Fatal dapsone hypersensitivity syndrome with hypothyroidism and steroid-induced diabetes mellitus

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Abstract:
Dapsone has been part of the World Health Organization multidrug therapy for the treatment of leprosy. While it has been efficacious in the management of leprosy, there are many patients who develop adverse drug reactions to the drug including life-threatening reactions such as dapsone hypersensitivity syndrome (DHS). We report a case of a patient who was prescribed dapsone as part of multidrug therapy for leprosy following which she developed DHS. Her condition worsened after tapering the oral steroids given to manage the DHS, and she was detected to have hypothyroidism. She developed diabetes mellitus and succumbed to septic shock.

Keywords:
Adverse drug reaction, dapsone, hypersensitivity

Introduction

Dapsone has been clinically used for the treatment of leprosy, Pneumocystis carinii pneumonia in AIDS patients and malaria prophylaxis in some countries. It is also the drug of choice for inflammatory dermatological conditions such as dermatitis herpetiformis, cicatricial pemphigoid, epidermolysis bullosa acquisita, erythema elevatum diutumum, and linear IgA bullous dermatosis to name a few.[1] While dapsone has demonstrated efficacy in these conditions, there are reports of patients who have developed adverse drug reactions (ADRs), some of which have been life-threatening and fatal.[2] Dapsone hypersensitivity syndrome (DHS) is a severe idiosyncratic drug reaction characterized by the triad of fever, rash, and systemic involvement which can cause severe organ dysfunction and was first described by Lowe and Smith.[3]

Case Report

A 45-year-old female patient presented to the hospital with generalized erythema with scaling over the entire body [Figure 1] for 20 days and history of fever withchills and cough with expectoration for 3–4 days [Figure 1]. The patient had been taking tablet dapsone100 mg daily and capsules rifampicin 450 mg daily for the treatment of leprosy. She had no history of headache or convulsions; chest pain, palpitation, dysuria, oliguria, hematuria, rash, bleeding from any site, hypertension, ischemic heart disease, or tuberculosis. Her chest X-ray was within normal limits. She had leukocytosis, but her hemoglobin and platelet count were normal. Her liver and renal function tests were abnormal [Table 1].

Skin biopsy revealed superficial perivascular lymphohistiocytic infiltrate with few eosinophils, epidermis was spongiotic with parakeratotic stratum corneum [Figure 2]. She was diagnosed as a case of DHS with...
lower respiratory tract infection with sepsis with acute kidney injury.

The patient was prescribed tablet prednisolone 30 mg once a day, tablet ranitidine 150 mg twice a day, tablet calcium lactate (500 mg) (2 tablets/day), cholecalciferol powder 60,000 IU once a week for 4 weeks and a single dose of table albendazole. Once her renal parameters were normal and general condition improved, she was advised high protein diet, tablet chlorpheniramine 4 mg twice a day, tablet hydroxyzine 25 mg at night, tablet paracetamol 500 mg twice a day, and white soft paraffin lotion for local application twice a day. She was also prescribed a lotion containing halobetasol and salicylic acid for local application at night, cetrimide (20% w/v) hair wash (after appropriate dilution), liquid paraffin for local application after bath, and fusidic acid (2% w/w) cream for local application on the erosions.

The patient was advised to take tablet prednisolone for 10 days with subsequent tapering of the dose. After stopping the steroid, the patient developed anasarca with skin discharge. She was readmitted to the hospital after 2 months. At that time, her blood culture revealed the presence of *Klebsiella pneumonia* which was sensitive to amikacin and ceftriaxone. The patient had moderate pulmonary hypertension with steroid-induced diabetes mellitus and hypothyroidism. She was prescribed injection insulin actrapid 4 units each in the morning, afternoon and evening. She was also prescribed tablet levothyroxine 50 µg once a day.

About 6 months after the diagnosis of erythroderma, she was admitted to the hospital again with dyspnea on exertion Grade IV, intermittent fever without chills for 8–10 days, cough with yellowish expectoration for 3–4 days. Her blood pressure was 100/70 mm Hg with pallor. She had general excoriation of skin, bilateral pedal edema and bilateral coarse crepitations. The patient was diagnosed to have pneumonitis and put on mechanical ventilation and other appropriate therapy but succumbed within a few days.

The cause of death was stated to be lower respiratory tract infection with septic shock in a case of erythroderma with hypothyroidism with diabetes mellitus.

**Discussion**

There has been an increase in DHS with multidrug therapy for leprosy.[4] A characteristic feature of DHS is that it can occur even at low doses of dapsone and has a variable time of onset ranging from 1 week up to 6 months after drug exposure.[3] In our patient, DHS developed after 3 weeks of drug exposure which is consistent with published literature.[2] Our patient developed sepsis with acute kidney injury. Dapsone-induced kidney injury has been reported in one patient in Brazil, however, the exact mechanism of toxicity is not known.[3] Dapsone is well absorbed from the gut and metabolized through N-acetylation and N-hydroxylation.[5] Dapsone N-hydroxylamine has been shown *in vitro* to have toxic effects on thyroid gland cells which is mediated through
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Conclusion

Dapsone is widely used for a variety of dermatological conditions. However, it is associated with ADRs including fatality as highlighted by the case report. Hence, it should be prescribed judiciously with monitoring throughout treatment.

Declaration 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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Our patient developed pulmonary hypertension which has not been reported earlier. As our patient had normal hemoglobin and total bilirubin at the time of the first presentation to the hospital, she did not develop hemolytic anemia which is commonly associated with dapsone use.[3]

Dapsone is a lipophilic drug and has been reported to persist in the body for up to 35 days due to its hepatic storage and enterohepatic circulation.[1] The management of DHS consists of withdrawal of the drug, supportive therapy in the form of volume replacement, nutritional support, antibiotics and skin care and treatment with systemic steroids.[2] In the majority of the published case reports, the patients’ condition improved on withdrawing the drug and treatment with steroids.[6] Our case is unique because she did not improve on withdrawing Dapsone. On the contrary, her condition worsened due to development of steroid-induced diabetes, an iatrogenic condition. DHS develops in about 0.5%–3.6% of patients and has a reported mortality of 9.9%.[2] The factors associated with higher risk of fatality in Dapsone hypersensitivity include mucosal involvement, hepatitis, higher age, disease occurrence in nonaffluent countries.[2]

Pharmacogenetic differences in formation and detoxification of dapsone metabolites have been reported to predispose patients to hypothyroidism. HLA-B*13:01 is confirmed to be a risk factor for DHS (odds ratio = 20.53; \( P = 6.84 \times 10^{-25} \)). HLA-B*13:01 present in 1%–12% Indians. India has the highest recorded prevalence of HLA-B*13:01 allele and the highest incidence of leprosy in the world.[7]

Causality assessment by Naranjo scale is probable (score 5) and possible by the World Health Organization-UMC causality assessment as she did not improve on dechallenge. Although the ADRs developed in this patient could be due to rifampicin, dapsone is the most likely suspect as the symptoms coincide with DHS and is in agreement with a published report where patients received dapsone concomitantly with clofazimine and rifampicin.[3]