward.

III. DISCUSSION

Methemoglobinemia is an uncommon condition that arises from either acquired or congenital abnormalities. The incidence rate for congenital methemoglobinemia is not clear. On the other hand, acquired methemoglobinemia are usually more prevalent and caused by exposure to chemicals that oxidizes hemoglobin either directly or indirectly.[2] Most reported cause of adult methemoglobinemia is overdosing of local anesthetics including lidocaine, prilocaine, and benzocaine.[8] Other than that, a case of pesticide poisoning described toxin-induced methemoglobinemia compounded by kidney damage and hypoxic brain injury.[9]

Hemodialysis is also one of the researched causes of methemoglobinemia, although seldom reported. According to a 2003 article, the pediatric hemodialysis center experienced methemoglobinemia and hemolysis, which may have been caused by a disinfectant that was not completely removed from the water system.[10] A 2009 retrospective review examined the relationship between the hospital's water disinfection schedule and the incidence of methemoglobinemia during extended hemodialysis and/or hemodiafiltration. The review found that even a standard hospital water disinfection technique can be linked to significant methemoglobinemia during extended hemodialysis, and that using reverse osmosis alone is insufficient to remove water contaminants from the water effectively.[4] Raising on this matter, a 2023 study that examined series of cases of dialysis patients came to the conclusion that methemoglobinemia, along with cyanosis, desaturation, and hemolytic anemia, can be the result of acute chlorine intoxication caused by the water used during hemodialysis sessions.[3]

In this case, this patient was admitted with normal baseline level of methemoglobinemia. It was detected by co-oximetry monitoring as the patient became symptomatic. Despite extensive toxicological investigation and medications screening the offending agent was not able to be determined. The event occurred within 12 hours after he first experienced dialysis, however the claim is made uncertain with the possibility of water contamination by disinfectant agents. Thorough inquiry regarding the disinfection system and reverse osmosis are unable to point any abnormalities and no other patients in the ICU underwent dialysis on the same day.

Supportive care and stopping the causative substances are the cornerstones of methemoglobinemia treatment. Methemoglobin levels over 30% or in patients exhibiting symptoms, regardless of level, should prompt consideration of the antidote, methylene blue.[7] Methylene blue serves as an electron donor by amplifying the reduction of methemoglobin to hemoglobin via alternative pathway which utilizes nicotinamide adenine dinucleotide phosphate hydrogen methemoglobin (NADPH-MetHb) reductase.[2] For individuals at risk of serotonin syndrome, the medication should be used with caution, and it should not be used in those with G6PD as it may cause hemolysis. It can be given 1-2 mg/kg

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intravenously over 5 minutes and repeated if needed with caution to toxicity.[9] Alternatively, the use of high dose ascorbic acid may be considered in patients associated with hemolysis.[8] However, in patient with renal impairment since the risk of developing renal failure due to hyperoxaluria is high, other treatment to be considered would be exchange transfusion and hyperbaric oxygen therapy.[9] Hence, since our patient did not respond well to methylene blue and had acute hemolysis with anuric kidney injury, he was promptly treated via CRRT and given packed cells transfusion which showed good outcome.

IV. CONCLUSION

Methemoglobinemia should be considered in patients presented with cyanosis and inconsistent oxygen saturation to partial pressure of oxygen value. Methylene blue is the specific antidote in the treatment of methemoglobinemia, however hemolysis must be excluded prior to prescription. Treatment with ascorbic acid is also reported with good prognosis as an alternative, except in cases of patients with renal impairment. Hemodialysis, exchange transfusion and hyperbaric oxygen might give better chances in patients with contraindication to the first two mentioned. Though rare, clinicians should be aware of complications that may arise due to undetected contamination of dialysis water and risk of significant methemoglobinemia during extended hemodialysis.

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