Dapsone Hypersensitivity Syndrome with Hepatic Involvement: A Rare Case Report

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KEY CLINICAL MESSAGE

Dapsone hypersensitivity syndrome (DHS) is a severe idiosyncratic drug reaction in response to dapsone characterised by the clinical symptoms of fever, skin eruption, and internal organ involvement including liver. Here we report a case who presented with fatigue, jaundice and mild upper abdominal pain 3 weeks after starting anti-leprosy drug regimen comprising dapsone. Examination showed icteric sclera and pallor over nails and palms, mild tenderness over right hypochondrium and there were regressing leprosy skin lesions over dorsum of right hand and left foot. We immediately discontinued antileprotics for 2 weeks and patient was put on oral steroids. Liver function tests were near normal during follow up and patient was advised to continue antileprotics as usual with counselling when to return. Clinically, early recognition of dapsone induced hepatitis (DIH) is important based on mucocutaneous findings to minimize injury. Laboratory monitoring should be frequently performed during treatment, including complete blood counts and liver function tests. Early detection, prompt withdrawal of dapsone, and minimal use of other sulfa drugs need to be emphasized for the management of DHS.

Keywords: Dapsone hypersensitivity syndrome, Dapsone induced hepatitis, leprosy, Sulfa drugs

1. INTRODUCTION

Chemically, dapsone (4, 40 -diaminodiphenylsulfone, DDS) is an aniline derivative, a drug of the sulfone class.[1] Dapsone is increasingly used in the treatment of a variety of dermatological disorders such as acne, dermatitis herpetiformis, psoriasis, and toxoplasma gondii infections and pneumocystis carinii pneumonia in acquired immunodeficiency syndrome (AIDS) patients and is drug of choice for leprosy commonly in combination with rifampicin and clofazimine in Nepal.[1-2] DHS is a severe idiosyncratic drug reaction in response to dapsone characterised by the clinical symptoms of fever, skin eruption, and internal organ involvement (lung, liver, neurological, hematological and other systems) and DIH can be considered as one of the spectrum of DHS.[2] In general, prevalence of DHS is 0.5-3%.[2-4] Here we report a case who presented

with fatigue, jaundice and mild upper abdominal pain 3 weeks after starting anti-leprosy drug regimen comprising dapsone.

2. CASE REPORT

2.1 Case history and examination

Our case is a 40-year-old man who presented to our primary health centre with complaints of fatigue, jaundice and mild abdominal pain for 1 week. He has been diagnosed as a case of multibacillary leprosy 3 weeks earlier and has been started on anti-leprosy drug regimen for 3 weeks (Rifampin 1200mg daily, Dapsone 100 mg daily and Clofazimine 50 mg daily). His total cumulative dose of dapsone was 2100 mg. Examination showed icteric sclera and pallor over nails and palms, mild tenderness over right hypochondrium and epigastrium with no evidence of hepatomegaly and there were regressing leprosy skin lesions over dorsum of right hand and left foot. Rest of the examination was unremarkable. His vitals were normal.

2.2 Investigation

Among investigations advised, his liver functions tests (LFTs) were marked deranged (Table 1).

Table 1. Laboratory investigation during initial visit

Variables	**Value**
Total leucocyte count ($\times 10^3$ /μL)	8140
Neutrophils	61
Lymphocytes	34
Total red cell count ($\times 10^3$ /μL)	3.9
Hemoglobin (mg/dl)	11.2
Erythrocyte sedimentation rate (mm/hr)	28
Total bilirubin (mg/dl)	4.3
Direct bilirubin (mg/dl)	1.9
Alanine transaminase (ALT)	183
Aspartate transaminase (AST)	164
Alkaline phosphatase (ALP)	486
Serum albumin (mg/dl)	3.2
Serum urea (mg/dl)	23
Serum creatinine (mg/dl)	0.9
Hepatitis B surface antigen (HBsAg)	Negative
Hepatitis C RNA Human Immunodeficiency Virus (HIV)	Non-reactive Non-reactive

Viral markers for hepatitis B, hepatitis c and HIV, and autoimmune profile were negative. CBC showed anemia and deranged LFTs (showing mixed pattern) whereas RFTs were normal.

2.3 Management and follow up

We immediately discontinued antileprotics for 2 weeks and patient was put on oral prednisone 40 mg per day for 1 week then 20 mg per day for another 1 more week. During follow up after 2 weeks, his LFTs were near normal (Table 2), and we prescribe him of ferrous sulfate with 200mg elemental iron per day for 14 days and continue antileprotics as usual with counselling when to return immediately to hospital at the earliest in case of fever, rash or abdominal pain. The diagnosis of DIH was made based on various clinical manifestations and laboratory abnormalities, ruling out other possible differential diagnoses.

Table 2. Laboratory investigations during follow up visit after 2 weeks

Variables	Value

Variables	Value
Total leucocyte count ($\times 10^3$ /μL)	7223
Neutrophils	65
Lymphocytes	32
Total red cell count ($\times 10^3$ /μL)	3.9
Hemoglobin (mg/dl)	11.4
Erythrocyte sedimentation rate (mm/hr)	16
Total bilirubin (mg/dl)	1.4
Direct bilirubin (mg/dl)	0.9
Alanine transaminase (ALT)	53
Aspartate transaminase (AST)	61
Alkaline phosphatase (ALP)	323
Serum albumin (mg/dl)	3.3
Serum urea (mg/dl)	24
Serum creatinine (mg/dl)	0.9

3. DIFFERENTIAL DIAGNOSIS

Dapsone hypersensitivity syndrome

Alcoholic fatty liver disease

Viral hepatitis

4. CONCLUSION

The hepatotoxicity of dapsone appears to occur by several mechanisms including injury to hepatocytes, induction of oxidative stress by DDS-NOH metabolite via N- hydroxylation pathway, induction of cholestasis via bile duct and bile flow obstruction, cholangitis due to focal bile ducts destruction, aggravation of hepatitis and hepatic fibrogenesis by iron overload due to the hemolysis. Clinically, early recognition of DIH is important based on mucocutaneous findings to minimize injury. Laboratory monitoring should be frequently performed during treatment, including complete blood counts and liver function tests. Early detection, prompt withdrawal of dapsone, and minimal use of other sulfa drugs need to be emphasized for the management of DHS. Patient should be on regular follow up and slow, gradual introduction of antileprotics may improve clinical outcome and patient compliance.

5. DISCUSSION

Dapsone is completely absorbed from the gut after its oral administration and then undergoes extensive biotransformation in the liver mainly by N-acetylation and N-hydroxylation. During biotransformation in liver microsomes, dapsone gets converted into DDS-hydroxylamine (DDS-NOH). The highly reactive hepatotoxic metabolite of DDS which is DDS-NOH intermediate reportedly induces in oxidative stress in the liver causing several side effects, including hemolytic anemia, agranulocytosis, and methemoglobinemia including liver injury which includes hepatic necrosis, cholestasis, hepatitis, granulomatous cholestatic hepatitis etc. The liver was the most common extra dermatologic organ involved in DHS. Mixed hepatitis is the most common pattern of liver injury.[4-6] It has been reported that hepatic involvement is seen in the early stages of leprosy itself. The presence of hepatotoxic drugs like rifampicin and other anti-tubercular drugs may aggravate dapsone-induced liver toxicity in these patients.[1] Dapsone induced hepatitis (DIH) is typically classified as either direct or idiosyncratic. Idiosyncratic hepatotoxicity is caused by agents that have little intrinsic toxicity which causes liver injury only in rare cases. DHS is a severe idiosyncratic adverse reaction with multi-organ involvement.[3] Direct hepatotoxicity is caused by the agents that are intrinsically toxic

to the liver. The injury caused by the agent that induces direct hepatotoxicity is common, predictable, dose-dependent, and reproducible.[1] Blood sulfone levels >2 mg/dl correlate with greater probability of liver damage, suggesting an intrinsic hepatotoxic effect. Both cholestatic and hepato-cellular reactions occur, but cholestasisis is the commonest form of injury.[2] The hyperbilirubinemia present in dapsone syndrome may partly be due to hemolysis in addition to hepatotoxicity. DIH occurs mostly within the first 4 to 6 weeks of therapy and shows 2 distinctive subtypes: the vast majority (90%) are associated with DHS, and a minority (10%) that lack DHS. DIH can vary from mild (which resolves with discontinuation of drug alone) to severe liver injury including acute liver failure and death. Features that characterize DHS such as skin reactions, fever, lymphadenopathy, and eosinophilia tend to overshadow features of liver injury and probably have contributed to under-recognition of hepatitis and an underestimation of its severity.[5] The temporal relationship between dapsone therapy and onset of clinical symptoms and objective data led us to believe that dapsone induced hepatitis in our patient. Mucosal involvement, hepatitis, higher age, and disease occurrence in resource poor settings were associated with a higher risk for a fatal outcome, with an overall fatality of 9.9%.[3] Liver failure was the most frequent cause of death. Other reasons for death were mostly due to drug reactions such as shock, lung failure and bone marrow failure.[3-4] The best approach to DHS is immediate discontinuation of the drug and prompt administration of oral or intravenous glucocorticoid pulse therapy. Some studies showed steroids leading to faster recovery and lower mortality than those not receiving steroids. Glucocorticoids are recommended with or without internal organ involvement. If used, glucocorticoids should be tapered gradually over one month, as dapsone avidly binds to proteins up to 35 days. Complete resolution of symptoms and laboratory abnormalities usually occurs with cessation of dapsone therapy.[4,5,7] Laboratory monitoring should be frequently performed during treatment, including complete blood counts and liver function tests. Continuation with dapsone should not be undertaken in these patients and patients must be informed that they are allergic to sulfa drugs.[3]

AUTHOR CONTRIBUTIONS

Bishal Koirala : Conceptualization; data curation; supervision; writing – original draft; writing – review and editing.

Priyanka Devkota : Data curation; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest in this study.

ETHICAL STATEMENT

The patient has provided written informed consent for the publication of this case report.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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