Dapsone Hypersensitivity Syndrome Masquerading as a Viral Exanthem: Three Cases and a Mini-Review

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Abstract

Introduction: We report 3 cases of dapsone hypersensitivity syndrome due to anti-malarial chemoprophylactic treatment with maloprim, in military servicemen, presenting like a viral exanthem. Clinical Picture: Three male military recruits presented with fever and rash, 6 to 8 weeks after commencing on weekly doses of maloprim. Treatment: A course of topical and systemic corticosteroids and oral antihistamines were started. Outcome: All cases showed gradual resolution of fever, rash and eventual normalisation of liver function test. Conclusion: A high index of suspicion was required before this uncommon syndrome can be recognised. Early institution of corticosteroid therapy and discontinuation of maloprim are the mainstays of treatment.

Key words: Antimalarials, Dapsone, Exanthema

Introduction

Dapsone hypersensitivity syndrome (DHS) is a rare condition mostly occurring in leprosy patients on multidrug therapy. Dapsone is also combined with pyrimethamine as maloprim (Beacons Chemicals Pte Ltd, Singapore), a fairly effective chemoprophylactic agent in the management of malaria.1

Drug reactions to maloprim in military personnel was first described in 1983 as fixed drug eruptions in Papua New Guinea military personnel,2 with further provocation tests localising the culprit component to dapsone. However, true DHS in local military servicemen was only recently described by Thong et al.3 We present 3 cases of servicemen with classical features of this syndrome, mimicking that of a viral infection.

Case Reports

Case 1

A 19-year-old Chinese serviceman presented with 1 week of rash. He was not glucose-6-phophatase dehydrogenase (G6PD)-deficient and had been taking weekly maloprim since enlistment. On completing the 6th dose, a rash erupted on both upper limbs progressing to the back. He developed a fever after the 7th dose associated with nausea, headache, myalgia, arthralgia and a mild productive cough. His army doctor diagnosed dengue fever.

On admission, he had a temperature of 37.2°C. There were no conjunctivitis or oral lesions but his posterior pharyngeal wall was infected. Cardiovascular, respiratory and abdominal examinations were unremarkable. Bilateral small subcentimetre cervical lymphadenopathy was palpable. There were erythematous, macular rashes over the upper limbs (Fig. 1) and trunk, appearing like a viral exanthem.

Over the next 4 days, he was febrile up to 38°C and the rash spread to his lower limbs (Fig. 2) and face, becoming a dusky red exanthematous eruption. Investigations revealed haemoglobin, 15.4 g/dL; leukocyte count, 8300/mm³ (polymorphs, 72.1%; lymphocytes, 13.7%; and eosinophils, 2.3%); and platelet count, 164,000/mm³. No malaria parasites were seen on blood film. Total serum bilirubin was 24.3 µmol/L; alanine transaminase, 212 µL; aspartate transaminase, 121 µL; alkaline phosphatase, 89 µL; and serum albumin, 38 gL. Erythrocyte sedimentation rate was 2 mm in the first hour and cold agglutinin was not detected. On day 5, 15% atypical mononuclear cells were noted and liver function tests worsened though clotting profile

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remained normal. Dengue duo IgM and IgG rapid strip test (PanBio, Australia) were negative on day 5. Mycoplasma, measles, rubella and Epstein-Barr virus serologies were all negative. His chest radiograph was unremarkable and blood cultures were negative.

He was subsequently referred to a dermatologist, who noted that he had been taking oral doxycycline for 3 months, for treatment of facial acne vulgaris. He had taken doxycycline intermittently in the past, without any side effects. A skin biopsy showed moderate perivascular mononuclear cell infiltrate in the upper dermis accompanied by capillary congestion, with mild basal increase in pigmentation and spongiosis in the epidermis, consistent with superficial perivascular spongiotic dermatitis (Fig. 3). Intravenous hydrocortisone 150 mg 6 hourly was initiated for 3 days, followed by oral prednisolone 30 mg daily for 2 weeks, oral hydroxyzine 25 mg when necessary and 0.025% topical bethamethasone cream twice daily.

His fever gradually resolved and transaminitis started improving. He was discharged on day 9. On follow-up, his liver function had completely normalised and his rashes had resolved.

Case 2

An 18-year-old Chinese serviceman complained of fever for 1 week associated with cough, sore throat, myalgia and a pruritic rash over the trunks and limbs. He was not G6PD-deficient and already had 4 weekly doses of maloprim. His army doctor diagnosed infectious mononucleosis.

On admission, his temperature was 39.4°C, blood pressure was 99/57 mm Hg and heart rate was 80 beats per min. There was no pedal oedema or mucosal lesions. He had a generalised maculopapular rash over the trunk and limbs. There were multiple 1- to 2-cm bilateral tender cervical lymphadenopathies. Cardiovascular and respiratory examinations were not significant. He had mild ascites and a mildly tender 3-cm hepatomegaly. Over the next 8 days he was febrile up to 39°C. Initial haemoglobin was 13.7 g/dL; leukocyte count, 13,200/mm³ (polymorphs, 51%; lymphocytes, 23%; and eosinophils, 0%); platelet count, 99,000/mm³; and atypical mononuclear cells, 23%. Total serum bilirubin was 25.3 µmol/L; alanine transaminase, 250 µL; aspartate transaminase, 144 µL; alkaline phosphatase, 138 µL; and serum albumin, 34 g/L. Blood urea, creatinine and electrolytes were normal. The platelet count dropped to 63,000/mm³ on day 5 without bleeding clinically. On day 8, prothrombin time prolonged to 16 s (control, 13.4 s) but activated partial thromboplastin time and disseminated intravascular coagulation markers were negative. Mycoplasma, leptospiral, measles, rubella and Epstein-Barr virus serologies were negative. Widal Weil Felix test, hepatitis A IgM, hepatitis Bs and Be antigen and hepatitis C IgG were also negative. An autoimmune screen revealed a negative antinuclear antibody, anti-double-stranded deoxyribonucleic acid, anti-smooth-muscle and anti-liver-kidney-microsome antibody. The chest radiograph was normal.
On day 4, he became mildly dyspnoeic on exertion and complained of increasing right hypochondrial pain. Clinical examination showed jaundice and increasing ascites. His serum bilirubin deteriorated to 80.9 µmol/L; alanine transaminase, 719 µL; aspartate transaminase, 579 µL; alkaline phosphatase, 609 µL; and low serum albumin of 21 g/L. Empirical bacterial coverage was started with intravenous ceftriaxone and metronidazole for possible hepatobiliary sepsis with disseminated intravascular coagulation. No blood product transfusion was required. An abdominal computed tomography scan confirmed moderate hepatomegaly with ascites. A bone marrow aspiration and trephine showed a moderate hypocellular marrow with slightly increased erythropoiesis with normoblastic maturation. Dermatology consult confirmed DHS and no skin biopsy was done. Antibiotics were discontinued and oral prednisolone 35 mg daily plus 0.05% topical betamethasone cream twice daily were started. The fever defervesced on day 9 and ascites began to resolve, with a faint rash at discharge on day 14. Liver function abnormalities continued to improve until normalisation 2 months later, at which prednisolone was tapered off without recurrence of symptoms.

**Case 3**

A 19-year-old Chinese serviceman was admitted with intermittent fever of 4 days’ duration associated with productive cough, rashes and bilateral red eyes. Being non-G6PD deficient, he received maloprim for 7 doses. He was seen by a general practitioner earlier and was prescribed amoxicillin/clavulanate for an upper respiratory tract infection. As 1 of his fellow servicemen had a bout of chickenpox recently, he was subsequently admitted for possible varicella infection with concomitant drug allergy.

On admission, his temperature was 39.1°C, blood pressure was 120/70 mm Hg and heart rate was 70 beats per minute. There was no periorbital oedema, but he had bilateral conjunctivitis. No oral lesions or cervical lymphadenopathy were found. He had an exanthematous rash on his trunk and limbs without any vesicles. Cardiovascular, respiratory and abdominal examinations were normal. DHS was suspected and concurred by the dermatologist. Investigations revealed haemoglobin, 14.3 g/dL; leukocyte count, 9100/mm³ (polymorphs, 63.8%; lymphocytes, 20.8%; and eosinophils, 0.4%); and platelet count, 231,000/mm³. Total serum bilirubin was 27.3 µmol/L; alanine transaminase, 283 µL; aspartate transaminase, 118 µL; alkaline phosphatase, 297 µL; and serum albumin, 40 g/L. Skin biopsy was not attempted, but the patient was initiated on oral prednisolone 30 mg daily, full strength topical betamethasone cream twice daily and spersadexoline (chloramphenicol plus dexamethasone) eye drops 4 times daily in both eyes. His fever resolved on day 3 and he was discharged on day 6. On follow-up 2 months later, his liver function tests were normal, and his rash had subsided completely.

**Discussion**

Maloprim, comprising dapsone (diaminodiphenyl-sulphone) 100 mg and pyrimethamine (2,4-diamino-pyrimidine) 12.5 mg, is an effective chemoprophylactic agent against chloroquine-resistant *Plasmodium falciparum* in endemic areas, with a low estimated incidence of fixed drug eruption of about 1 in 4500 exposures in 1988. Provocation tests done locally on 11 national servicemen, with confirmed drug eruption from maloprim, have shown that the majority had reproducible skin reaction to dapsone, though 2 patients showed polysensitivity between dapsone and pyrimethamine. Furthermore, as little as dapsone 1 mg can provoke a positive reaction on challenge.

Dapsone was first synthesised in 1908, though its antibacterial properties were discovered in 1937. Its chief use is in leprosy, where it was called the “sheet anchor” in treatment of the disease. DHS was first noted by Lowe in 1949, where 12% of a series of 305 Nigerian leprosy patients developed a rash within 2 to 5 weeks of commencement of treatment. It was described as a glandular fever precipitated by sulphone therapy because of a rise in Paul Bunnell titre in affected patients. It is a rare severe infectious mononucleosis-like illness with exudative tonsillitis, lymphadenopathy and mononucleosis associated with prominent exfoliative dermatitis, hepatitis and eosinophilia. Occurring in the first 6 weeks of drug use, DHS was coined by Allday and Barnes in 1951. Maloprim causing the syndrome was initially described in 1988.

Hypersensitivity reactions to dapsone were common in the late 1940s and early 1950s, which were thought to be due to the large doses prescribed (300 mg dapsone per day). After a period of low incidence between 1970 and 1982, a second rise in cases was reported after 1982 during the implementation of multidrug therapy for leprosy. Nevertheless, true hypersensitivity reactions are not dose-related with regards to occurrence and severity. The problem is not solved by giving the drug in gradual increments. Furthermore, a small dose may be dangerous in a previously sensitised person. Small amounts of dapsone, when combined with ultraviolet light, were sufficient to trigger off the hypersensitive reaction. This is somehow further influenced by individuals with a probable genetic predisposition to developing the syndrome. Cutaneous manifestations in DHS may range from erythroderma, papuloerythematous eruptions, erythema multiforme, toxic epidermal necrolysis and the Stevens-Johnsons syndrome. The general consensus is that it is still an extremely safe drug, and hence its widespread use, though DHS is not as rare as previously thought; early onset and partial forms are
becoming more common. \[\text{13}\] Richardus and Smith \[\text{14}\] suggested the following criteria for the diagnosis of true dapsone hypersensitivity reaction:

1. Symptoms appearing within 8 weeks of commencement of dapsone and disappearing upon discontinuation of the drug.
2. Symptoms could not be ascribed to any other drug given simultaneously.
3. Symptoms not attributable to lepra reactions.
4. No other diseases liable to cause similar symptoms.

The reaction was classified as “dapsone syndrome” when, in addition, symptoms started between the 2nd and 8th week of treatment and at least 2 signs or symptoms: fever, skin eruption, lymphadenopathy and liver abnormalities (hepatomegaly, jaundice and/or deranged liver function tests).

A challenge administration of dapsone, after the original reaction had resolved, was not considered necessary due to the risks posed to patients.

Ageing and pre-existing liver disease may offer relative protection against adverse effects due to lower enzymatic activity. This leads to lower production of toxic metabolites. However, these are unproven factors. Biopsy of inflamed erythroderma skin has been reported to show predominantly mononuclear cell collections around adnexae and small blood vessels, but no leukocytosis or eosinophilia. \[\text{15}\] This was consistent with the skin biopsy of the patient described in case 1. Post-mortem histological examination of a dapsone and disappearing upon discontinuation of the drug.

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The 3 patients in our case series presented with a characteristic history of delayed drug rash mimicking a viral illness. They illustrate the clinical spectrum of the severity of DHS among military recruits, all with prior consultation by primary care physicians or army doctors. Possible mimicking diagnoses ranged from dengue fever and infectious mononucleosis to acute varicella zoster. Delayed recognition of the syndrome led to extensive investigations in the first 2 cases. A thorough drug history and duration of drug exposure helped in the diagnosis, supported by transaminitis on liver function test and a characteristic rash. Resolution of symptoms, rash and liver function abnormalities upon commencement of corticosteroids confirmed the diagnosis and mainstay of treatment. Failure to discontinue dapsone has been known to result in fatal outcome \[\text{17}\] and prolonged morbidity. Early initiation of systemic corticosteroid therapy is beneficial and alternative antimalarial chemoprophylaxis in military recruits should be offered.

**Conclusion**

DHS may masquerade as a virus-like illness, especially with its delayed pattern of drug-induced rash. A high index of suspicion must be present among primary care physicians, who are among the first points of contact with military personnel. Other common patient groups include leprosy patients on multidrug therapy and travellers on maloprim prophylaxis. Immediate discontinuation of the drug and early commencement of systemic corticosteroid are vital to decrease mortality and morbidity.

**REFERENCES**