Introduction

Dapsone is one of the most common drugs used by a dermatologist, its FDA-approved indications being leprosy and dermatitis herpetiformis.\(^1\) It is also increasingly used as an alternative agent in the prevention of *Pneumocystis jiroveci* in patients with reduced cell-mediated immunity in conditions, such as HIV, leukemia, and poststem cell transplant.\(^2\) Methemoglobinemia is a known adverse effect of dapsone. Normally, up to 2% of methemoglobin (MetHb) is routinely generated as a result of oxidative stresses in the body. However, regulatory mechanism ensures that the levels are kept under control. Usually, MetHb levels in excess of 30% are associated with clinically relevant signs and symptoms.\(^3\) We report a case of low-grade methemoglobinemia causing atrial fibrillation (AF) in a case of Hansen’s disease on dapsone.

Case Report

A 50-year-old male patient diagnosed as a case of Hansen’s disease (pure neuritic) with left ulnar quiet nerve palsy, who was undergoing treatment with three-drug WHO-multi drug therapy (MDT) and oral prednisolone 60 mg/day for 1 month, complained of a self-remitting episode of sudden-onset palpitation lasting 30 min. The episode was not triggered by physical activity, and there was no associated history of chest pain, diaphoresis, or loss of consciousness. There was no history of similar episode earlier and he was tolerating his medication well with good compliance to therapy. The patient was also being treated with tablet amiodipine 5 mg daily for steroid-induced hypertension (HTN) for the past 2 weeks with good blood pressure control. Examination revealed a tachycardia of 154 bpm, which was irregular, a blood pressure of 122/74 mm Hg, respiratory rate of 20/min, and SpO\(_2\) on pulse oximetry of 88% at room air. There was subtle cyanosis of the lips. Electrocardiogram (ECG) was ordered, which showed features of atrial fibrillation (AF) in the form of ventricular tachycardia of 158 bpm with absent “P” waves and irregular ventricular rhythm [Figure 1]. Blood was drawn for investigating with clinical suspicion of methemoglobinemia, which revealed a chocolate brown color [Figure 2]. MetHb levels by photospectroscopic method were 3.66% with hemoglobin (Hb) of 13 g/dl. Complete blood count, serum electrolytes, biochemistry including renal function tests, cardiac enzyme markers, and bedside echocardiography were essentially normal. The patient was managed in an intensive care setting, where tablet dapsone and tablet amiodipine were...
immediately stopped followed by oxygen inhalation at 6 l/min, tablet metoprolol 25 mg BID, and tablet Vitamin C 500 mg TID. His tachycardia eventually settled with pulse rate of 80/min which was regular and a SpO2 of 98% at room air.

**Discussion**

Dapsone or 4′4′-diaminodiphenylsulfone is a synthetic lipid-soluble drug which inhibits folate synthesis and impairs neutrophil function. Both these properties have found use in various indications such as leprosy and dermatitis herpetiformis, which are FDA approved, as well as a multitude of novel indications such as other autoimmune bullous dermatoses, vasculitis, and neutrophilic dermatoses.[1]

Dapsone is metabolized in the body by two principal pathways, N-acetylation and N-hydroxylation by N-acetyl transferase and cytochrome p450, respectively. While the acetylated metabolites are pharmacologically inactive, hydroxylamine metabolites (especially, dapsone mono-hydroxylamine) are retained in circulation for a long time via extensive enterohepatic recirculation and are readily taken up by erythrocytes where they are responsible for hematologic adverse effects in the form of methemoglobinemia and hemolytic anemia.[2] Methemoglobinemia is the presence of increased concentration of MetHb in the blood and occurs when iron moiety of Hb is oxidized from ferrous (Fe^{2+}) to ferric (Fe^{3+}), state thereby making it incapable of oxygen transport and causing tissue hypoxia. Small amounts of MetHb are routinely formed daily in response to oxidative stress, but protective mechanisms ensure that the concentration remains below 2%. These include cytochrome b5-MetHb reductase pathway which reduces MetHb to Hb using nicotinamide adenine dinucleotide as a co-factor and is the major pathway for removing 95%–99% of endogenously produced MetHb. A second pathway accounts for about 5% reduction in MetHb. It involves nicotinamide adenine dinucleotide phosphate (NADP)-MetHb reductase which is dependent on glucose 6-phosphate dehydrogenase and is inducible by exogenous agents such as methylene blue. Methemoglobinemia may be hereditary or acquired. Among acquired causes, dapsone and benzocaine are the most common culprits, other agents being drugs such as sulfonamides, chloroquine, and nitric oxide and chemicals such as nitrates, chlorates, and aniline dyes.[3,4] MetHb levels of 10%–20% are tolerated well, beyond which clinical symptoms appear in the form of dyspnea, nausea, tachycardia at 30% and lethargy, stupor, decreasing consciousness at levels beyond 55%. Higher levels may cause seizures, cardiac arrhythmias, and cardiac failure. Hemolytic anemia may follow methemoglobinemia caused by dapsone, sulfones, or phenacetin.[5] AF is the most common arrhythmia with a prevalence of 1%–2% in general population. It is characterized by acute-onset disorganized atrial activity, leading to impaired atrial function with potential for causing embolic stroke and worsening heart failure. It is diagnosed on ECG by the absence of P waves and irregular rate of QRS complexes.[5] Important risk factors for AF include increasing age, smoking, HTN, diabetes mellitus, myocardial infarction, valvular heart disease, and hyperthyroidism among others.[6] Our patient presented with a solitary episode of palpitations which remitted spontaneously and on examination was consistent with diagnosis of AF. The presence of cyanosis and a raised MetHb of 3.66% was consistent with mild methemoglobinemia. Although it is a known complication of dapsone, the occurrence of arrhythmia at a lower concentration of MetHb was an uncommon finding. This may be explained by a “multiple hit hypothesis” where presence of comorbid conditions, such as anemia, cardiac, or respiratory disease which impair oxygen transport can exacerbate low level of MetHb to cause symptoms. Furthermore, as opposed to high levels of MetHb, patients with low-grade methemoglobinemia may not present with dramatic hypoxia or large saturation gap.[4,7] In this particular case, the presence of steroid-induced HTN and the use of glucocorticoids itself could have contributed to the lower threshold for symptoms at an otherwise relatively lower concentration of MetHb. Studies have shown that HTN is associated with 1.8-fold increase in new-onset AF, with higher pulse pressure shown to increase this risk.[8] However, HTN, in this case, was of recent-onset, drug-induced, well-controlled and with low pulse pressure. As per a study by Christian et al.,
the use systemic steroid almost doubles the risk of AF, which is four times higher in new users of steroid as in this case, though the causal relationship was found to be dose dependent in another study.[6,9] Though individually, these conditions do stand the patient to cognizable risk of AF; however, the triggering event of low-grade methemoglobinemia probably best explains the occurrence of new-onset AF in an otherwise well-preserved patient of Hansen’s disease. Our patient was managed in an intensive care setting with oxygen inhalation and high-dose ascorbic acid for methemoglobinemia and amlodipine replaced with metoprolol, a beta-blocker for HTN, and to serve as a protective agent against future risk of AF. Various agents such as high-dose Vitamin C and E, activated charcoal, hyperbaric oxygen, N-acetylcysteine, cimetidine, hemodialysis, and plasma exchange have been mentioned in literature for the management of methemoglobinemia, but first-line therapy remains methylene blue. It is administered as a 1% solution at the rate of 1–2 mg/kg every 3–5 min and acts via its active metabolite, leucomethylene. It is recommended for patients with symptomatic hypoxia and a MetHb of over 20%. Ascorbic acid is a strong reducing agent, and although there is no concurrence on the dosing, it can be administered intravenously as 300 mg/kg IV bolus, 300 mg IV in 24 h, and 10 g IV in 6 h or as 300 mg to 600 mg orally in three or four daily divided doses, as was done in our case.[3,4,10] Figure 3 explains the metabolism of MetHb in the body with the mechanism of action of various treatments available. Beta-blockers, though generally not considered the first choice for management of HTN, are useful for acute and chronic rate control in AF patients.[9] Dapsone was withdrawn and MDT was modified by adding minocycline 100 mg and ofloxacin 400 mg daily. HTN resolved on tapering of steroids. The patient has been asymptomatic since. The case highlights the possibility of low concentration of methemoglobinemia as the cause of cardiac arrhythmia in a patient on dapsone, explained with the “multiple hit hypothesis.”

Declarations of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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