Case Study

Dapsone Hypersensitivity Syndrome in a Leprosy Patient

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ABSTRACT

Introduction: Dapsone Hypersensitivity Syndrome (DHS) is a rare potentially fatal systemic idiosyncratic adverse reaction, with multiorgan involvement also known as sulphone syndrome which is particularly seen in leprosy patients who are on world health organization recommended multidrug therapy (WHO-MDT regimen). DHS is a variant of drug rash with eosinophilia and systemic symptoms (DRESS syndrome) caused by dapsone. Even though reaction common in the leprosy patients there is need such reporting to identify the most venerable patient pool.

Case: Here we present a case of DHS developed after 25 days in a female patient with a history of PB-MDT regimen treatment, high grade intermittent fever associated with nausea, myalgia, headache since 20 days; swelling of face, bilateral lower limbs and erythematous rashes were observed all over the body since 4 days. She was presented with fever (102.2^0 F), posterior cervical and axillary lymphadenopathy and moderate bilateral lower limb pitting pedal edema was present. Multiple erythematous papules coalesced all over body predominantly involved on the face, trunk and extremities. The main laboratory data on admission were showed, hemoglobin: 9.6 g/dL; WBC: 14.6 x 10^3/ µL; neutrophils: 48% mild left shift, lymphocyte: 20% reactive forms; eosinophils: 16%; increased serum levels of aspartate amino transferase, alanine transaminase and alkaline phosphatase. Patient was improved and discharged on treating with antipyretics, antibiotics, oral and topical corticosteroids and antihistamines.

Keywords: Corticosteroids, dapsone hypersensitivity syndrome, DRESS syndrome, eosinophilia, leprosy and WHO-MDT regimen

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INTRODUCTION

Dapsone is a diaminophenyl sulphone which has been successfully used to treat Leprosy since decades and also to treat a range of dermatological inflammatory diseases such as chronic bullous dermatoses, dermatitis herpetiformis (DH), vesicobullous dermatoses, cutaneous vasculitis due to its anti-inflammatory and antibacterial activity [1-2]. The common side-effects associated are peripheral neuropathy, hepatitis, nausea, dizziness fatigue, insomnia, psychosis where as methaemoglobinaemia and hemolytic anemia are dose related [3-4]. Dapsone Hypersensitivity Syndrome (DHS) as first described by Aldday & Barnes (1951) is a rare potentially fatal systemic idiosyncratic adverse reaction, with multiorgan involvement also known as sulphone syndrome [5]. DHS is a rare adverse reaction seen particularly in leprosy patients who are on world health organization recommended multidrug therapy (WHO-MDT regimen) [6]. It is typically characterized by fever, rash, hemolytic anemia, exfoliative dermatitis, lymphadenopathy, atypical lymphocytosis; hepatitis, agranulocytosis, nephritis,

pneumonitis hypothyroidism and other systemic symptoms which may occur individually or in combination [3, 7].The delay in identification withdrawal of drug and treatment initiation of the syndrome can lead to irreversible severe organ malfunction, prolonged morbidity and even mortality [3-4]. Hence there is urgency in reporting these kinds of cases in order to identify most susceptible patient population and to avoid such complications. The present case report emphasizes the dapsone hypersensitivity syndrome in a female who was on PB-MDT regimen.

CASE:

A 35 year old woman who was on Paucibacillary (PB) leprosy multi drug treatment regimen (standard PB-MDT regimen for adults includes Rifampicin: 600 mg once a month Dapsone: 100 mg daily for six months) [8] for past one month which was prescribed by local physician with high index suspicion of Hansen's disease; presented with a history of high grade intermittent fever associated with nausea, myalgia, headache since 20 days; swelling of face, bilateral lower limbs and erythematous rash was observed all over the body with itching and papules since 4 days. Hence the PB-MDT regimen was discontinued by her one day prior to the presentation in our hospital. Symptomatic treatment was given by local physician and referred here for further management. On examination she was febrile (102.2^0 F) with posterior cervical and axillary lymphadenopathy and moderate bilateral lower limb pitting pedal edema was present. Well defined hypo pigmented macule on right elbow medial aspect and scaly macules over left buttock with decreased sensation (temperature, pain and touch) and no palpable nerves in peripheries of patch. Multiple erythematous papules coalesced all over body predominantly involved on the face, trunk and extremities. Desquamation over bilateral ear lobes and generalized xerosis was present.

Split Skin Smear test from hypo pigmented macules over right elbow and left buttock regions were negative. Even though Split Skin Smear was negative due to definite decrease in sensation over hypo pigmented patches dermatologist diagnosed as Borderline tubercular Hansen's disease. Systemic examination was unremarkable. Hematological parameters of patient on Day 1 and on Day 5 after admission are listed in (**Table 1**).

Table 1: Hematological parameters of patient on Day 1 and on Day 5 after admission

Parameters	Values on Day 1	Values on Day 5
Red blood cell Count	2.80×10^6/µL	3.19×10^6/µL
Hemoglobin	9.6 g/dL	9.7 g/dL
Hematocrit	27.4 %	30.1 %
Total white blood cell count	14.6×10^3/ µL	14.4×10^3/µL
Absolute eosinophil count	2.336×10^3/ µL	3.799×10^3/ µL
Neutrophils	48% mild left shift	19 %
Lymphocyte	20% reactive forms	45% reactive forms
Monocyte	7%	7%
Eosinophils	16%	29 % eosinophilia
Erythrocyte sedimentation ratio	52 mm/hr	46 mm/hr

Peripheral blood picture showed: Sparsely distributed, Normocytic normochromic, Anisocytosis, Polychromasia. Liver function tests revealed total bilirubin 0.7 mg/dL with a direct of 0.4 mg/dL, AST 203.0 IU/L , ALT : 169.0 IU/L, ALP: 303.0 U/L, serum albumin 3 g/dL, globulin 3.20 g/dL. Serological tests for hepatitis A virus, hepatitis B virus, hepatitis C virus and Widal test were negative. Quantitative buffy coat technique (QBC), Immunochromatography for malaria, antibodies to leptospira (IgM), antibodies to *Orientia tsutsugamushi* (scrub typhus - IgM) and Weil Felix test (OX K, OX 19 and OX 2) were negative.

USG abdomen and pelvis was showing mild hepatomegalay with normal echo-texture, distended gall bladder with wall thickening and no calculus. Skin biopsy was not done due to patient's economical constrains.

Dapsone was stopped along with the rifampicin prior to the admission. Patient was treated with antipyretics, antibiotics, oral and topical corticosteroids, antihistamines and multivitamins. Patient was improved; fever reduced within 72 hours and disappeared completely in six days. Rashes were improved and were disappearing with desquamation along with reduced itching, facial puffiness and pedal edema. No fresh rashes or lesions appeared thereafter. Patient was discharged in six days.

DISCUSSION

Dapsone is one of the commonly implicated drugs next to aromatic anticonvulsants (carbamazepine, phenobarbital, lamotrigine and phenytoin), allopurinol, sulphonamides and antiretrovirals in drug induced systemic hypersensitivity syndrome [9]. DHS is associated with drug rash with eosinophilia and systemic symptoms called DRESS syndrome which is a serious condition characterized by the onset of skin rash, accompanied by fever, malaise, weakness, lymphadenopathy, hematological disorders like eosinophilia, atypical lymphocytosis and single or multiple organ involvement [10]**.** A variant of the DRESS syndrome caused by dapsone can be considered as DHS [3]. DRESS Syndrome also can be caused by other medications like fluoxetine, mexiletine, captopril, NSAIDS (Non-steroidal anti-inflammatory drugs), terbinafine, calcium channel blockers, minocycline and metronidazole [10]. DHS may occur in 3-6 weeks after initiation of therapy with dapsone [1]. Diagnosis of DHS is based on clinical findings such as fever, skin rash, lymphadenopathy, hepatitis and other systemic features along with history of exposure to sulphone drugs and or dapsone treatment [11]. The findings of skin biopsy may not be specific [5].

In the present case, the diagnosis was based on the patient's medication history (25 days of PB-MDT regimen), presence of fever, eosinophilia, atypical lymphocytes, maculopapular erythematous rash, and deranged liver function tests following after excluding other exposure to drugs and close differential diagnoses namely stevens-johnson syndrome (SJS), toxic epidermal necrolysis (TEN), hypereosinophilic syndrome, still's disease, complicated malaria and leptospirosis (Immunochromatography for malaria and antibodies to leptospira (IgM) which were negative) [5, 10]. According to Scoring System for Classifying DRESS syndrome cases given by Kardaun *et al* [12] the present case had score six, which means this is a definite case of DRESS Syndrome. Rechallenge cannot be done with dapsone, as it can cause potentially lethal effects.

The pathogenesis of the DHS remains unknown, may be multifactorial, involving immunological mechanisms and particular drug detoxification pathways [10]. Previous studies were suggesting that the variations in production (eg. increased quantity or activity of cytochrome P450 polymorphic enzymes) and detoxification of reactive metabolites (e.g. deficiency of glutathione synthetase) play an important role in hypersensitivity reactions of sulphonamide [13]. The alternative routes of dapsone metabolism include cytochrome P450 enzymes mediated N-hydroxylation to the hydroxylamine, a potentially toxic metabolite and N-acetyltransferase mediated acetylation to a nontoxic metabolite were considered as risk factors for hemolytic anemia [14].

DHS is not a dose-related, whereas dapsone hepatotoxicity is a dose-dependent effect [15]. An increase in the frequency of DHS is still being observed followed by the introduction of MDT for leprosy world-wide [16]. It is being argued that the cause can be due to unexplainable interaction between other drugs of WHO-MDT and dapsone [11]. A retrospective study conducted by Kaluarachchi SI *et al* was showing female were more susceptible to adverse drug reactions than male subjects who were on WHO-MDT regimen for leprosy, irrespective of age group [17].

Management involves prompt withdrawal of dapsone. This is the only way to reduce morbidity and mortality rates in severe adverse drug reactions like DRESS syndrome, TEN and SJS where the accumulation of reactive drug metabolites were thought to be involved in pathogenesis.

Symptomatic management involves antipyretics, topical steroids for fever and skin care respectively [10]. Depends on severity of clinical manifestations, oral or systemic corticosteroids can be initiated [3]. However, due to lack of data from randomized controlled trials to evaluate the effectiveness of corticosteroids, steroids administration remains controversial [1, 10].

Tapering of systemic corticosteroids should be done, because dapsone can persist up to 35 days in organs by protein binding and enterohepatic circulation [1, 3, 18]. The early diagnosis, withdrawal of drug and prompt treatment is essential to prevent deleterious, potentially fatal effects due to major organ dysfunction and mortality.

CONCLUSION

Clinicians must be aware about the potential and lethal effects of DHS while prescribing for leprosy and other various indications. Physicians, pharmacists and other health care professionals should educate the patients who are all on dapsone therapy regarding the side effects, which helps in early diagnosis of syndrome, prompt withdrawal of drug and in reducing morbidity and mortality rates. And there is an extensive need to identify group of patients who are venerable to hypersensitivity reactions before starting dapsone therapy.

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