CASE REPORT

A case report of fatal dapsone-induced agranulocytosis in an Indian mid-borderline leprosy patient

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Summary  Fatal agranulocytosis in an Indian male receiving 100 mg of dapsone daily, hospitalized for mid-borderline leprosy in type I reaction with triple nerve paralysis is reported. Various case reports concerning dapsone-induced agranulocytosis are reviewed.

Introduction

For the last 60 years, dapsone has been used successfully as both an antibacterial and anti-inflammatory agent in leprosy and a range of dermatological disorders. Various haematological adverse effects, including methaemoglobinemia, haemolysis and fatal agranulocytosis, have been reported.1 Other rare adverse effects such as pulmonary eosinophilia without cutaneous allergic manifestations have also been reported.2 We have also reported dapsone-induced eosinophilia without pulmonary and cutaneous allergic manifestations.3 The first case of dapsone-induced agranulocytosis was reported in 1958 in a patient receiving dapsone for dermatitis herpetiformis.4 In 1970, a report was published concerning 16 US soldiers in Vietnam who developed agranulocytosis after receiving 25 mg of dapsone daily for malaria prophylaxis with a 50% fatality rate.5

Agranulocytosis has also been reported as a complication of weekly maloprim, a combination of dapsone and pyrimethamine for malaria prophylaxis.6,7 There have been other reports of dapsone-induced agranulocytosis in patients with dermatitis herpetiformis and other dermatosis.8–10

The first case of dapsone-induced agranulocytosis in a leprosy patient was reported in 1986 in a young Melanesian male receiving unsupervised treatment with 100 mg of dapsone daily for indeterminate leprosy.11 There have been only a few case reports of dapsone-induced agranulocytosis in leprosy patients.11,12 We report a case of dapsone-induced agranulocytosis in a hospitalized Indian male patient who was receiving treatment for mid-borderline leprosy in type I reaction with triple nerve paralysis.
Case history

A 60-year-old man presented to us with skin lesions on face, body and limbs of 6 months duration and inability to lift the left hand of 6 weeks duration. Examination showed a large punched-out plaque on the abdomen and multiple papules and nodules and plaques of varying sizes on the face, body and limbs. Wrist drop and total claw hand were present on the left side. Routine blood investigation showed the following: haemoglobin 14.5 g%, total count 6000/mm³, differential count of neutrophils 66%, lymphocytes 33%, eosinophils 1% and erythrocyte sedimentation rate of 30 mm in the first hour.

Skin smear for AFB showed a BI of 1.5+ and skin biopsy revealed features suggestive of borderline leprosy. A diagnosis of mid-borderline leprosy in type I reaction with triple nerve paralysis was made. He was admitted and treated with multibacillary multi-drug therapy (MBMDT) consisting of 100 mg dapsone daily, rifampicin 600 mg pulse, clofazimine 50 mg daily, 300 mg pulse and 60 mg of prednisolone. In view of the triple nerve paralysis, a cockup splint was applied to the left hand. After 3 weeks of treatment, he developed low-grade fever, cough, breathlessness and left sided chest pain. On examination, the patient had rhonchi on the left side of the chest and decreased air entry in the left lower zone. There was no skin rash or organomegaly. Routine blood investigation showed a total count of 800/mm³. Differential count and peripheral smear showed a drastic reduction in neutrophils. X-ray of the chest showed consolidation in the left lower zone. ECG was found to be within normal limits. A diagnosis of pneumonia secondary to agranulocytosis was made. The patient was started on parenteral cefotaxime 1 g and was shifted to the ICU for further management. Unfortunately he did not respond to the treatment, and died a few hours later. Blood culture and bone marrow study could not be performed as his condition deteriorated rapidly.

Discussion

Dapsone is both an antibiotic and an anti-inflammatory agent. It is primarily used in the treatment of leprosy. It has also been used successfully to treat actinomycetoma, in prophylaxis and treatment of Pneumocystis carinii pneumonia and for malaria.1

As an anti-inflammatory agent, dapsone has been used to treat many skin diseases characterized by the abnormal infiltration of neutrophils or eosinophils, such as erythema elevatum diutinum, dermatitis herpetiformis, Sneddon Wilkinson disease, linear IgA dermatosis, pustular psoriasis, pyoderma gangrenosum and Sweet’s syndrome.1 It is also used as an antineutrophilic agent in the treatment of brown recluse spider bites.3

Agranulocytosis is a rare but potentially fatal adverse effect of dapsone. It results in reduced immunity to infections. Death is usually due to infections, particularly pneumonia and/or septicemia.11 The mechanism of dapsone-induced agranulocytosis is not clear, but the hydroxylamine metabolite of dapsone is reported to be responsible.6,10 It is toxic to bone marrow and may produce maturation arrest of neutrophils.10 Metabolites of dapsone may also induce the formation of antibodies against neutrophil precursors in the marrow.1,10

Dapsone has been implicated as a cause of agranulocytosis in various case reports of patients treated for dermatitis herpetiformis, leprosy, rheumatoid arthritis, acne, temporal arteritis, granuloma annulare, leukocytoclastic vasculitis, ‘dermatitis’ and cicatricial pemphigoid, as well as in patients receiving the drug for malaria prophylaxis.4,6,7,9–12

Dapsone has been administered to millions of leprosy patients. When a report of
Dapsone-induced agranulocytosis was published in 1970, concerning 16 US soldiers in Vietnam who were receiving dapsone for malaria prophylaxis, Jopling wondered whether dapsone could induce agranulocytosis, considering the fact that millions of patients were under treatment for leprosy with dapsone without developing agranulocytosis. He also sought an explanation by the supposition that other drugs were being taken at the same time and that a combination of drugs might have been responsible. However, later dapsone-induced agranulocytosis was also reported from leprosy patients. In most of the reported cases of dapsone-induced agranulocytosis, including ours, patients also received other drugs along with dapsone. Nevertheless, dapsone is considered as the most probable cause of agranulocytosis. In patients who were receiving maloprim, it was concluded that agranulocytosis was an idiosyncratic reaction to dapsone exacerbated by the concomitant administration of pyrimethamine.

There have been only a few cases of dapsone-induced agranulocytosis in patients treated for leprosy, the last being reported in the year 1992, since the drug was first introduced for the treatment of leprosy in 1940s. The incidence of dapsone-induced agranulocytosis seems to depend on the patient population being treated. It was suggested that the incident depends on an interaction between the drug and the patient’s immune system. The crude incidence in patients treated for dermatitis herpetiformis, a presumed autoimmune disease, was one in 450 patients in Sweden. It is suggested that when dapsone is prescribed for dermatitis herpetiformis, the risk of agranulocytosis increases by 25-fold.

Our patient died of pneumonia secondary to agranulocytosis. He was also receiving a high dose of corticosteroids, which probably masked the symptoms of pneumonia at the onset and also contributed to the rapid deterioration of his condition. There has been no report of prolonged irreversible agranulocytosis caused by dapsone, although mortality of about 20% or more has been reported. It is self-limiting following the withdrawal of the causative drug. However, after discontinuation of a dosing regimen, dapsone may remain in the body for 35 days. This situation is probably due to combination of extensive protein binding and enterohepatic circulation.

This is the first case report of dapsone-induced agranulocytosis from our hospital, which has been serving the needs of leprosy patients for the past 112 years. According to the hospital records, 38,156 patients have received dapsone since the introduction of this drug in the early 1950s up to December 2002. A total number of 72 patients registered for treatment in 2001, the year in which this fatality occurred. Also, probably this is the first case report from India, where millions of leprosy patients have received dapsone as a part of monotherapy or multidrug therapy during the past 50 years.

References