ORIGINAL RESEARCH PAPER

Internal Medicine

DAPSONE INDUCED METHEMOGLOBINEMIA : AN UNCOMMON CAUSE OF HYPOXEMIA (A CASE REPORT)

KEY WORDS: dapsone, methemoglobinema, methylene blue.

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ABSTRACT

Dapsone is a drug commonly used as a second line therapy for various chronic inflammatory disorders. Out of various side effects associated, methemoglobinemia is a less commonly known adverse effect of dapsone. A patient diagnosed to have immune thombocytoepnia, received dapsone as a steroid sparing drug , who later got admitted in outside hospital for symptoms of breathlessness, fever. The patient was empirically treated with antibiotics , and later referred here for further management. Owing to the clinical and radiological disparity, patient was initially suspected and later diagnosed to have methemoglobinemia. Methemoglobinemia was confirmed by an arterial and venous blood gas sample. Patient was then treated with methylene blue, which led to a drastic improvement in her clinical condition. In a couple of days patient was discharged, and was followed by the hematology team for immune thrombocytopenia. The case highlights the importance for keeping a high suspicion for methemoglobinema in cases of hypoxemia and using ABG (arterial blood gas) as a tool for the diagnosis.

INTRODUCTION:

Dapsone is an aniline molecule belonging to sulfone category of drug used in various dermatological and in refractory autoimmune conditions. Right from its discovery of sulfonamide related anti-microbial properties, its recent usage has been related to its various broad spectrum anti-inflammatory properties as well [1] . It's usage as a potent anti-inflammatory drug has been more popular owing to its lesser side effects and as a bridging option for " steroid sparing effect"[2,3] before one can switch to step up therapy of immunosuppressants in chronic inflammatory disorders.

Amongst others, dapsone has been commonly used as a second line therapy in refractory immune thrombocytoepnia [4,5,6] especially because of its good safety & efficacy profile and low cost.

Case Description:

A 59years elderly female, who was a diagnosed case of Immune Thrombocytopenia since 2020 got recently admitted in June 2023 for mild oral bleed and severe thrombocytopenia , for which she received Intravenous immunoglobulin therapy and was henceforth discharged on Tab Wysolone 60mg once daily and Tab Dapsone 100mg twice a day.

Patient since then started having moderate grade fever for 10-15days along with dry cough and breathlessness initially which worsened in the next couple of days.

She was then admitted in a local hospital where she was diagnosed to have a lower respiratory tract infection and was started on iv antibiotics and oxygen therapy. She also underwent high resolution computed tomography of chest which revealed ground glass opacities in left upper lobe with mild interstitial edema like changes. Patient received the following medications:
Inj cefoperazone sulbactam iv
Inj dexmethasone iv
Tab. Azithromycin
Tab. Levofloxacin
Post the treatment of duration of almost a week , she was discharged on oral antibiotics and tab wysolone and tab dapsone as before.

A couple of days after discharge , patient again worsened with increasing breathlessness and got admitted in the previous hospital but later referred here, for further management.

Patient's initial vitals being,
Conscious oriented, afebrile , GCS 15, mild central cyanosis present in lips, mild bluish discolouration of fingernail tips bilaterally.

Pulse 108/min regular , normal volume, all peripheral pulses felt and equal
Blood pressure- 128/78mmHg without any support
Cardiovascular system- within normal limits
Respiratory system- bilateral basal rhonchi ++ and occasional coarse crepitations.
RR 34/min, SPO2- 87% on oxygen therapy by Hudson's face mask on 15ltr/min
In view of severe breathlessness and tachypnea , patient was put on Noninvasive ventilatory support initially with FiO2 of 70%, peep 5cmH2O, Pressure support of 12cmH2o. Spo2 now still was fixed at 87%.
There was no improvement in SPO2 even with a 100% Fio2. An urgent bedside Chest Xray was done to rule out an acute emergency like pneumothorax. ECG done – sinus tachycardia.

The ABG done had the following findings:

pH	7.482
Pco2	30.5mmhg
Po2	117.6mmhg
Hco3	22.3mmol/l
BE	-1.2mmol/l
So2	97.7%
FO2hb	75.5%
FCOHb	1.2%
FMetHb	21.5%
FHHb	1.8%
Na	138.1mmol/l
K	3.56mmol/l
Ca++	1.06mmol/l
Cl	110mmol/l
Anion gap	9.4

The normal PO2 values and the contrasting low SPO2 values, revealing what is called a " saturation gap", and the values of

FMetHb as measured in the co-oximetry being 21.5% (normal range in the machine <1.5%) caused a suspicion of diagnosis of symptomatic Methemoglobinemia. The levels were also confirmed with a repeat sample of both arterial and venous blood gas which showed very high FMetHb values.

A repeat ABG was done to avoid any technical errors.
2D ECHO was done- normal LV function and normal RV function. Cardiac enzymes were normal. Bilateral lower limb venous Doppler was Normal.

High resolution computed tomography chest was repeated- showed areas of atelectasis changes in left upper lobe.
Initial blood investigations showed
Hb- 9.4gm%, TLC – 16300/ul with predominant neutrophilia, platelet – 1.70lakh.
Normal renal function & liver function test.
D-dimer- 4755ng/ml, CPK – 27U/L, NTproBNP- 454pg/ml
S. Procalcitonin- 0.06ng/ml.
FLU PCR panel and Covid RTPCR were negative.
Patient was started on IV fluids, bronchodilators and empirical antibiotics. All maintenance therapy for immune thrombocytopenia was withheld.

Hematological opinion was sought regarding Immune thrombocytopenia and its related medication causing methemoglobinemia. Pulmonologist opinion was also considered. With the very high index of suspicion and considering the severe symptoms , it was decided for methylene blue administration as a treatment for the same.

Empirically IV vitamin C was started in doses of 1gm iv Q8th hrly. Family was made aware regarding the diagnosis and the related medication. Quantitative levels of G-6PD were sent (17.5units /gm, normal range 8.6-18.6).

Considering the diagnosis, IV Methylene blue 60mg (as per 1mg/kg) was administered slowly over 30mins. The patient was continued on NIV with 100% Fio2.

After a transient drop in SPo2 till 80%, post administration of methylene blue, the saturation rose to around 95% and then to 99%.

A series of repeat ABG was done which showed the following :

	Immediately after methylene blue	After 5 mins
Ph	7.541	7.493
Pco2	30.4	36.9
Po2	122.3	108.7
Hco3	25.5	27.7
BE	3.0	4.2
SO2	98.7	97.8
FO2Hb	94.2	94.5
FCOHb	2.6	2.9
FMetHb	2.0	0.5
FHHb	1.2	2.1
Na	138.3	134.5
K	2.88	3.92
Ca++	0.92	1.02
CL	109	103
Angap	6.7	7.7

With definitive improvement in the clinical symptoms and the normalisation of Spo2 as well as the decreasing levels in FMetHb in the co-oximetry ABG, our diagnosis of " Dapsone induced methemoglobinemia" was confirmed.

With serial ABGs being done every 6th hrly, there was no further elevation in the FMetHb levels.

Soon patient's cyanosis also improved significantly and symptoms also subsided.

Antibiotics were also de-escalated eventually. With chest physiotherapy and spirometry patient was weaned off from NIV initially , then on Nasal prong oxygen therapy over the next few days of hospital stay. Patient was then also weaned off from nasal prongs and was clinically stable and maintained normal saturation on room air.

With no further complications during the rest of the hospital stay, patient was planned for discharge and another Hematology follow up advice was sought for maintenance medications for immune thrombocytopenia. Along with symptomatic treatment, patient was discharged on Tab prednisone 20mg twice a day.

DISCUSSION:
Dapsone was first introduced in 1943 as an effective chemotherapeutic agent for leprosy and is still an important drug for treatment of this disease and associated Lepra reactions.

Other indications of dapsone use are dermatitis herpetiformis, maduromycosis, panniculitis due to alpha-1 antitrypsin deficiency and Pneumocystis carinii pneumonia in HIV patients.

Amongst the broad spectrum of causes for meth-hemoglobinemia, drugs are supposedly the major ones. In a multicenter study, dapsone has been shown to be a major cause of drug-induced meth-hemoglobinemia.[7]

Pathophysiologically, Methemoglobinemia is a condition where in there is diminished oxygen-carrying capacity of circulating hemoglobin due to the conversion of some or all of the four iron species from the reduced ferrous (Fe2+) state to the oxidized ferric (Fe3+) state which is unable to bind and transport oxygen. This conversion of the reduced Fe to oxidised Fe can occur either congenitally or by acquired processes due to exposure to direct oxidizing agents (e.g. benzocaine and prilocaine), indirect oxidation (e.g. nitrates), or metabolic activation (e.g. aniline and dapsone).

In normal physiology, the activity of NADPH methb reductase and cytochrome b5 reductase enzymes convert any oxidised Fe forms to reduced Fe, but these processes are overwhelmed in the environment of oxidising agents.

Although the presentation may vary in severity based mostly of the percentage of MethHB, the degree of symptom severity also depends on the duration & magnitude of exposure to the agent, the rate of accumulation, one's ability to clear the methHB, and the underlying health status of the patient.

%MetHb	Symptoms
<15	Usually symptomatic
15-30	Cyanosis, anxiety, light-headedness, fatigue, headache
30-50	Tachypnea, confusion, syncope
50-70	Seizures, Arrythmias, metabolic acidosis, coma
>70	Death

Refractory hypoxemia and saturation gap are the most important diagnostic clues to this condition, where there is a fixed SpO2 and a falsely normal Sa02 and Po2. A saturation gap greater than 5% presents in cases of elevated abnormal forms of hemoglobin such as carboxyhemoglobin, methemoglobin, and sulfhemoglobin[8]. And further evaluation from co-oximetry will confirm the diagnosis.

Methylene blue usually is the treatment of choice[9,10]
The enzyme NADPH-MetHb reductase reduces methylene blue to leukomethylene blue using NADPH from the G6PD-dependent hexose monophosphate shunt pathway which

then reduces methemoglobin to hemoglobin. Methylene blue is recommended when methemoglobin exceeds 20-30%, or at lower levels, if the patient is symptomatic.

Treatment decision should be made on clinical presentation and should not be withheld for confirmatory laboratory values. The methylene blue dose is 1-2 mg/kg (0.1-0.2 mL/kg of 1% solution) intravenously over 5 minutes.[11]. The dose can be repeated in 30-60 minutes if significant symptoms or levels remain above the treatment threshold.

Paradoxical increase in MethHb levels can occur especially in G6PD deficiency[12] patients or when toxic doses of methylene blue are used (>7mg/kg). Caution should also be taken while administering in pregnancy and in those susceptible to serotonergic syndrome [13]

Ascorbic acid is the agent used, especially when methylene blue is not available[14] and in cases of methemoglobinemia and G6PD deficiency[15]. Doses range from 0.5 g iv twice a day for a total of 16 doses, 1 g every 12 hr × 14 doses, 1.5.2 g iv × 3–4 infusions, 5 g every 6 hr × 6 doses, or even 10 g × one dose [16]

Other therapies tried in refractory cases are hyperbaric oxygen therapy[17,18] and therapeutic red cell exchange[19,20].

CONCLUSION:

Methemoglobinemia is a life-threatening but potentially reversible condition which requires a high index of suspicion and appropriate lab diagnosis for confirmation. The condition highlights the importance of interpreting and relying on a basic lab parameter like an arterial blood gas, especially in today's era of advanced radio-imaging techniques.

A contrasting discrepancy in the patient's vitals and lab parameters and a saturation gap would be enough to clinch the diagnosis. Our case report also highlights the importance that, therapeutic doses of drugs like dapsone can also cause methemoglobinemia even in the absence of any other underlying hematological abnormality. Hence a proper clinical history of symptoms, drug exposure and apt recognition would be helpful to treat this condition.

Declaration:

The authors hereby certify that appropriate consent have been taken from the patient and their relatives about the clinical information to be published with all anonymity and privacy protected with regards to the patient's identity. The authors declare that they don't have any conflict of interest.

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