Sulfone syndrome - A Case Series

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Dapsone Hypersensitivity Syndrome (DHS) is an uncommon dose-unrelated side effect of dapsone which is characterized by an infectious mononucleosis-like syndrome, occurring in a genetically predisposed individual with viral reactivation. Herein we report a series of 4 patients with DHS associated with certain unusual complications like pneumonitis and nephritis in one patient each. Commonly known symptoms and signs were fever, rash and raised liver transaminases, which were present in all the patients. These occurred after a latency of minimum of 2 weeks of consumption of dapsone with a dose ranging from 50mg to as high as 300mg in one patient. All the patients were managed conservatively with dapsone withdrawal; three patients were treated with oral steroids, while one patient was prescribed oral cyclosporine due to the contraindications for steroid use. The cutaneous lesions resolved in 2 weeks, while the liver enzymes took a little longer duration of more than 4 weeks to attain normalcy.

Keywords: Dapsone Hypersensitivity Syndrome, Cyclosporine.

Introduction

Dapsone Hypersensitivity Syndrome (DHS) or “Sulfone syndrome” is an idiosyncratic side effect characterized by an infectious mononucleosis-like eruption, conceptualized under the umbrella term of DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) (Bhatia & Hall III 2021). This syndrome was initially described in leprosy patients being treated with dapsone by Lowe & Smith as “glandular fever” (Lowe & Smith 1949) and rechristened as “Dapsone syndrome” by Allday and Barnes (Allday & Barnes 1951). It is a multi-organ involvement syndrome presenting with the triad of fever, rash, and internal organ involvement caused by an interplay of type I, type IV, and perhaps also type III hypersensitivity reactions mediated by activated cytotoxic T lymphocytes (Smio et al 1994). After the initial reports of DHS during the early years of its use, very few cases were reported thereafter; however, a steady rise in the cases of dapsone syndrome was observed in the late 1980s with the introduction of dapsone to treat other diseases as well as multidrug therapy (MDT) in leprosy. The incidence of DHS ranged from 1.3 to 3.6% across various studies (Lowe & Smith 1949, Smith 1988, Richardus & Smith 1989, Rege et al 1994). A few authors opined that this apparent increase in the DHS after the introduction of MDT may be due to the increased patient compliance and clinic attendance by the leprosy patients and awareness of DHS among the medical personnel. Additionally, dapsone was also being used for other non-leprosy indications (Rao &...
Lakshmi 2001). We observed a series of 4 cases of dapsone syndrome at our centre, Dr. B. R Ambedkar Medical College, and Hospital over a period of 5 years, which are summarised in the present case series.

**Case reports**

The clinical and laboratory details of 4 cases of DHS which were observed and being reported in this manuscript are depicted in Table 1.

**Case 1:**

A 35-year-old female with papulopustular acne vulgaris was prescribed oral dapsone 100mg twice daily with topical benzoyl peroxide 2.5% for 6 weeks. During treatment and follow-up pustules and erythema of the acne reduced by the end of 2 weeks. A week later, the patient developed fever and itching which progressed to a diffuse maculopapular rash leading to exfoliative skin spent.

### Table 1: Case summaries of the 4 patients with dapsone hypersensitivity syndrome.

<table>
<thead>
<tr>
<th>Particulars</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
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<tr>
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<td>13</td>
<td>28</td>
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<td>F</td>
<td>M</td>
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<td>M</td>
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<td>Vasculitis</td>
<td>Borderline Tuberculoid leprosy</td>
<td>Dermatitis Herpetiformis</td>
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<tr>
<td>Latency</td>
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<td>4 weeks</td>
<td>6 weeks</td>
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<td>Manifestations</td>
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<td>Maculo-papular Purpuric</td>
<td>Exfoliative dermatitis</td>
<td>Exfoliative dermatitis</td>
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<td>Systemic symptoms</td>
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<tr>
<td>Fever</td>
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<td>Lymphadenopathy</td>
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<td>Hepato-biliary involvement</td>
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<td>Splenomegaly</td>
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<td>Kidney involvement</td>
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<td>Leukocytosis</td>
<td>Raised*</td>
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<td>Leukocytosis with eosinophilia</td>
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<td>Liver transaminases</td>
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<td>Transaminases</td>
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<td>Treatment</td>
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<td>Oral cyclosporine</td>
<td>Oral steroids</td>
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<td>Prognosis</td>
<td>Improved</td>
<td>Improved</td>
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dermatitis, with oedema of the face (Fig. 1). The patient also had jaundice, lymphadenopathy, and tender hepatomegaly. Blood examination showed leucocytosis with lymphocytosis and elevated SGOT (Serum Glutamic oxaloacetic Transaminase) and SGPT (Serum Glutamic Pyruvic Transaminase). Skin biopsy revealed lymphocyte histiocytic infiltrate in the dermis. Based on the constellation of symptoms with an antecedent history of dapsone prescription and intake, a diagnosis of dapsone syndrome was arrived at. The patient was hospitalized and dapsone was withdrawn. She was started on injectable dexamethasone at 12mg initially and later switched to oral prednisolone (1mg/kg) at the end of 2 weeks. The oral steroids were tapered gradually tapered and stopped over a period of another month. The cutaneous lesions healed with desquamation at the end of 2 weeks, while the liver enzymes normalized by 3 weeks, with no recurrence of rash or dermatitis on stopping the medications.

**Case 2:**

A 34 years old male presented with palpable purpura bilaterally over lower extremities, associated with pain and swelling of joints for 2 weeks. A biopsy of the cutaneous lesions showed features suggestive of leukocytoclastic vasculitis and since the patient was diabetic, he was started on oral dapsone 300mg in divided doses after evaluating his complete hemogram and liver enzymes. After 4 weeks, the patient developed a pruritic photosensitive maculopapular rash involving the face, extremities, and trunk, which progressed to a purpuric rash over the extremities sparing palms and soles and mucosa with intense facial suffusion (Fig. 2A & B). This was associated with fever. Differentials of morbilliform drug rash and viral exanthema were considered and investigated. A complete hemogram revealed eosinophilic leucocytosis and a liver function test showed raised liver enzymes. Hepatomegaly and splenomegaly were observed on ultrasonography of the abdomen and pelvis.
His blood sugar was raised, and a biopsy revealed basal cell degeneration with dermal oedema and perivascular aggregates of inflammatory cells comprising predominantly eosinophils, which was suggestive of a drug reaction (Fig. 3). The patient was diagnosed with dapsone syndrome and was
managed symptomatically with antihistamines and antipyretics. Dapsone was stopped and the patient was started on oral cyclosporine 200 mg in divided doses for 3 weeks, with complete resolution. Oral cyclosporine was tapered and stopped in due course of another 3 weeks.

Fig. 3: Case 2- Histological image showing focal basal cell degeneration with perivascular inflammatory cells comprising eosinophils (H&E; 40X).

Fig. 4: Case 3- Ill-defined erythematous and edematous plaque over the left cheek extending onto the lips.
**Case 3:**
A 13 years old female presented with progressive swelling of the upper lip for 3 months. Examination showed an ill-defined hypo anaesthetic erythematous plaque over the upper lip on the left side involving the philtrum extending onto the left cheek with no feeding nerves (Fig. 4) There were two partially defined xerotic, hypo-anaesthetic plaques with satellite lesions over the right buttock and left forearm. No peripheral nerves were enlarged and there were no sensory or motor deficit. A slit skin smear was negative for AFB, and a biopsy of the face lesion, revealed features suggestive of borderline tuberculoid leprosy (Fig. 5). Patient was started on Multibacillary- multi drug therapy (MB-MDT) for child consisting of a single monthly supervised dose of rifampicin 450mg, clofazimine 150mg, dapsone 50mg on Day 1, followed by, dapsone 50 mg daily and alternate day clofazimine 50mg for 28 days. Five weeks later the patient presented with fever, sudden onset of diffuse papular rash involving all parts of the body sparing the palms and soles (Fig. 6A). Facial oedema and crusting of the lips were also present (Fig. 6B). The patient was tachypnoeic with oxygen saturation of 95% with 2 litres of oxygen inhalation. He was febrile had icterus and supra-clavicular non-tender lymphadenopathy. There were no features suggestive of type 1 lepra reaction. The blood picture revealed leucocytosis with lymphocytosis and liver enzymes were elevated. Ultrasonography showed hepato-splenomegaly, and bilateral interstitial infiltrates were noted on the chest radiograph. A diagnosis of dapsone hypersensitivity was made. The patient was hospitalized and managed symptomatically. All drugs were stopped, and injectable dexamethasone was started 8 mg daily for one week which was tapered to 4 mg the next week with improvement of skin lesions. After 2 weeks, equivalent oral steroids were started at 30mg
daily, which were later tapered over the next 4 weeks. After a washout period of 1 week for oral steroids, a rechallenge test for leprosy treatment was attempted. The sequential introduction of rifampicin and clofazimine did not elicit any adverse reaction. The patient had no reaction even after 6 weeks and continued rifampicin and clofazimine for treatment of leprosy.

Case 4:
A 28 year old male patient who was diagnosed with dermatitis herpetiformis was advised dapsone 300 mg in divided doses and a gluten-free diet. Within 2 weeks of drug intake, the patient presented with diffuse erythema, and oedema of the whole body associated with scaling. Scaling was also present on palms and soles; however, the mucosa was spared (Fig. 7). The patient had severe pruritus and a burning sensation. The patient denied a history of exposure to any airborne allergens or any previous history suggestive of psoriasis. He gave a history of cold intolerance and shivering. Bilateral pitting pedal oedema was present, and the patient had supraclavicular and inguinal lymphadenopathy. The patient was febrile, and tachycardia was present. With a differential of exfoliative dermatitis due to dapsone, the patient was further investigated. His blood picture revealed lymphocytic leucocytosis with haemolytic anaemia and raised liver enzymes. Ultrasonography showed mild hepatomegaly. RBC cells and casts were noted on the urine sample on routine microscopic examination along with mild proteinuria. The patient was hospitalized, and fluid and electrolyte balance were maintained. Two days later the patient developed oliguria and haematuria. A repeat urine analysis revealed plenty of RBC cells with mild proteinuria. A possibility of dapsone-induced nephritis was suspected, and his repeat renal function tests showed marginally raised serum creatinine. Dapsone was stopped and he was started on an injection of dexamethasone 16
mg for 1 week, tapered to 8 mg the next week, and later switched to oral prednisolone at 60 mg, which was then reduced and stopped over a period of another 4 weeks. Cutaneous lesions healed in 2 weeks, while the liver enzymes took a little longer than 4 weeks to attain normalcy. Renal parameters reverted to normal by 3 weeks.

DHS was diagnosed based on the criteria proposed by Richardus & Smith (1989) in all these cases which include:

1. Presence of at least two signs or symptoms: fever, skin eruption, lymphadenopathy, and liver abnormalities (hepatomegaly, jaundice, and/or deranged liver function tests).
2. Symptoms appear between the second and eighth week after the commencement of dapsone and disappear upon discontinuation of the drug.
3. Symptoms not ascribed to any other drug given simultaneously.
4. Symptoms not attributable to lepra reactions.
5. No other diseases are liable to cause similar symptoms.

All the patients fulfilled the above criteria with fever, skin rash, and liver abnormalities, a latency of a minimum of 2 weeks was observed before the onset of symptoms which was present in almost all the cases. During the study period of five years, 56 new cases of leprosy were administered MDT. Of these, only one patient developed signs and symptoms of dapsone syndrome. A retrospective study conducted in Taiwan reported a 1.66% incidence of dapsone syndrome in non-leprosy indications (Sheen et al. 2009) which is comparable to the incidence among leprosy patients (Rege et al. 1994, Richardus & Smith 1989, Lowe & Smith 1949). The dose of dapsone in leprosy is 100mg and in other conditions, it may reach 400 mg per day (Zhu & Stiller 2001). DHS is not a dose-dependent side effect, as there is no correlation between the dosage and occurrence of dapsone hypersensitivity (Smith 1988). Studies have depicted a higher occurrence of dapsone syndrome in patients less than 40 years of age (Kumar et al. 1998) which may be related to the decreasing enzyme activity in the liver with advancing age, as the DHS is thought to be related to the toxic intermediates produced on hydroxylation of dapsone (Zhu & Stiller 2001). All of our cases were less than 40 years of age.

One of the criteria proposed by Richardus & Smith to diagnose DHS is the development of symptoms two to eight weeks after dapsone administration (Richardus & Smith 1989). However, cases have been reported as early as 6 hours to as late as 6 months (Rao & Lakshmi 2001, Kumar et al. 1998, Singal et al. 1993.) The
latency of hypersensitivity is related to the previous sensitization to the sulfone drug, with patients having earlier onset if sensitized earlier (Kumar et al 1998). In the present series, all the patients developed symptoms after 2 weeks of initiation of dapsone.

Dermatitis in DHS ranges from pruritus, and papular erythematous eruptions, to the most severe erythroderma and Stevens-Johnson-like eruption (Richardus & Smith 1989). Other uncommon morphologies are eczematous dermatitis, vesicles, bullae, photosensitivity (Kumar et al 1998), mucosal erosions, and conjunctivitis (Agarwal & Agarwalla 2005). Two of our patients had exfoliative dermatitis and the other two patients had a maculopapular rash with a characteristic periorbital and facial oedema. One patient with maculopapular rash also had palpable purpura which may be related to his primary disease of leucocytoclastic vasculitis. The severity of cutaneous lesions is affected by the duration of dapsone intake after sensitization as it improves rapidly after discontinuation (Rao & Lakshmi 2001). None of our patients had mucosal involvement.

The DHS is associated with systemic symptoms like fever (88.9-100%), hepatomegaly (28.6-78%), lymphadenopathy (34.9-82.4%), splenomegaly (11.8-25.3%), pneumonitis (11.5-18.7%). (Wang et al 2017, Agarwal & Agarwalla 2005, Kumar et al 1998, Richardus & Smith 1989, Tian et al 2012). In a study comprising of 63 patients of DHS, nephritis, gastrointestinal symptoms and neurological discomfort was observed in 2/63 (3.2%) of patients whereas toxic myocarditis, and electrolyte disturbances were seen in 1/63 (1.6%) of patients (Tian et al 2012). In the current case series fever and hepatic involvement were seen in all the cases. Splenomegaly and lymphadenopathy were observed in two and three cases respectively. Uncommon complications like nephritis and pneumonitis were observed in one patient each. Pulmonary manifestations of the DHS may include eosinophilic pneumonia with associated systemic eosinophilia, hypersensitivity pneumonitis, and pleural effusion. This can cause rapid clinical deterioration and death, if untreated or unrecognized (Kosseifi et al 2006). Hepatocellular injury and haemolytic anaemia are characterized by hyperbilirubinemia (47.1-84.6%) and elevated transaminases (100%) (Agarwal & Agarwalla 2005, Kumar et al 1998) which can progress to liver failure and death if not recognized and treated properly with immediate withdrawal of dapsone. Cholangitis and cholestasis characterized by raised alkaline phosphatase have a less severe course (Itha et al 2003). DHS is often associated with a mortality ranging from 5.8 to 23%, attributed to fulminant hepatitis causing hepatic failure as reported in various studies (Kumar et al 1998, Pandey et al 2007, Richardus & Smith 1989, Agarwal & Agarwalla 2005). The other causes of death due to DHS are pneumonitis and agranulocytosis (Pandey et al 2007, Richardus & Smith 1989).

Anaemia (46.5%) raised erythrocyte sedimentation rate (92.3-100%), eosinophilia (15.4-41.2%) and leucocytosis (69.2%) are some of the haematological abnormalities seen in patients with DHS (Agarwal & Agarwalla 2005, Kumar et al 1998). Agarwal & Agarwalla (2005) observed hypoproteinaemia and hypoalbuminemia in 42.3% and 34.6% of patients. They also observed reticulocytosis and atypical lymphocytes in 15.4% and 46.1% of patients, respectively. All our patients had raised liver enzymes and leucocytosis, while eosinophilia and haemolytic anaemia were encountered in one patient each.

Dapsone withdrawal remains the mainstay of treatment in DHS. After discontinuation, cutaneous lesions were found to resolve within 10 days; while liver enzymes may take up to
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50 days to come to the normal level. However, steroids may help in faster remission and should be reserved for severe cases (Kumar et al 1998). Once steroids are started these should be tapered slowly over a period of 4-6 weeks. This can be attributed to a significant enterohepatic circulation and a strong protein binding of both dapsone and its metabolite mono-acetyl diamino diphenyl sulfone (MADDS) which results in a long elimination half-life ranging between 24-36 hrs, with a single oral dose remaining in the circulation as long as 30 days. Three of our patients were managed with oral steroids, while one patient was treated with oral cyclosporine. Cyclosporine can be used as an alternative to steroids (Zhang et al 2017) as it impairs the production of CD4, CD8 T cells, and interleukin 5 (IL-5) which may contribute to the pathogenesis of DHS (Bhatia & Hall III 2021).

DHS is a hypersensitivity reaction that occurs due to the interplay of impaired pharmacokinetics and accumulation of drug metabolites in a genetically predisposed individual with an altered immune reaction which may also be induced by the reactivation of viral infection. HLAB*13:01 (Zhang et al 2017) is considered a risk factor for the DHS with a sensitivity of 85.5% and specificity of 85.7% in predicting DHS. Absence of this risk factor may reduce the risk by a factor of 7 (from 1.4% to 0.2%). It is present primarily in Asians and is absent in Europeans and Africans. In India, the allele frequency ranges from 1-12%. The Single Nucleotide Polymorphisms involving HLA-B*13:01 loci alter the specificity of the peptide motif whereby dapsone and/or its metabolite triggers structural changes in the antigen-recognition site allowing it to recognize peptides that are altered (self-peptides) and mount an immune response (Zhang et al 2013). The hydroxylamine toxic metabolite of dapsone, produced by hydroxylation is implicated in the potentially fatal side effects of dapsone like methemoglobinemia, haemolysis, agranulocytosis, and DHS. This hydroxylation is in equilibrium with the acetylation of the dapsone, which produces a non-toxic metabolite acetyl-dapsone. Based on the acetylation ratio (mono acetyl dapsone: dapsone) subjects are divided into “slow” and “rapid” acetylators which are genetically determined. Though debatable, it was noted that patients with slow acetylation and rather than fast hydroxylation are likely to experience adverse reactions to dapsone. The higher incidence of adverse events to dapsone due to slow acetylation in patients with AIDS also supports this observation (Zhu & Stiller 2001). The metabolite can combine/modify major histocompatibility complex (MHC), on the surface of the immune cells (antigen-presenting cells), facilitate the T cells recognizing the antigen (Tian et al 2012). The altered immune status due to the pre-existing condition may facilitate the reactivation of HHV-6 which may cause severe hypersensitivity syndrome and flaring of the syndrome. Other frequently associated viruses linked to DHS are human herpes virus 7, Epstein Barr Virus (EBV), Cytomegalovirus (CMV), and influenza A and B viruses (Agarwal & Agarwalla 2005). The role of viral infections in inducing DHS, in the initiation and amplification of drug reactions remains unexplained but a precarious cell mediated immunity induced by the infection, may precipitate DHS.

The series highlights the clinical features of DHS presenting with varied morphology, ranging from maculopapular rash to purpura and exfoliative dermatitis associated with systemic signs and end-organ involvement. Nephritis and pneumonitis are some of the rare complications encountered in the present series. Oral cyclosporine is a promising treatment modality in cases where steroids are not indicated, and patients may require steroids for 4-6 weeks.
References
