

## Case Report

# A 50-Year-Old Male with Dapsone Hypersensitivity Syndrome

Lubna Khondker<sup>1</sup>, Farhana Wahab<sup>2</sup>, Azmiree Binte Aslam<sup>3</sup>

Received: September 17, 2017 Accepted: April 15, 2018

doi: <http://dx.doi.org/10.3329/jemc.v8i2.36736>

### Abstract

*Dapsone, diamino-diphenyl sulfone, is an antibacterial and anti-inflammatory drug which is used worldwide for treating many diseases, such as leprosy, dermatitis herpetiformis, linear IgA bullous dermatosis, chronic bullous dermatosis of childhood, bullous eruption of systemic lupus erythematosus, erythema elevatum diutinum, leukocytoclastic vasculitis, polyarteritis nodosa and other kinds of vasculitis, prurigo nodularis, nodulocystic acne, cutaneous mycetoma, pustular psoriasis, malaria, pneumocystis carinii pneumonia etc. Since it is widely used, the adverse effects of this drug attract the attention of doctors from different specialities. Dapsone can cause several adverse effects, the most serious one is idiosyncratic systemic hypersensitivity syndrome, namely dapsone hypersensitivity syndrome (DHS), which is potentially fatal, characterized by fever, facial edema with infiltrated papules, generalized papulopustular or exanthematous rash which may extend to exfoliative dermatitis, eosinophilia, lymphadenopathy, hematologic involvement and organ involvement such as hepatitis, nephritis, pneumonitis, encephalitis, myocarditis occurring after 3–6 weeks of drug therapy. Here we have described a case of dapsone hypersensitivity syndrome developed after dapsone therapy for prurigo nodularis. The case is being reported to emphasize the need for timely diagnosis and prompt treatment of this rare complication for successful outcomes. Physicians should be aware of this infrequent but potentially fatal severe form of adverse reaction that can mimic other conditions.*

**Key words:** Dapsone; DHS (Dapsone hypersensitivity syndrome); Prurigo nodularis

J Enam Med Col 2018; 8(2): 108–113

## Introduction

Dapsone hypersensitivity syndrome (DHS) can be considered as a manifestation of DRESS (drug rash with eosinophilia and systemic symptoms) syndrome.<sup>1</sup> DRESS is an adverse reaction that can be seen with the use of many drugs such as dapsone, sulfonamides, allopurinol, cyclosporine, azathioprine, minocycline, antiviral drugs, anticonvulsant and gold salt.<sup>2</sup> DHS differs from other drug reactions because it can occur after prolonged exposure of offending drug and even up to 6 months after exposure. DHS is an idiosyncratic multi-organ disease. It has a frequency

of 0.2–0.5% in patients on dapsone therapy.<sup>1</sup> DHS was described first by Allday, Lowe and Barnes as a hypersensitivity vasculitis syndrome. This syndrome typically presents with a triad of fever, skin eruption, and internal organ (lung, liver, neurological and other systems) involvement. Richardus and Smith proposed the following criteria to diagnose a case of dapsone hypersensitivity syndrome (DHS): 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

1. Associate Professor, Department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka

2. MD Resident of Dermatology and Venereology, BSMMU, Dhaka

3. Diploma Student of Dermatology and Venereology, BSMMU, Dhaka

**Correspondence** Lubna Khondker, E-mail: [lubnaderma@gmail.com](mailto:lubnaderma@gmail.com)

with dapsone, 3) The symptoms are not attributable to lepra reaction and 4) No other disease liable to cause similar symptoms is diagnosed.<sup>3-8</sup>

The exact mechanism behind DHS is not known. But few hypotheses have been proposed. Among these, it might be combination of type I and type IV, and perhaps type III hypersensitivity reactions. It could be a modified graft versus host disease mediated by activated T-lymphocytes.<sup>9</sup> According to Prussick and Shear<sup>10</sup>, there are some evidences suggesting the metabolic differences in the production and detoxification of reactive metabolites which are important factors in sulfonamide hypersensitivity reactions. After absorption dapsone is metabolized in liver via N-acetylation and N-hydroxylation. N-acetylation has no relation with the adverse effects. However, hydroxylamine which is known as a toxic intermediate metabolite and formed by N-hydroxylation may cause hemolytic anemia and DHS. The metabolite can combine or modify some immunologically-significant chemicals, such as major histocompatibility complex (MHC), on the surface of the immune cells (antigen-presenting cells), then facilitate the T cells recognizing the antigen. Drugs are haptens which should be combined with proteins to form a complete antigen. The bioactivation and protein haptentation of sulphonamides, including sulfamethoxazole (SMX) and dapsone, produce the drug's metabolite and cellular protein forms a covalent product which induced the cellular toxicity.<sup>10</sup>

DHS are generally self-limiting reaction and respond well after withdrawal of dapsone and by starting oral or parenteral glucocorticoids (depending upon severity). 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. Nutritional support, fluid and electrolyte balance, control and prevention of infections (cellulitis, sepsis) and skin care are also required. Vitamin E supplement is found to be beneficial in dapsone induced hemolysis.<sup>11</sup>

## Case report

A 50-year-old hypertensive male recently diagnosed as a case of prurigo nodularis was prescribed 100 mg dapsone daily. After getting medication for one month he developed fever which was high grade, intermittent and was associated with chills and rigor. After seven days his body was studded with morbiliform eruption that progressed to generalized exfoliation in the next few days. He also developed yellowish coloration of sclera and urine and pruritus. Dapsone was stopped after 45 days of therapy. On physical examination, he was febrile (102°F) and anemic. Pedal edema and painless inguinal lymphadenopathy were present. Skin evaluation revealed generalized erythema and scaling along with few erosions scattered all over the body. Multiple hyperpigmented nodules and pustules symmetrically distributed over both legs. Palms and soles showed epidermal detachment in the form of large sheets. Complete blood picture showed Hb 10.6 gm/dL, WBC 15×10<sup>9</sup>/L, erythrocyte sedimentation rate 40 mm in the first hour, eosinophil 35% and platelet count 415×10<sup>9</sup>/L. Liver function test revealed alkaline phosphatase 222 U/L, gamma glutamyl transferase (GGT) 97 U/L, aspartate aminotransferase (AST) 23 U/L, alanine aminotransferase (ALT) 22 U/L, prothrombin time 16.7 second, serum albumin 25 gm/L. Ultrasonography of abdomen revealed mildly enlarged prostate. Routine biochemical analysis showed random blood sugar 5.3 mmol/L and serum creatinine 2.44 mg/dL. Urine analysis showed pus cells 20–30/HPF, protein (+), epithelial cell 2–5/HPF and RBC 1–2/HPF. Pus for aerobic and anaerobic culture showed profound growth of Klebsiella species with sensitivity to cotrimoxazole, gentamicin, netilmicin, meropenem, and amikacin. Serum electrolyte showed sodium 130 mmol/L, potassium 5.1 mmol/L and chloride 98 mmol/L. Based on patient's medical history, clinical findings and laboratory tests, a diagnosis of DRESS was made. The patient was put on prednisolone 40 mg/day with H1 blocker, hydroxyzine and acetaminophen. Cefuroxime 500 mg 12 hourly was given initially, then intravenous meropenem was added in adjusted dose for renal impairment. His high temperature along with skin erosion and scaling subsided gradually and

creatinine level became normal. Prednisolone was tapered to 30 mg after four weeks of therapy and continued to taper slowly in the following weeks.



Fig 1. Morbiliform eruption that progressed to exfoliation

## Discussion

Vinod et al<sup>11</sup> presented a 17-year-old male with complaints of high grade fever associated with chills and rigors, jaundice and itchy skin rash for 10 days. One month prior to current admission, he was given dapsone 100 mg/day by a dermatologist for suspected lichen planus. He had discontinued the medication 10 days earlier when he developed the above complaints. On admission, he had high grade fever (103–104°F), deep icterus, palpable lymph nodes in the cervical and axillary regions. There was no organomegaly. He had a toxic look, was agitated and confused with generalized skin erythema and extensive scaling suggesting exfoliative dermatitis. There was angular cheilitis with a crusted lesion over the lip and subconjunctival hemorrhage, but oral mucosa and penile mucosa were normal. Patient later developed shock (BP 70/40 mm Hg) and right internal jugular central venous catheter was placed. Noradrenaline was started as the hypotension did not respond to fluid challenge. Empirical broad spectrum antibiotics (meropenem and vancomycin) were given keeping the possibility of severe sepsis with septic shock, in view of breach in integrity of the skin. Laboratory evaluation revealed neutrophilic leucocytosis with eosinophilia (Hb 12.3 g/dL, leucocytes 12,700/ $\mu$ L, platelets 2,10,000/ $\mu$ L, neutrophils 78%, lymphocytes 12%, eosinophils 10%), bilirubin 13.5 mg/dL (direct 10.2 mg/dL), AST 239 IU/L, ALT 430 IU/L, alkaline phosphatase 538 IU/L, hypoalbuminemia (2.8 g/dL), coagulopathy (prothrombin time 26 s (control 14 s), aPTT 48 s (control 28–34 s), normal urine examination and renal function tests. Tests for malaria, leptospirosis, typhus fever, cytomegalovirus (CMV), Epstein Barr virus (EBV), ELISA for HIV-1 and 2, hepatitis A, B, E and C were negative. Antinuclear antibodies were negative. Repeated blood and skin swab cultures were sterile. Chest radiography and abdominal sonography were unremarkable. Patient's blood pressure improved and noradrenaline was stopped after four days of admission. He continued to have high grade fever despite being on antibiotics for five days. A diagnosis of dapsone systemic hypersensitivity syndrome was made based on history of dapsone intake, followed by fever, skin rash, eosinophilia, lymphadenopathy

and hepatitis. He was given oral prednisolone 50 mg/day (1 mg/kg) from day six. He improved over next 10 days with gradual subsidence of fever, rash and hepatitis. Antibiotics were discontinued after 10 days and he was discharged on day 18 of admission. Prednisolone 1 mg/kg/day was continued for one month and then tapered off over next six weeks, with complete normalization of liver function and resolution of lymphadenopathy.<sup>11</sup>

Gavilanes A<sup>12</sup> reported a 31-year-old white married man born in Japeri, Rio de Janeiro, Brazil who was diagnosed with lepromatous leprosy and admitted four weeks after the start of World Health Organization (WHO) multidrug therapy (MDT). He presented at the outpatient department with prostration, fever, nausea and vomiting. On physical examination there was dehydration, pallor, jaundice, facial and lower limb edema, pain on abdominal palpation at the right upper quadrant and painless cervical and inguinal lymph nodes. Skin evaluation revealed generalized exanthema that later progressed to an exfoliative dermatitis. Signs of erythema nodosum leprosum (ENL) were not detected and no enlarged or painful nerves were found. Dapsone hypersensitivity syndrome (DHS) was diagnosed. MDT was withdrawn and prednisone 50 mg/day was prescribed. On admission severe anaemia and abnormal liver functions as well as hyperbilirubinaemia were found. Significant eosinophilia and atypical lymphocytes were not observed. Abdominal ultrasonography showed mild hepatomegaly, steatosis, splenomegaly, thickened gallbladder wall and normal bile ducts. Eighteen days after admission the patient showed clinical and laboratory improvement and was discharged. Prednisone dose was tapered gradually. He was seen weekly until he was medically stable. Treatment for leprosy was restarted with supervised monthly ofloxacin 400 mg, clofazimine 300 mg and rifampicin 600 mg and daily 400 mg ofloxacin and 50 mg clofazimine.<sup>12</sup>

From 2006 to 2009 China has registered 6243 new leprosy patients. Among these patients, only 63 patients were diagnosed as having DHS. Among the 63 cases, 43 were male and 20 were female. The average age of the patients was 38 years ranging

from 11 to 76 years and most of them (41.3%) were 20–40 years of age. Most patients were multibacillary (MB) patients, and the average bacillary index (BI) of these patients was 2.1. Moreover, most patients had no disabilities (66.7%) or reactions (81%), or other systemic diseases at the time of diagnosis, which meant that most patients' general condition were good. All 63 patients developed one or more symptoms between 14 days and 2 months after MDT, 27 (42.9%) of whom had an incubation period of about one month (mean 32.8 days). The main clinical manifestations were focused on two organs – the skin and the liver. The former caused different kinds of eruptions such as maculopapule, excoriation, blisters, edema, ulcer, and the latter caused jaundice, hepatosplenomegaly or abnormal hepatic function. The eruptions mainly appeared on the trunks of the patients (71.4%). The main complaint was fever (56/63, 88.9%). Besides eruptions, lymphadenopathy (34.9%) and other systemic involvements included hematological system (19.0%), kidney (3.2%) and others (9.5%) such as gastrointestinal symptoms (2/63), neurological discomfort (2/63), toxic myocarditis (1/63), and electrolyte disturbances (1/63). The management of DHS included discontinuation of dapsone, systemic glucocorticosteroid, hepatic protection, vitamins and topical glucocorticosteroid cream. The treatment of DHS is individualized according to the severity of DHS. For patients with severe DHS, the systemic glucocorticosteroid regimen used dexamethasone at an initial dosage of 15–20 mg daily in intravenous instillation for 7–10 days and dexamethasone dosage was tapered based on the patient's body temperature. Once temperature returned to normal, the dose was changed to oral prednisone at 20–30 mg for at least one month. Hepatic protection measures were given to patients — glucose, albumin, vitamin C, and avoiding giving them drugs mainly metabolised in the liver. The duration of the course of DHS varied among patients, from one week to more than four weeks. The average duration time for full recovery was 38.1 days among our patients. Seven (11.1%) patients died of DHS. There was a significant difference between the patients who recovered and those who died in the delay time from DHS onset to receiving treatment.<sup>13</sup>

The criteria for DRESS syndrome proposed by Bocquet et al<sup>14</sup> are as follows: 1) cutaneous drug eruption, 2) hematologic abnormalities, including eosinophilia greater than  $1.5 \times 10^9$  eosinophils/L or the presence of atypical lymphocytes and 3) systemic involvement including adenopathy greater than two cm in diameter, hepatitis (liver transaminases values  $>2$  N), interstitial nephritis, interstitial pneumonia, or carditis.<sup>14</sup> These criteria emphasize two important characteristics — multiple organs involvement and eosinophilia. Our patient had an absolute eosinophil count of  $5250/\text{mm}^3$  with involvement of liver (cholestatic pattern) and kidney. Liver involvement displays a mixed hepatocellular and cholestatic pattern. Cholestatic pattern has a less severe course characterized by high ALT and moderate transaminase levels. Hepatitis may progress to liver failure. In the literature the dermatosis is not well-defined. Some authors describe it as a rash while others as a morbiliform rash or even as an exfoliative dermatitis. Some authors described skin involvement in DRESS as variable and therefore the 'R' in DRESS was subsequently changed from 'rash' to 'reaction'.<sup>15-17</sup> Our patient initially presented with generalized exanthem which progressed to a diffuse exfoliative dermatitis.

Dapsone is well-absorbed from the gut and primarily metabolized through N-acetylation and N-hydroxylation (oxidation). The hydroxylamine and the hydroxylated metabolites are potent oxidants and cause hematologic adverse effects, predominantly hemolysis. It is excreted by the kidney, but has significant enterohepatic circulation. It has a long elimination half-life of 24 to 30 hours on an average. Strong protein binding of the drug itself (70–90%) and its major metabolite, monoacetyl-dapsone (99%), contribute to the long half-life. Hypersensitivity reaction differs from other drug reactions and occurs during first six weeks of initiating the treatment to as late as six months. The side-effects are very low if plasma concentration of dapsone is below 5 mg/L.<sup>18</sup> In our patient rashes appeared by the end of 5 weeks.

## Conclusion

Generally DHS is a self-limiting drug reaction and most patients recover following cessation of dapsone therapy and starting treatment with oral corticosteroid. Mortality was reported to be 12–23% in severe DHS. Physicians, dermatologists, rheumatologists and leprologists prescribing dapsone for various clinical conditions should be aware of potentially fatal DHS to ensure timely diagnosis and appropriate management.

## References

1. Puri AS, Gupta R, Ghoshal UC, Khan E, Aggarwal R, Nail SR. Hepatic injury in sulfone syndrome: hepatitis or cholestasis? *Indian J Gastroenterol* 1995; 14: 20.
2. Pandey B, Shrestha K, Lewis J, Hawksworth RA, Walker SL. Mortality due to dapsone hypersensitivity syndrome complicating multi-drug therapy for leprosy in Nepal. *Trop Doct* 2007; 37: 162–163.
3. Shiohara T, Inaoka M, Kano Y. Drug-induced hypersensitivity syndrome (DIHS): a reaction induced by a complex interplay among herpes viruses and antiviral and antidrug immune responses. *Allergol Int* 2006; 55: 1–8.
4. Leslie KS, Gaffney K, Ross CN, Ridley S, Barker TH, Garioch JJ. A near fatal case of the dapsone hypersensitivity syndrome in a patient with urticaria. *Clin Exp Dermatol* 2003; 28: 496–498.
5. Rao PN, Lakshmi TS. Increase in the incidence of dapsone hypersensitivity syndrome -- an appraisal. *Lepr Rev* 2001; 72: 57–62.
6. Christiansen J, Tegner E, Irestedt M. Dapsone hypersensitivity syndrome in a patient with cutaneous lupus erythematosus. *Acta Derm Venereol* 1999; 79: 482.
7. Reeve PA, Ala J, Hall JJ. Dapsone syndrome in Vanuatu: a high incidence during multidrug treatment (MDT) of leprosy. *J Trop Med Hyg* 1992; 95: 266–270.
8. Richardus JH, Smith TC. Increased incidence in leprosy of hypersensitivity reactions to dapsone after introduction of multidrug therapy. *Lepr Rev* 1989; 60: 267–273.
9. Roujeau JC. Clinical heterogeneity of drug

- hypersensitivity. *Toxicology* 2005; 209(2):123–129.
10. Prussick R, Shear NH. Dapsone hypersensitivity syndrome. *J Am Acad Dermatol* 1996; 35: 346–349.
  11. VinodKV, ArunK, Dutta TK. Dapsone hypersensitivity syndrome: a rare life threatening complication of dapsone therapy. *J Pharmacol Pharmacother* 2013; 4(2): 158–160.
  12. Gavilanes MC, Palacio AL, Chellini PR, Nery JAD, Rego JGA. Dapsone hypersensitivity syndrome in a lepromatous leprosy patient – a case report. *Lepr Rev* 2015; 86: 186–190.
  13. Tian W, Shen J, Zhou M, Yan L, Zhang G. Dapsone hypersensitivity syndrome among leprosy patients in China. *Lepr Rev* 2012; 83: 370–377.
  14. Bocquet H, Martine B, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (drug rash with eosinophilia and systemic symptoms:DRESS). *Semin Cutan Med Surg* 1996; 15(4): 250–257.
  15. Itha S, Kumar A, Dhingra S. Dapsone induced cholangitis as a part of dapsone syndrome: a case report. *BMC Gastroenterol* 2003; 3: 21.
  16. Karp WB, Subramanyam SB, Robertson AF. Binding of dapsone and its analogues to human serum albumin. *J Pharm Sci* 1985; 74: 690–691.
  17. Rege VL, Shukla P, Mascarenhas MF. Dapsone syndrome in Goa. *Indian J Lepr* 1994; 66: 59–64.
  18. McKenna KE, Robinson J. The dapsone hypersensitivity syndrome occurring in a patient with dermatitis herpetiformis. *Br J Dermatol* 1997; 137: 657–658.