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# DAPSONE HYPERSENSITIVITY SYNDROME IN A PATIENT WITH HANSENS'S DISEASE

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ABSTRACT

**Introduction:** Adverse drug reactions (ADRs) are one of the leading causes of death in hospitalized patients. ADR is a response to a drug which is noxious, unintended and occurs at doses normally used in human for prophylaxis and treatment. Dapsone, a potent antiparasitic and anti-inflammatory compound, is mainly used in the treatment of leprosy and a variety of blistering skin diseases. It may cause a severe adverse drug reaction with multiorgan involvement known as dapsone hypersensitivity syndrome. We report a case of dapsone hypersensitivity, manifesting as fever, rash, and hepatosplenomegaly, hemolytic anemia.
**Discussion:** A forty six old male, known case of Hansen's disease for the last 1 month. He had been on Dapsone for 1 month as the prescribed by dermatologist for Hansen's disease. Later the patient developed red rash all over the body, red skin lesions, fever with chills, epistaxis, nasal stuffiness, multiple nodules on body, hepatosplenomegaly, photophobia and watery eye. A Clinical diagnosis of Dapsone induced hypersensitivity syndrome was made Dapsone was stopped immediately. During the hospital administration, patient was managed symptomatically for fever, skin rash, and systemic corticosteroids were given as standard treatment.He was discharged with special warnings and also advised to continue MB-MDT treatment without dapsone.
**Conclusion:** By the withdrawal of the drug, the condition of the patient was improved. So the drug withdrawal is the first line for management of Dapsone induced hypersensitivity syndrome.

## INTRODUCTION

Dapsone (4,4'-diaminodiphenylsulfone) is used to treat a variety of infectious, immunological and hypersensitivity disorders such as leprosy, dermatitis herpetiformis, linearIgA bullous dermatosis and chronic bullous dermatosis of childhood, bullous eruption of systemic lupus erythematosus, erythema elevatum diutinum, leukocytoclastic and other kinds of vasculitis, malaria, pneumocystis carinii pneumonia.

Commonly encountered adverse effects of dapsone include dose unrelated (idiosyncratic) skin hypersensitivity reactions and dose-related hemolytic anemia, methemoglobinemia, hepatotoxicity. Hypersensitivity reactions occur only in 1.4% of persons who are treated with dapsone, and it can be fatal in medical settings with low resources. People with porphyria, anemia, cardiac disease, lung disease, HIV infection, G6PD deficiency, and liver impairment have higher risks of adverse effects when using dapsone.[1]

A rare, potentially fatal idiosyncratic systemic hypersensitivity syndrome namely dapsone hypersensitivity syndrome, is characterized by fever, skin rash, eosinophilia, lymphadenopathy, hepatic, pulmonary and other systemic manifestations. Dapsone Hypersensitivity Syndrome can cause irreversible organ damage or even death if it is not diagnosed early and managed or treated properly. [2]

Cutaneous lesions ranges from erythematous papules to plaque, pustules and eczematous lesions, which usually resolve within 2 weeks after discontinuation of dapsone, rarely some patients may develop Steven Johnson syndrome and toxic epidermal necrolysis.[3]

Pulmonary manifestation are very common in a patient of Dapsone Hypersensitivity Syndrome, among them infiltrative lung disease such as hypersensitivity pneumonitis, pulmonary eosinophilia and pleural effusion are common.[4]

Hematological manifestation characterized by hemolysis, methemoglobinemia and bone marrow suppression, and in gastrointestinal system manifestations it can lead to hepatitis, cholangitis, hepato-splenomegaly and pancreatitis.

Dapsone Hypersensitivity Syndrome can also involve nervous system which includes psychosis and peripheral neuropathy and kidney which can lead to nephrotic syndrome and papillary necrosis and endocrine which leads tohypothyroidism.[5] Other adverse effects include insomnia and psychosis. Other manifestations of this syndrome include hepato-biliary dysfunction such as jaundice, hepatomegaly and cholangitis, splenomegaly, photosensitivity, elevated sedimentation rate.[6]

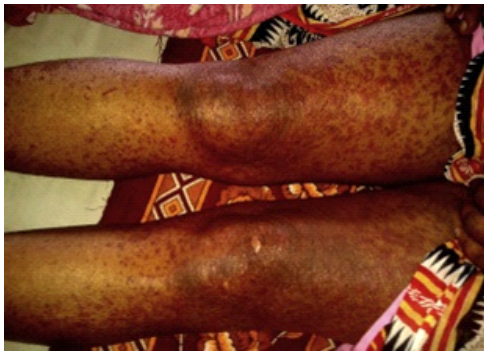
Genetic factors have been shown to play an important role in drug-induced hypersensitivity reactions. A few mechanisms have been proposed. For one, Dapsone Hypersensitivity Syndrome is a combination of type I, type IV, and perhaps type III Gel and Coombs hypersensitivity reactions. Alternately, Dapsone Hypersensitivity Syndrome could be a modified graft versus host disease mediated by activated T-lymphocytes. Dapsone Hypersensitivity Syndrome is not a dose-related effect, whereas dapsone hepatotoxicity is a dose-dependent effect.[7]

Laboratory tests can include a complete blood count and differential, comprehensive chemistry profile, sedimentation rate, urine analysis, arterial blood gases and a chest roentgenogram. In selected cases, chest computed tomography, hepatic ultrasound and/or liver or skin biopsy may be required. Skin biopsy is not a specific test but assists in excluding vasculitis or hematological malignancies. It might be important to obtain a thyroid stimulating hormone level in patients 3–4 months after the diagnosis of **Dapsone hypersensitivity syndrome.** [8]

The management involves discontinuation of dapsone, systemic steroids.[9] Here we report a case of Dapsone hypersensitivity syndrome.

## CASE PRESENTATION

A forty six old male, known case of Hansen's disease for the last 1 month. He had been on Dapsone for 1 month as prescribed by dermatologist for Hansen's disease. Later, after 1 month of using dapsone the patient developed red rash all over the body, red skin lesions, fever with chills, epistaxis, nasal stuffiness, multiple nodules on the body, hepatosplenomegaly, lymphadenopathy, photophobia and watery eye. The rash developed on face was very itchy which spread to trunk, upper and lower limbs and spread through out the body. He was admitted in the Dermatology ward in tertiary care hospital. On admission he had high grade fever, blood pressure was 110/80 mm Hg, and heart rate was 80 beats/min. Patient was pallor and had pruritic maculopapular erythematous rash on the extremities, face, on the back, lower and upper limb, hepatosplenomegaly. Laboratory investigations revealed that patient has decreased level of haemoglobin in the blood. HCT, MCH, MCV was also decreased. Red cell distribution width was increased which indicated anemia. His liver function tests were abnormal with a direct bilirubin of 1.6 mg/dl, indirect bilirubin of 2.0 mg/dl, aspartate aminotransferase of 69 U/l, alanine aminotransferase - 45 U/l, alkaline phosphatase - 180 IU/l . Increased liver enzymes showed hepatic impairment. Leukocyte count and esinophils were also increased, it shows that sign of inflammatory response. A Clinical diagnosis of Dapsone induced hypersensitivity syndrome was made Dapsone was stopped immediately. During the hospital administration, the patient was managed symptomatically for fever, skin rash. Multi bacillary-multi drug treatment was started without dapsone. For supportive care the patient protected from secondary bacterial infection, maintained proper nutrition, fluid and electrolytes balance and Proper skin dressing for fast wound healing. For systematic treatment, tobramycin eye drops were administered. The patient was treated with intravenous corticosteroids for 11 days and the dose was gradually decreased on the 7$^{th}$ day. The dose of corticosteroid reduced gradually based on the serial laboratory reports and patient recovery. The patient was treated with Oral Anti histamine for relieving itching. Topical Betamethasone cream was added. Cefotaxine was given to prevent further secondary infections. Finally the patient was discharged on the 20$^{th}$ day as he recovered. He was discharged with special warnings and also advised to continue MB-MDT treatment without dapsone. Topical Betamethasone and liquid paraffin was advised on discharge.



## DISCUSSION

Dapsone is used for treatment or prophylaxis of several infections like leprosy, Pneumocystis jirovecii infection, toxoplasmosis, malaria, cutaneous mycetoma, in several dermatological conditions like bullous dermatoses, acne, cutaneous vasculitis and dermatitis herpetiformis and in immune thrombocytopenic purpura. Dapsone is one of the commonly encountered drug in drug induced systemic hypersensitivity syndrome, apart from anticonvulsants, sulfonamides, allopurinol, non-steroidal anti-inflammatory drugs and minocycline. Dapsone hypersensitivity syndrome is a rare dose independent adverse effect reported with dapsone use in leprosy, malaria prophylaxis, dermatitis herpetiformis, lichen planus and various other conditions. Dapsone hypersensitivity syndrome can develop several weeks to as long as six months after treatment initiation and the incidence ranges from 0.5% to 3%. [10].

The dapsone hypersensitivity syndrome associated with **D**rug **R**ash, **E**osinophilia and **S**ystemic **S**ymptoms, as noted in our present case, is called **DRESS** syndrome.[11] Our patient had severe systemic manifestations-namely hepatitis with mixed hepatocellular and cholestatic features, hemolytic anemia, skin hypersensitivity, as reported earlier. Various cutaneous manifestations like erythroderma/exfoliative dermatitis, papular erythematous/pustular eruptions, erythema multi-forme, Stevens-Johnson syndrome and toxic epidermal necrolysis have been described in Dapsone Hypersensitivity Syndrome.[12] Although acute pneumonitis (eosinophilic pneumonia) with hypoxia and pleural effusion has been reported in DHS,[13] pulmonary manifestation was not seen in this patient. Jaundice present in DHS is partly due to hemolysis and partly due to hepatotoxicity. In hepatotoxicity both hepatocellular injury and cholistatic pattern has been found. Cholistatic pattern has less severe course, it presents with high alkaline phosphatase and moderately elevated ALT/AST levels; while hepatocellular toxicity can be fatal and characterized by markedly elevated AST/ALT levels. [14] As in our case there was marked elevation of transaminase levels as well as alkaline phosphatase levels suggestive of mixed injury to the liver.

The diagnosis of DHS is based on clinical findings of fever, skin rash, lymphadenopathy, hepatitis and other systemic features, along with history of antecedent dapsone exposure. Skin biopsy findings are non-specific.[15] In the present case, the diagnosis was based on typical clinical manifestations following 4 weeks of dapsone intake, after excluding other drug was further supported by prompt response to systemic steroids. Rechallenge with dapsone is not recommended, as it can be hazardous.

Pathogenesis of DHS is not clear but proposed mechanisms concludes that metabolites of dapsone, which form haptens with the production of anti-dapsone antibodies.[16] 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. [17] The inter-individual variability in the metabolism of dapsone by N-hydroxylation to hydroxylamines by the hepatic microsomal cytochrome P-450 system has been implicated in the haematological toxicity[12] (methemoglobinemia, hemolytic anemia and agranulocytosis) but its role in determining the risk of Dapsone hypersensitivity syndrome is unclear.

The management involves prompt discontinuation of dapsone, administration of systemic steroids (oral prednisolone 1 mg/kg/day or intravenous methylprednisolone in equivalent doses and also dexamethasone can be used in the management of Dapsone Hypersensitivity Syndrome with supportive care. Gradual tapering of prednisolone (over more than a month) is recommended by considering that dapsone persists in the body up to 35 days.[18] Nutritional support, fluid and electrolyte balance, control and prevention of infections (cellulitis, sepsis) and skin care are also required. Vitamin E supplement found to be beneficial in dapsone induced hemolysis.

Our patient was treated with systemic corticosteroids-Dexamethasone as the first line treatment and Dapsone was discontinued, Topical betamethasone cream was given which reduces the itching, swelling and redness of the affected areas. Mortality as high as 12-23% has been reported in severe Dapsone Hypersensitivity Syndrome. [19] Thus, a high index of suspicion for early diagnosis, along with prompt treatment are essential to prevent fatalities

Physicians, dermatologists, rheumatologists and leprologists prescribing dapsone for various clinical conditions should be aware of fatal effects of dapsone hypersensitivity syndrome, which can present with fever, rash and multi-organ involvement to ensure timely diagnosis and appropriate management.

## CONCLUSION

DHS, although a rare condition, but could prove fatal if not treated appropriately and timely. The physician's high suspicion is decisive for the betterment of the patient. As in the reported case of DHS with hepatic manifestation, hematologic manifestation, the withdrawal of dapsone and administration of steroid render improvement in patient's condition. People with porphyria,

anemia, cardiac disease, lung disease, HIV infection, G6PD deficiency, and liver impairment are at higher risks of adverse effects when using dapsone. Hence precaution should be taken in these individuals and monitoring of liver function is recommended. So every physician must be aware about this unusual rare fatal adverse effect of dapsone.

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