Title

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CLINICAL VIGNETTE

Cyanosis in a Patient with Chronic Idiopathic Thrombocytopenic Purpura (c ITP) Treated with Dapsone

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Case

A 38-year-old Rh-negative male is followed with chronic primary immune thrombocytopenia (c ITP). He presented to our office in his 20s with grade 4 thrombocytopenia due to primary ITP. He initially responded to IVIG and steroids, but soon relapsed with refractory disease and underwent therapeutic splenectomy. Unfortunately, he relapsed again shortly after splenectomy, despite confirmed absence of an accessory spleen and has been managed for chronic and relapsing ITP. He was initially treated unsuccessfully with azathioprine, vincristine, IVIG, steroids, eltrombopag and rituximab. His c ITP was finally controlled with a combination of maintenance low dose prednisone (5mg/d), periodic rituximab pulses and long-term high dose romiplostim. We also attempted to procure fostamatinib which was denied by insurance.

With concern about the long-term toxicities of romiplostim and the somewhat blunted platelet response to the maximal therapeutic dose, he underwent bone marrow evaluation. Bone marrow biopsy revealed mild generalized fibrosis (MF-1 out of 3) with focal regions demonstrating mild/moderate fibrosis (MF-1/MF-2 out of 3). The bone marrow was otherwise normocellular with approximate 60% cellularity. All hematopoietic elements were present with progressive maturation. Megakaryocytes were increased with a subset showing hyperchromatic nuclei and atypical nuclear lobulation.

Given the increased bone marrow fibrosis due to the long-term use of romiplostim, we opted to switch to dapsone. The main goal was to allow reversal of romiplostim induced marrow fibrosis with a romiplostim treatment free interval. Shortly after initiation of dapsone, during planned dose escalation, he developed asymptomatic hypoxia and cyanosis. Examination revealed low room air oxygen saturation of 85% and slate-blue skin discoloration, most notable on fingers and mucous membranes. He was directed to the emergency room with a tentative diagnosis of dapsone induced methemoglobinemia. In the emergency room, ABG noted methemoglobin levels of 14.4%. He was given a single 70 mg dose of Methylene blue in the ED which near immediately restored the skin discoloration. ABG the next day revealed a methemoglobin level of 4.3% and normal oxygen saturations. He was discharged with full clinical recovery.

Discussion

Dapsone (4,4'-diaminodiphenylsulfone) is a synthetic sulfone[1] used infrequently in management of refractory c ITP. Dapsone efficacy was initially reported by Khan and Dutta et al.[2,3] However, the retrospective analysis by Colella et al[4] further established the role of dapsone in c ITP. This study of 122 patients primarily with c ITP reported complete responses in 24% of the patients and approximately 50% of patients with durable responses while on therapy. Interestingly, the authors noted a common mild methemoglobinemia, with symptomatic methemoglobinemia reported in < 5% of patients.[4]

Methemoglobinemia is a condition of obligatory hemoglobin trapping in the ferric state. Ferrous iron is the reduced form of normal hemoglobin. In the ferric state the hemoglobin can no longer bind oxygen with markedly reduced oxygen carrying capacity with severe hypoxia and cyanosis.[5-7] Acquired methemoglobinemia is reported with multiple compounds including chlorates, inorganic, and organic nitrates as well as drugs including local anesthetics and sulfa drugs including dapsone. Dapsone is known to be a potent cause of acquired methemoglobinemia. This is due to formation of the metabolite hydroxylamine from N-hydroxylation of dapsone. Dapsone is also associated with hemolysis, hepatitis, coma, seizures, and metabolic acidosis.[5-7] Methemoglobinemia should be considered in differential diagnoses of cyanosed patients with normal ABGs, PaO_2 and cardio-respiratory status.

When more than 30% of normal Hb is converted to methemoglobin, the condition could become fatal requiring prompt management. Management of clinically significant acquired methemoglobinemia includes discontinuing the offending agent and providing methylene blue and ascorbic acid. Methylene blue is the drug of choice in the management of methemoglobinemia. Methylene blue reduces the methemoglobin back to hemoglobin using the enzyme nicotinamide adenine dinucleotide phosphate-methemoglobin reductase. Depending on the clinical scenario, patients could also be treated with gastric lavage and activated charcoal. In methylene blue refractory settings, exchange transfusions or hyperbaric oxygen may be considered. In mild methemoglobinemia with methe-

moglobin levels < 20%, supportive measures and discontinuation of the offending agent may be more than adequate.[8-10]

It is important to emphasize that the use of methylene blue in dapsone induced methemoglobinemia is limited by the long half-life of dapsone. The recurrence or rebound of methemoglobinemia may be due to persistent and protracted dapsone absorption from the gastrointestinal tract. The literature suggests concurrent use of ascorbic acid. Ascorbic acid provides a reducing environment that may mitigate the rebound methemoglobinemia.[11,12]

We report a case of dapsone induced methemoglobinemia when used for refractory c ITP. We hope to increase awareness of the association between dapsone and methemoglobinemia. Drug induced methemoglobinemias are often poorly recognized leading to delayed diagnosis. Drug induced methemoglobinemia should always be considered in the differential diagnosis of central cyanosis if both the ventilatory and the circulatory systems are intact. More specifically, health-care professionals should be aware of dapsone induced methemoglobinemia and become familiar with the management of this condition. Severe acquired methemoglobinemia is a rare condition that could become fatal if undiagnosed.

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