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A rare case report on dapsone induced haemolytic anaemia in a hansen's disease patient with type-1 leprae reactions

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Abstract
Dapsone also known as diaminodiphenyl sulfone is a principal drug in a multidrug regimen recommended by the WHO used for the treatment of leprosy. It is a potent anti-inflammatory and anti-parasitic compound mainly used in the treatment of wide variety of dermatological inflammatory diseases. A 58 years old male patient was admitted in the dermatology ward with chief complaints of body pains, scaly red raised lesions all over the body since 10 days. His past medical history includes h/o BB (Borderline Borderline) leprosy & started MB–MDT (is a combination of Tab. Dapsone, Tab. Rifampicin, Tab. Clofazimine) since 2 months. Now he developed ↑ erythema & scaling of lesions in body & body pains, burning sensation of eyes since 10 days. Dapsone is associated with seven fold increased risk of hemolytic anemia so better vigilance is necessary for implementation of safe and effective treatment for each individual.

Keywords: dapsone, leprosy, hemolytic anemia, erythema, vigilance

Introduction
Dapsone also known as diaminodiphenyl sulfone is a principal drug in a multidrug regimen recommended by the WHO used for the treatment of leprosy. It is a potent anti-inflammatory and anti-parasitic compound mainly used in the treatment of wide variety of dermatological inflammatory diseases such as dermatitis her petiformis, chronic bullous dermato sis, Pneumocystis jiroveci pneumonia, erythema elevatum diutinum, epidermolysis bullosa acquisita, linear IgA bullous dermatosis and cicatricial pemphigoid and in malaria prophylaxis [1-5]. Dapsone is bacteriostatic and probably acts by a mechanism similar to that of the sulfonamides, interfering with folate synthesis, both have a similar range of antibacterial activity and are antagonized by para-aminobenzoic acid [6]. Dapsone upon long term usage may lead to a variety of adverse effects including hemolytic anemia, methemoglobinemia, exanthematous eruption, toxic epidermal necrolysis or Steven Johnsons syndrome, agranulocytosis, nephritis, pneumonitis, and hypothyroidism. Dapsone hypersensitivity syndrome (DHS) is a severe and distinct idiosyncratic adverse reaction with multiorgan involvement. During therapy for leprosy, two types of reactions may occur i.e., Type I: Reversal reaction includes erythema, followed by swelling of skin and nerve lesions in tuberculoid patients; skin lesions may ulcerate and multiply, and acute neuritis may cause neural dysfunction. Type II: Erythema nodosum leprosum, occurs primarily in lepromatous leprosy, with an incidence of about 50% during the first year of therapy [7]. Signs and symptoms of leprosy includes tender erythematous skin nodules, fever, malaise, orchitis, neuritis, albuminuria, iritis, joint swelling, epistaxis and depression; skin lesions may ulcerate. The mechanism of dapsone induced hemolytic anemia includes oxidant hemolysis, caused by dapsone's metabolite hydroxylamine, is a common side effect, and Screening for glucose-6-phosphate dehydrogenase (G6PD) deficiency is recommended before the drug is started in order to prevent potential hemolytic reactions. Differences in dapsone metabolism, which affect the production and detoxification of its reactive metabolites, might be responsible for differential susceptibility of people to the adverse effects of dapsone.[8]The incidence of dapsone induced hemolytic anemia in patients with normal G6PD level ranges from 23 % to 76%). In SCT recipients, the incidence of hemolysis is 87% [9]. Anemia caused by dapsone induced hemolysis can be mild and asymptomatic or severe requiring blood transfusion.

Case
A 58 years old male patient was admitted in the dermatology ward with chief complaints of body pains, scaly red raised lesions all over the body since 10 days. He was apparently normal 10 days back then he developed red raised, scaly lesions over extremities then progress to involve trunk face and also complaining of slipping of chappels since 1 month, numbness of hands since 2 months. His past medical history includes h/o BB (Borderline Borderline) leprosy & started MB -MDT (is a combination of Tab. Dapsone, Tab. Rifampicin, Tab. Clofazimine) since 2 months. Now he developed ↑ erythema & scaling of lesions in body & body pains, burning sensation of eyes since 10 days. Not a known DM/HTN/Asthma/epilepsy. No h/o fever. Personal history of patient includes mixed diet, appetite was normal, occupation is cooli, sleep was inadequate, bowel & bladder habits are

Normal. He is a Known alcoholic and smoker since 20 years and his family history was irrelevant.

On general examination the patient was conscious and coherent. Upon physical examination all vitals are found to be normal. On systemic examination i.e., upon cutaneous examination- Erythematous scaly plaques all over body including face was observed. Laboratory findings revealed decreased Hb level-4.0 gm/dl [↓↓] than that of normal level and increased ESR with 25mm/hr.Peripheral smear report impression shows moderate degree of macrocytic hypo chromic anaemia with neutrophil leucocytosis. Based on the subjective and objective evaluation the patient was diagnosed as Hansen's disease with Type 1 leprae reactions (which was shown in figure 1) and Dapsone Induced Haemolytic Anaemia. The treatment includes; on day 1: Patient was prescribed withInj. Decadran given in dose of 2CC intravenously once a day, Continue MB- MDT therapy (Tab.Dapsone given in a dose of 100 mg orally once a day, Tab. Rifampicin given in a dose of 100 mg orally once a day, Tab. Clofazimine given in a dose of 50 mg 0rally once a day), Tab. Pantop given in a dose of 40mg orally once a day, Tab. Paracetamol given in dose of 500mg orally twice a day, Cap. A & D given in a dose 5400 IU orally once a day, Tab. Levomont in dose of 10 mg orally once a day, Tab. calcium in a dose of 500 mg orally once a day, and high protein diet was advised. On day 2: Same treatment was continued along with that 1 packed cell RBC transfusion was done, Tab. B-complex given in dose of 67 mg orally once a day, Glycerin lotion for E/A, Ciprofloxacin eye drops 4drops twice a day, Lacryl PF 2% gel at bed time. On day-3: Same treatment was continued along with Tab. Iron folic acid given in a dose of 333 mg orally once a day. On day-4: Same treatment was continued and Tab. Cetirizine given in dose of 10 mg orally once a day was added. On day-5: Same treatment was continued and 1 packed cell RBC transfusion was done. On day-6: Patient was discharged with the following medication i.e., Continue tapered dose of MB-MDT, Tab. IFA in a dose of 335.5mg orally twice a day, Tab. Calcium in a dose of 500 mg orally once a day, Glycerin lotion E/A twice a day, Tab. Pantop in a dose of 40 mg orally once a day, Tab B-complex in a dose of 67 mg orally once a day, Tab. Cetrizine in a dose of 10 mg orally once a dayand Cap. A&D in a dose of 5400 IU orally once a day.

Based on the above information here we have suspected this is an ADR of Tab. Dapsone and also the reason for hospital stay.

Causality assessment: To evaluate the relationship between the drug and reaction, we have performed causality assessment by using scales like WHO causality assessment scale, Naranjo's scale and Karch Lasagna scale and analysis of observed ADR (Table 1) & (Table 2)

Table 1: Causality assessment of suspected ADR

ADR Scale	WHO-UMC	Naranjo's	Karsch and Lasagna
Assessment	Probable	Probable	Possible

Table 2: Analysis of observed ADR

Severity Assessment	Level-4 (b)
Predictability	Type-A
Preventability	Probably preventable

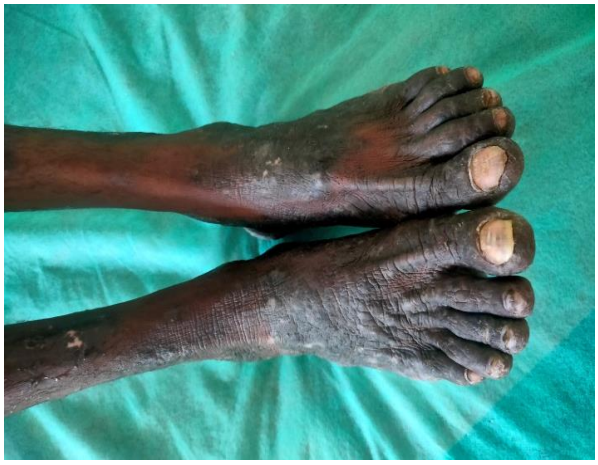

Fig 1: Shows Hansen's disease with Type-I leprae reactions

Results and Discussion

Dapsone is a synthetic sulphone which was similar to the sulphonamide drugs, targeting dihydropteroate synthase a key enzyme in bacteria. Despite early reports of widespread resistance following monotherapy, dapsone is found to be very useful in combination with rifampicin in WHO MDT regimens for leprosy. Its main role in paucibacillary leprosy is probably to prevent the emergence of rifampicin-resistant organisms. In combination with Clofazimine, dapsone is bactericidal, though not as powerful as single-dose rifampicin. Dapsone has both antimicrobial and anti-protozoal properties and anti‑inflammatory effects resembling those of non-steroidal anti‑inflammatory drugs; hence, due to this dual action, it is used in many infectious, immunological, and hypersensitivity disorders.Leprosy [also known Hansen's disease] is an infectious disease caused by "mycobacterium leprae'' which involves the skin and peripheral nerves characterized by lesions of the peripheral nerve, skin and mucous membrane. Hemolytic anemia induced by dapsone involves Oxidant hemolysis, caused by dapsone's metabolite hydroxylamine, is a common side effect, and screening for glucose-6-phosphate dehydrogenase (G6PD) deficiency is recommended before the drug is started in order to prevent potential hemolytic reactions. We report a case of dapsone induced hemolytic anemia in a patient with Hansen's disease of Type I leprae reactions. Dapsone-induced hemolytic anemia is mostly reported in patients with G6PD deficiency. The occurrence of hemolysis in patients with normal G6PD level suggests that hemolysis may be a dose-related event as may be seen with elevated dapsone levels in patients with renal dysfunction or due to concurrent administration of medications that use the cytochrome P-450 isoenzyme system. There are reports of dapsone-induced hemolytic anemia in transplant recipients with normal G6PD levels [10]. All of them were receiving tacrolimus, which share the cytochrome P-450 isoenzyme system. Our patient did not have renal failure and was not on any drugs that share the cytochrome P-450 isoenzyme system. Alternatively, there may be mutations in the hexose monophosphate shunt or glutathione metabolism that lead to glutathione depletion and subsequent hemolysis, Which may be possible in our case [8]. in the majority of the published literature, the patients' condition improved on

permanent discontinuation of the drug and corrective treatment with steroids.

Conclusion

This case study concludes that Dapsone is associated with seven fold increased risk of hemolytic anemia; so better vigilance is necessary for implementation of safe and effective treatment for each individual. In order to prevent serious adverse drug reactions of this drug close monitoring of the drug during treatment course is necessary and creating awareness of the patients receiving this drug is essential to regularly monitor their haemoglobin levels upon long term usage of the drug. So, early detection of the cases and proper treatment of this disease should be the main aim of our treatment to get rid of this disabling disease.

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