Dapsone Syndrome: Hepatitis-B Infection a Risk Factor for Its Development?

TO THE EDITOR:

Dapsone has been the sheet anchor of a multitude of dermatologic therapies. "Dapsone syndrome," also known as "sulfone syndrome," is a distinct hypersensitivity reaction which is reported to occur in less than 0.5% of patients who take the drug. Recently, we encountered four cases of dapsone syndrome in a short span of 1 year during which a total of 180 patients had received dapsone from our Department. Four patients (two men and two women) aged between 20 and 55 years were referred from the Medicine Department with a diagnosis of infectious mononucleosis in two patients and infective hepatitis in the other two. All four patients had been on dapsone (three for leprosy and one for lichen amyloidosis) and all had developed symptoms 3 to 4 weeks after intake of dapsone. All of them developed constitutional symptoms, jaundice, hepatomegaly and pruritic generalized erythematous maculopapular exanthem that progressed to exfoliative dermatitis. Lymphadenopathy (cervical, axillary and inguinal) was observed in two, while one each had purpura and splenomegaly. None of the patients had a previous history of allergy to any drug. The clinical features were compatible with dapsone syndrome in all four patients, and we proceeded to investigate them.

The typical clinical presentation and corroborative laboratory findings (The Table) unmistakably pointed to the diagnosis of "dapsone syndrome." All of the medications were withdrawn, and the patients were started on parenteral dexamethasone 8 mg daily which was gradually tapered over a period of 6 weeks. Three of the patients had a favorable outcome with prompt resolution of constitutional symptoms and a more gradual improvement of other symptoms. However, in spite of our best efforts, the fourth patient took a turn for the worse. One week after admission to the ward, he went into hepatic coma with a fatal outcome.

Dapsone syndrome usually develops 5 to 6 weeks after the initiation of dapsone therapy. Hence, it is also called "five week dermatitis." It was first described by Lowe ([4]) and Allday and Barnes ([1]). It is a drug-induced hypersensitivity reaction—an idiosyncratic multiorgan disease. Although the exact immune mechanisms behind dapsone syndrome are still unclear, a combination of type I, type IV, and perhaps type III Gel and Coombs' hypersensitivity reactions are implicated in its pathogenesis. It is also suggested that dapsone syndrome may be a modified graft-versus-host disease-type re-

THE TABLE. *Laboratory investigations.*

Investigations	Case I	Case II	Case III	Case IV
Total and differential leukocyte count, ESR, Hb and peripheral smear	Normal	Lymphocytosis; atypical lymphocytes	Lymphocytosis; atypical lymphocytes	Normal
Reticulocyte count	4.5%	Normal	Normal	Normal
Renal function tests	Normal	Normal	Normal	Normal
Liver function tests				
Total bilirubin	2.2 mg%	9.6 mg%	16.4 mg%	2.3 mg%
Conjugated bilirubin	0.8 mg%	2.2 mg%	10 mg%	1.6 mg%
Serum glutamate pyruvate transaminase	125 IU/L	113 IU/L	77 IU/L	57 IU/L
Serum alkaline phosphatase	14 KAU	11 KAU	26 KAU	8.3 KAU
Prothrombin time	Normal	Normal	49 sec.	Normal
HBsAg	Positive	Positive	Positive	Negative
Paul Bunnel test	Negative	Negative	Negative	Negative

action, mediated by activated T lymphocytes ([6]). The generation of toxic metabolites like nitrosamines and possibly other compounds through the N-hydroxylation pathway of dapsone metabolism coupled with genetic and environmental factors are also believed to be involved in the genesis of the dapsone syndrome ([2]). The clinical features include constitutional symptoms, cutaneous lesions in the form of papular exanthem or exfoliative dermatitis or, rarely, as erythema multiforme, toxic epidermal necrolysis or Stevens-Johnson Syndrome, jaundice, hepatitis, lymphadenopathy and mononucleosis (the last two have been attributed by Lowe to activation of the Epstein-Barr virus) ([3,4]). Management includes avoidance of dapsone and the prompt institution of corticosteroid therapy which is life saving. Steroids should be tapered gradually over a period of more than 1 month, because dapsone is found to persist in the body for up to 35 days. The condition usually lasts for 2 to 4 weeks and recovery is the rule; however, it can end fatally in some patients.

Three out of four of our patients were detected to have associated hepatitis-B as a risk factor for the dapsone syndrome. So screening for this infection is essential before starting dapsone in any patient, whatever the indication may be. Many reports indicate that there has been an increased incidence of dapsone syndrome in recent years ([3,7]). Among 180 patients treated during 1 year, four developed the dapsone syndrome (4/180). All of the cases were initially wrongly diagnosed as infectious mononucleosis or infective hepatitis. Other factors contributing to the re-emergence of the dapsone syndrome could be a heightened awareness of the condition, the use of multidrug regimens in leprosy, and wider use of dapsone.

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