Case Report: A Case of Type 1 Leprosy Reaction and Dapsone Hypersensitivity Syndrome Complicating the Clinical Course of Multibacillary Leprosy

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Abstract. Type 1 reactions, characterized by increasing lesion erythema, pain, and nerve damage, commonly complicate leprosy. Dapsone hypersensitivity syndrome (DHS) is a potentially fatal reaction occurring 6–8 weeks into dapsone therapy. We present a case of intercurrent Type 1 reaction and DHS in a multibacillary leprosy patient recently started on multidrug treatment.

A previously healthy 47-year-old man was referred to a tertiary care tropical disease clinic with a 4-month history of increasing redness and tenderness of multiple elevated plaques on the skin of his face, ears, neck, back, arms, abdomen, and legs, which had not been noted previously. He had immigrated to Canada from the Philippines 4 years before presentation. At presentation, he denied fever, sweats, weight loss, cough, and gastrointestinal symptoms. He did not report any weakness, but complained of numbness in the fingertips bilaterally and three toes of the right foot. He was on no medications and had no significant past medical history. Family members were all asymptomatic.

On examination, the patient was afebrile. Peripheral nerves, including the greater auricular, radial cutaneous, ulnar, and common peroneal nerves, were all thickened bilaterally, with tenderness of the radial cutaneous and ulnar nerves bilaterally. Power was 5/5 throughout with normal deep tendon reflexes. Gait was normal. Examination of the skin revealed multiple asymmetric and well-demarcated raised, erythematous plaques across the chest, abdomen (Figure 1), arms, back, legs, and face, with reduced sensation to pinprick in all lesions. A clinical diagnosis of leprosy with Type 1 reaction was suspected. Slit-skin smears and a skin biopsy demonstrating lymphohistiocytic granulomatous inflammation of cutaneous nerves with edema and demonstrated acid-fast bacilli (including globi) confirmed a diagnosis of multibacillary leprosy. Other investigations at consultation included chest X-ray, which was normal, and baseline blood work, including G6PD testing, which revealed a normal level of enzyme activity. The patient was started on daily dapsone (100 mg), rifampin (600 mg), and ofloxacin (400 mg). In addition, he was started on 40-mg daily (0.82 mg/kg) of oral prednisone for the treatment of his Type 1 reaction. Calcium, vitamin D, and a proton pump inhibitor were included in his therapy. Close follow-up with a tertiary care tropical disease clinic was arranged.

Approximately 7 weeks after initiation of therapy, the patient presented to the hospital with a 5-day history of fever, productive cough, diffuse confluent pruritic maculopapular rash, and jaundice. Laboratory investigations were notable for anemia (hemoglobin 100 g/L), hyperbilirubinemia (251 $\mu\text{mol/L}$), and biochemical hepatitis (alkaline phosphatase [ALP] 333 U/L rising to 749 U/L, aspartate transaminase [AST] 227 U/L,

and alanine transaminase [ALT] 255 U/L rising to 493 U/L over the subsequent week). Chest X-ray was normal. Although rifampin toxicity was also suspected at admission, a presumptive diagnosis of dapsone hypersensitivity syndrome (DHS) was made.

All medications other than prednisone were stopped on admission. He was discharged after a 6-day admission. After resolution of his hepatitis (8 weeks post-admission), the patient was successfully rechallenged on rifampin and ofloxacin, confirming a diagnosis of DHS. He continued on dual therapy with daily rifampin and ofloxacin, given the recommendation that cessation of dapsone in the context of toxicity requires no further adjustment to the multidrug therapy (MDT) regimen.¹ A corticosteroid taper was initiated after normalization of his liver function tests (LFTs) and resolution of his rash (approximately 4 months into leprosy treatment). After a year of dual therapy, he remained clinically well with resolution of his Type 1 reaction and only mild hyperpigmentation of old lepromatous patches. At his 5-year posttreatment follow-up visit, there has been no evidence of relapse or reaction.

DISCUSSION

Leprosy is a serious infection with substantial morbidity caused by the obligate intracellular acid-fast bacillus *Mycobacterium leprae*, which typically manifests as anesthetic skin

FIGURE 1. Raised, erythematous, and anesthetic plaques of multibacillary leprosy in Type 1 reaction. This figure appears in color at www.ajtmh.org.

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lesions and peripheral nerve enlargement and/or impairment.² Treatment of multibacillary leprosy consists of multidrug therapy to prevent drug resistance. The WHO advises treatment for 12 months with a combination of dapsone, rifampin, and clofazimine, although as illuminated in this case, clofazimine is routinely replaced with ofloxacin because of difficulties with drug availability in Canada, and stigma associated with clofazimine hyperpigmentation.^{3,4} Type 1 reactions, as seen in this case, correspond to either upgrading or downgrading cell-mediated immunity to *M. leprae*, and are characterized by increasing pain, tenderness, erythema, and swelling of pre-existing lepromatous plaques. If untreated, Type 1 reactions can lead to permanent loss of nerve function. Up to 50% of multibacillary leprosy patients will undergo Type 1 reaction before (typically downgrading), during (typically upgrading), or after multidrug treatment, with common triggers including initiation of therapy, pregnancy, parturition, and puberty, although they also occur without any clear inciting event.² Early administration of corticosteroids is essential to preserve nerve function in Type 1 reactions and prevent downstream effects, including secondary infections, limb deformity, and digital necrosis.³

Unlike typical leprosy reactions that are quite common, DHS is an important and often-overlooked complication related to leprosy treatment. Dapsone is a sulfone compound that exhibits both antimicrobial and anti-inflammatory properties. It has remained widely used in the treatment of both multibacillary and paucibacillary leprosy since the 1940s.⁵ Oral formulations are also used in the prophylaxis and treatment of other infections, including toxoplasmosis and *Pneumocystis jiroveci* pneumonia; inflammatory skin conditions, including dermatitis herpetiformis, linear IgA dermatosis, bullous systemic lupus erythematosus, and pemphigus vulgaris; and immune thrombocytopenia. Although generally well tolerated, serious side effects of dapsone can occur, including hemolysis, methemoglobinemia, peripheral neuropathy, and Stevens-Johnson syndrome. Routine G6PD testing is recommended before use, as G6PD deficiency is associated with an increased risk of hemolysis. Conversely, G6PD deficiency is associated with a decreased risk of methemoglobinemia.

Dapsone hypersensitivity syndrome was first described in 1949, as a syndrome of exfoliative dermatitis, fever, and hepatitis, and has now been recognized as an idiosyncratic dose-independent hypersensitivity reaction.^{5,6} Typically occurring 4–6 weeks after introduction of the drug, DHS classically presents with the triad of fever, rash, and internal organ involvement, most frequently hepatitis. Common clinical and laboratory features are reported in Table 1. Dapsone hypersensitivity syndrome is in the spectrum of reactions termed “drug reactions with eosinophilia and systemic symptoms”.⁷ Histopathologically, the findings in DHS are nonspecific but may include those features of a generic drug eruption, such as mild to severe inflammatory cell infiltrates of the dermis (monocytic, lymphocytic, and eosinophilic), capillary congestion, and erythrocytic extravasation, as well as spongiosis, acanthosis, and vacuolation of the epidermis. Special stains for complement and immunoglobulin deposition as seen in autoimmune vasculitis and viral inclusions will be negative. A systematic review proposing diagnostic criteria for DHS demonstrated that 59% of cases were classified as “complete” DHS with fever, rash, lymphadenopathy, and hepatitis, whereas 41% had three or fewer such features and were

TABLE 1

Signs and symptoms reported in dapsone hypersensitivity syndrome^{8,14}

Very common (> 80% of cases)
Fever
Hepatitis
Any skin symptoms
Common (50–80% of cases)
Lymphadenopathy
Pruritus
Leukocytosis
Anemia
Eosinophilia
Less common (10–50% of cases)
Mucosal involvement
Exfoliative dermatitis
Splenomegaly
Nausea and vomiting
Atypical lymphocytosis
Hemolytic anemia

classified as “partial” DHS.⁸ Of those with leprosy in the analysis, 71% of patients with complete DHS were classified as paucibacillary.⁸ The incidence of DHS ranges from 0.5% to 3%,⁹ and, in retrospective studies, the mortality rate has been approximately 11%.¹⁰

The mechanism by which DHS occurs is unknown but is postulated to be related to production and impaired detoxification of reactive metabolites of dapsone, which then form haptens with anti-dapsone antibodies.^{11,12} A recent genome-wide association analysis also suggested the presence of human leukocyte antigen (HLA)-B*13:01 as a risk factor for the development of DHS (odds ratio (OR): 20.53, $P = 6.84 \times 10^{-25}$) with a sensitivity of 85.5% and specificity of 85.7% for predicting DHS.¹³ The prevalence of this allele, however, is quite varied across different ethnic populations, with rates as low as 0% in Europeans, to 2–20% in Chinese populations, and as high as 28% in Papuans and Australian aboriginals.¹³ Given the wide geographic and ethnic variation of allelic frequency, coupled with the situation of such testing in specialized reference centers (primarily for the purpose of hematopoietic stem cell matching in well-resourced countries that are not endemic for leprosy), the practical application of this particular HLA typing in advance of dapsone initiation in the leprosy population warrants further investigation. In populations known to have a high frequency of this HLA subtype, where laboratory infrastructure and testing capacity exist, pre-initiation typing could be considered, although the potential benefit of DHS cases averted must be weighed against the cost of testing and delayed initiation of treatment.

Based on a systematic review of 114 studies including 336 patients, the overall prevalence of hypersensitivity reactions to dapsone was 1.4% (95% CI = 1.2–1.7) with a case fatality of 9.9%.¹⁴ Increased age (OR: 2.95, 95% CI = 1.07–8.11) and leprosy as the indication for dapsone therapy (OR: 5.14, 95% CI = 1.09–24.27) were demonstrated by multivariate analysis to be risk factors for fatal outcome.¹⁴ Delayed drug cessation demonstrated no risk of increased mortality (OR: 1.88, 95% CI = 0.28–6.15).¹⁴

Treatment of DHS consists of dapsone withdrawal and initiation of corticosteroids, typically at prednisone doses of 30–60 mg per day, followed by a slow taper once evidence of end organ involvement resolves. Close monitoring of organ function following initiation of taper is paramount. To date,

TABLE 2
Comparison between DHS and rifampin toxicity

Features	DHS ^{13–17}	Rifampin toxicity ^{18–20}
Primary presenting signs and symptoms	Fever Hepatitis Skin symptoms Exanthema/erythema Erythroderma Rash Lymphadenopathy	Fever Rash Abdominal discomfort Type III immune-mediated reactions (flu-like syndrome) Episodes of fever in association with rigors, arthralgia and myalgia, and sometimes rhinorrhea Type I anaphylactic reactions Hypotension with or without angioedema, bronchospasm, urticaria, or erythroderma Urticarial or diffuse erythematous rash consistent with Type I anaphylactic reactions Erythematous papules and vesicles seen in Type III immune-mediated reactions
Rash characteristics	Generalized rash Pruritus Often initially benign morbilliform eruption and may develop into exfoliative dermatitis	
Laboratory abnormalities	Leukocytosis Hemolytic anemia Eosinophilia Abnormal liver function tests (mixed hepatocellular and cholestatic pattern)	Thrombocytopenia Leukopenia Hemolytic anemia Decreased C3 and C4 levels in complex-mediated Type III immune reactions
Frequency of reaction	Estimated prevalence of 1.4%	Type III immune-mediated reactions and mild cutaneous reactions in 0.5–5% of patients Major adverse effects, including Type I anaphylactic shock, in 0.02% of patients
Time from administration to reaction	Symptoms manifesting between 2 and 8 weeks of dapsone administration	Flu-like syndrome after 3–6 months of intermittent use Symptoms occur within 1–4 hours of drug administration and last for up to 8 hours Type I anaphylactic reactions within minutes
Other organ and systemic involvement	Hepatic Renal Cardiac Pulmonary Pancreatic Thyroid	Hepatic Gastrointestinal Renal Hematologic Dermatologic Extensive systemic involvement in anaphylactic reactions
Risk mitigation	HLA-B*13:01 significantly associated with DHS	Higher risk of rifampin toxicity if HIV positive and/or on prior rifampin treatment

DHS = dapsone hypersensitivity syndrome.

there have been no randomized trials evaluating prednisone use in the treatment of DHS; however, the duration of treatment is typically at least 1 month, which is predicated on the heavily protein-bound nature of dapsone in tissue for up to 35 days.¹⁵ Rechallenging with dapsone should be avoided because of the putative formation of anti-dapsone antibodies. Resolution of DHS can take 4 weeks, and potentially longer, with most rashes resolving in a period of 2 weeks.¹⁴ Delayed onset hypothyroidism has been reported following various drug hypersensitivity reactions, so routine thyroid function testing is suggested by some experts 3 months after recovery.¹⁵

In summary, DHS is a rare but potentially fatal complication of dapsone use that will affect a small minority of leprosy patients on dapsone-containing MDT, and can present in a similar manner to rifampin toxicity (Table 2). Although the mechanism of DHS remains unclear, there is a possible genetic component to the reaction. HLA-B*13:01 testing in high-risk populations may be a useful screening tool but is not yet a widely available test, nor are there established guidelines to help direct interpretation of results.¹⁶ In the absence of pre-emptive testing and risk stratification, a high level of clinical suspicion is paramount in patients presenting with compatible features in the weeks after dapsone initiation so that dapsone can be withdrawn and corticosteroid therapy can be initiated.

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