An unusual case of dapsone syndrome

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ABSTRACT
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 an unusual case of dapsone hypersensitivity, manifesting as bone marrow suppression and peripheral pancytopenia in addition to fever, rash, and hepatosplenomegaly.

Key words: Dapsone hypersensitivity, dapsone syndrome, leprosy, multidrug treatment

INTRODUCTION
Dapsone hypersensitivity reaction was reported as early as 1950 by Lowe and was so named by Allday and Barnes. Hypersensitivity to dapsone is thought to be the major cause of this syndrome. With the advent of WHO multidrug therapy for leprosy, more cases of dapsone syndrome have been reported.

CASE REPORT
A 34-year-old man who was on multidrug treatment for lepromatous leprosy for the past two months presented with history of high-grade fever of two-week duration associated with pruritic rash. On admission, his temperature was 40°C, blood pressure was 110/70 mm Hg, and heart rate was 112 beats/min. He had pallor and pruritic maculopapular exanthematous rash on the extremities and face and hepatosplenomegaly. The other system examinations were unremarkable.

Investigations revealed initially hemoglobin - 7.3 g%; white blood cell count - 4 000/mm³ (neutrophils, 76%; lymphocytes, 20%; and eosinophils, 4%), erythrocyte sedimentation rate of 30 mm in the first hour and a platelet count - 160 000/mm³.

After two days, his hemoglobin dropped to 4.9 g%, the total leukocyte count to 2 000/mm³, and the platelet count to 1 lakh/mm³. Reticulocyte count was 0.8%. Peripheral smear showed normocytic normochromic anemia and leucopenia.

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 UI, alanine aminotransferase - 28 UI, alkaline phosphatase - 145 UI, serum albumin - 2.3 g/dl, and prothrombin time - 13 seconds. Viral hepatitis serology (IgM antibody to hepatitis A antigen, hepatitis B surface antigen, and hepatitis C antibody) were negative.

The levels for urea, creatinine, uric acid, and electrolytes were within normal limits.

His HIV screening, blood culture, and urine culture were negative. Abdominal ultrasound showed uniform liver enlargement with a slight increase in echo texture, and there was no evidence of portal hypertension or biliary obstruction. His chest radiograph was normal.

Bone marrow trephine biopsy showed multiple granulomas with adjacent scattered hematopoietic elements showing erythroid precursors with normoblastic and megaloblastic maturation, few myeloid maturing cells and megakaryocytes, and grade 2 myelofibrosis. Special stains done on trephine biopsy were positive for lepra bacilli.

A diagnosis of DHS (Dapsone hypersensitivity syndrome) was thus based on the patient’s treatment history, presence of fever pruritic maculopapular erythematous rash, hepatosplenomegaly and deranged liver function tests, and evidence of bone marrow suppression.

Dapsone was stopped and corticosteroids were
given both orally (prednisolone 30 mg/d) and topically. He was also given blood transfusion. His clinical condition improved after two weeks and laboratory test results returned to normal levels within 3 weeks. His blood counts returned to normal. A repeat bone marrow was done after 8 weeks of starting steroids, which showed persistence of lepra bacilli. Disappearance of granulomas on repeat biopsy supports the diagnosis of drug-induced bone marrow granuloma. The steroids were slowly tapered and stopped over a period of nearly three months. He did not get a recurrence of fever or bone marrow suppression after stopping steroids. He was continued on clofazimine and rifampicin as alternative drugs after stopping dapsone.

**DISCUSSION**

Dapsone (4, 4'-diamino-diphenyl sulfone) is the parent compound of sulfone drugs. Though synthesized in 1908, its antibacterial characteristics were not noticed until several decades later. Dapsone has been used as a first-line treatment for leprosy since the 1950s.

Dapsone is absorbed well from the gut and primarily metabolized through N-acetylation and N-hydroxylation (oxidation). The hydroxylamine metabolite and other hydroxylated metabolites are potent oxidants and have been thought to cause the hematologic adverse effects associated with dapsone, including methemoglobinemia and hemolytic anemia. It is excreted by the kidney, but has significant enterohepatic circulation. It has a long elimination half life, between 24 to 30 hours on the average. This is important to keep in mind incase adverse reactions emerge after a long metabolite impact period.

Hypersensitivity reaction occurs during first 6 weeks of initiating the treatment.

It differs from other drug reactions in that it can begin after prolonged exposure to the offending agent and can occur up to 6 months or more after exposure.[2-3]

The features include fever, eosinophilia, mononucleosis, jaundice, hepatosplenomegaly, and cutaneous manifestations. Cutaneous manifestations may occur in the form of erythoderma, maculopapular eruption, erythema multiforme, toxic epidermal necrolysis, and Stevens-Johnson syndrome.[6,8] The eruption, which is often initially morbilliform, may develop into overt exfoliative dermatitis.

Liver involvement displays a mixed hepatocellular and cholestatic pattern.[4]

The main toxicity of dapsone relates to its effects on hematopoiesis. Agranulocytosis occurs rarely, but a dose-related hemolysis and methemoglobinemia are more common; hemolysis occurs especially in patients with glucose-6-phosphate dehydrogenase deficiency. Dapsone also causes bone marrow suppression, but case reports of pancytopenia are few. Two cases have been reported of dapsone-induced neutropenia with bone marrow suppression in patients with ocular cicatricial pemphigoid[7] and granuloma annulare.[8]

Other side effects include a predominantly motor peripheral neuropathy, anorexia, and headache. There are also reports of thyroiditis presenting as hyperthyroidism and also myocarditis. Hypoalbuminemia present in our patient is also a feature of dapsone hypersensitivity, which is probably due to binding of dapsone to the circulating serum albumin.[9]

Hyperbilirubinemia present in dapsone syndrome may partly be due to hemolysis in addition to hepatotoxicity. Both hepatocellular and cholestatic injury have been described.[10] Hepatocellular injury is characterized by elevated transaminases, with liver biopsy showing predominantly eosinophilic lobular and portal infiltration. Hepatitis may progress to liver failure and death. Cholestatic pattern may have less severe course and is characterized by high alkaline phosphatase level and modest transaminases level. The liver biopsy may show granulomas. The mechanism of injury, including hepatotoxicity in dapsone syndrome, seems to be hypersensitivity reaction. Severe cases require corticosteroid therapy to which it responds well.

Granulomatous inflammation may be seen in the bone marrow in a diverse group of processes such as infections, neoplasms, and hypersensitivity reactions where the commonly implicated drugs include sulfonamide, procainamide, and phenytoin. Disappearance of the granuloma on a subsequent biopsy supports the diagnosis of drug-induced granuloma.[11,12]

Richardus and Smith[9] have mentioned the following criteria to diagnose a case of dapsone hypersensitivity:

1. The symptoms appear within 8 weeks after commencement of dapsone and disappear after the discontinuation of the drug.
2. The symptoms cannot be ascribed to any other drug given simultaneously with dapsone.
3. The symptoms are not attributable to lepra reaction.
4. No other disease liable to cause similar symptoms is diagnosed.

The reaction was classified as dapsone syndrome when symptoms start between the second and eighth week of treatment and at least two of the following signs or symptoms are present: fever, skin eruption, lymphadenopathy, liver pathology (hepatomegaly, jaundice, and/or abnormal liver function tests.

As hypersensitive reactions have become more frequent in
both multi- and paucibacillary cases on MDT, combination with rifampicin may be an important factor in contributing to the rise of hypersensitivity reactions, as suggested by Richards and Smith. They also considered other factors like increased awareness, low dose of dapsone administered before 1976, and changes in manufacturing of dapsone being responsible for the observed rise.

The long elimination half-life of dapsone averaging between 24 and 30 hours is thought to be due to significant enterohepatic recirculation of the drug. Strong protein binding of the drug itself (70-90%) and its major metabolite, monoacetyl dapsone (99%), contribute to that long half-life. Systemic corticosteroids have been used to treat DHS. Since dapsone persists up to 35 days in organs through protein binding and enterohepatic recirculation, slow tapering off of the corticosteroid therapy over at least one month with close monitoring of organ function is required. Abrupt discontinuation may cause a relapse.

Generally, DHS is a self-limiting drug reaction and most patients recover following cessation of dapsone therapy and starting treatment with oral corticosteroid; Deaths, however, have been reported. Physicians should be aware of this infrequent but potentially fatal severe form of adverse reaction that can mimic other conditions. The treatment regime followed in such cases is as follows. For PB leprosy, give monthly Rifampicin pulse and daily Clofazimine therapy. And for MB leprosy, give monthly Rifampicin and Clofazimine pulse and daily Clofazimine therapy.

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