

Presumed Dapsone-induced Drug Hypersensitivity Syndrome Causing Reversible Hypersensitivity Myocarditis and Thyrotoxicosis

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Abstract

Introduction: A 22-year-old Malay soldier developed dapsone hypersensitivity syndrome 12 weeks after taking maloprim (dapsone 100 mg/pyrimethamine 12.5 mg) for anti-malarial prophylaxis. **Clinical Picture:** He presented with fever, rash, lymphadenopathy and multiple-organ involvement including serositis, hepatitis and thyroiditis. Subsequently, he developed congestive heart failure with a reduction in ejection fraction on echocardiogram, and serum cardiac enzyme elevation consistent with a hypersensitivity myocarditis. **Treatment:** Maloprim was discontinued and he was treated with steroids, diuretics and an angiotensin-converting-enzyme inhibitor. **Outcome:** He has made a complete recovery with resolution of thyroiditis and a return to normal ejection fraction 10 months after admission. **Conclusion:** In summary, we report a case of dapsone hypersensitivity syndrome with classical symptoms of fever, rash and multi-organ involvement including a rare manifestation of myocarditis. To our knowledge, this is the first case of dapsone-related hypersensitivity myocarditis not diagnosed in a post-mortem setting. As maloprim is widely used for malaria prophylaxis, clinicians need to be aware of this unusual but potentially serious association.

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Case Report

A 22-year-old Malay soldier doing his National Service was warded with a 6-day history of an itchy generalised rash associated with fever and lymphadenopathy. Prior to this episode, he was well and not known to have any major illnesses. He had presented to his army doctor the previous week complaining of fever and abdominal pain and was prescribed Anarex[®] (orphenadrine/paracetamol) and hyoscine. He developed a rash a day after taking the above medication. On closer questioning, the patient revealed that he had also been taking maloprim (comprising dapsone 100mg and pyrimethamine 12.5 mg) for malaria prophylaxis for the past 12 weeks. On examination, he had a low-grade temperature of 37.5°C, with an erythematous papular rash with pustules involving the face, trunk and limbs. There was no oral or genital ulceration. In addition, there was tender inguinal and cervical lymphadenopathy. His heart

sounds were dual and the lungs were clear. There was no organomegaly or ascites.

Investigations revealed leukocytosis and eosinophilia (white cell count $14.8 \times 10^3/\mu\text{L}$, eosinophils 14%, haemoglobin 14.4 g/dL, platelets $297 \times 10^3/\mu\text{L}$) and hepatitis (total bilirubin 12.3 $\mu\text{mol/L}$, normal = 3 to 24 $\mu\text{mol/L}$; alkaline phosphatase 160 U/L, normal = 32 to 103 U/L; alanine transaminase 482 U/L, normal = 9 to 36 U/L; aspartate transaminase 143 U/L, normal = 15 to 33 U/L). Coagulation profile was unremarkable [PT 14.8 s, PTT 36 s]. Viral hepatitis markers (HBs Ag, anti-HAV IgM and anti-HCV) were negative. Renal function (creatinine 107 $\mu\text{mol/L}$) and urine microscopy were normal. Blood cultures were negative. Chest radiograph showed cardiomegaly with clear lung fields. Skin biopsy (Fig. 1) from the trunk revealed superficial perivascular dermatitis with eosinophils consistent with a drug eruption. There was mild acanthosis and

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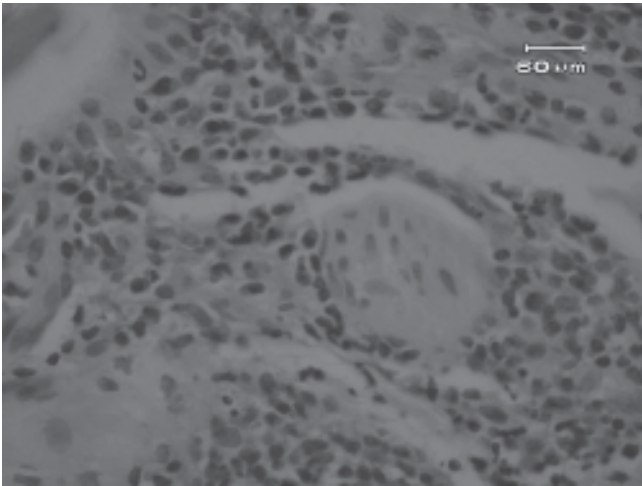


Fig. 1. Skin biopsy showing perivascular lymphocytic infiltrates with occasional polymorphs and eosinophils (haematoxylin and eosin; original magnification $\times 60$).

hyperkeratosis of the epidermis with no bulla present. The papillary dermis was oedematous and showed heavy lymphocyte infiltration with occasional polymorphs. Several eosinophils were present in the deep perivascular infiltrate. The clinical impression was dapsone hypersensitivity syndrome and he was started on prednisolone 40 mg per day, chlorpheniramine and cloxacillin.

Twelve days into admission, his condition deteriorated when he developed chest pain and breathlessness. Electrocardiogram showed sinus tachycardia with right bundle branch block configuration. Cardiac enzymes were elevated (creatinine kinase 4793 U/L, normal = 40 to 210 U/L; creatinine kinase-MB mass 72.58 ng/mL, normal = <5.0 ng/mL; troponin-T 4.150 ng/mL, normal = 0 to 0.1 ng/mL). Arterial blood gas showed hypoxaemia (pH 7.492, $p\text{CO}_2$ 27.1 mmHg, $p\text{O}_2$ 63.4 mmHg, HCO_3^- 20.3 mmol/L). Computed tomography (CT) pulmonary angiogram showed a right pleural effusion but did not demonstrate any evidence of pulmonary embolism. Two-dimensional trans-thoracic echocardiography showed a structurally normal heart. The left ventricle was moderately dilated. There was global hypokinesia with ejection fraction of 15%. The right ventricle was also dilated with impaired systolic function. 24-hour Holter monitoring was normal and the coronary angiography showed normal coronaries. A thyroid function was done because of tachycardia and he was found to be thyrotoxic (free serum thyroxine 43 pmol/L, normal = 10 to 20 pmol/L; thyroid stimulating hormone 0.008 mU/L, normal = 0.5 to 5.0 mU/L; thyroid stimulating hormone receptor antibody 0.5 IU/L, normal = 0-1.5 IU/L; thyroglobulin antibody 188.6 U/ML, normal = 0 to 60 U/ML; thyroid peroxidase antibody 115.2 U/ML, normal = 0-60 U/ML). Thyroid Tc-99m scan showed markedly reduced

uptake in both lobes in keeping with thyroiditis. Thyroid ultrasound showed normal echogenicity. A diagnosis of thyroiditis was made and he was treated with propylthiouracil 200 mg tds. He was managed in the medical intensive care unit, and continued on a daily dose of prednisolone 40 mg. The right-sided effusion and dyspnoea resolved with diuresis. His condition gradually improved with resolution of the fever and hepatitis. Steroids were tailed down over a period of 2 months. His rash resolved completely after 4 months.

A second 2-dimensional trans-thoracic echocardiography was performed 3 months after the index admission. This showed recovery of the left ventricular systolic function, with an ejection fraction of 50% to 55%. The left ventricle was still mildly dilated. However, there was resolution of the segmental wall motion abnormalities. The systolic function of the right ventricle was still impaired. He was started on perindopril 1 month after the onset of his illness. The final 2-dimensional trans-thoracic echocardiography done 10 months after his illness showed complete recovery of cardiac function. Both diastolic and systolic function had returned to normal. The left ventricular ejection fraction was 62% and the chambers were no longer dilated. Perindopril was stopped after 5 months. He is now well with no evidence of internal disease. His liver function has normalised. Propylthiouracil was discontinued after 5 months and his latest thyroid function test was normal (free serum thyroxine 12.05 pmol/L, thyroid stimulating hormone 3.459 mU/L).

In summary, the diagnosis of dapsone hypersensitivity syndrome was made based on the presence of fever, eosinophilia, lymphadenopathy, rash and multiple internal organ involvement including thyroiditis, myocarditis, hepatitis and serositis.

Discussion

Maloprim (comprising dapsone 100 mg and pyrimethamine 12.5 mg) is routinely administered as anti-malarial prophylaxis to soldiers in our local population training on off-shore islands who are not glucose-6-phosphatase deficient. Cases of hypersensitivity syndrome due to dapsone have been reported in Singapore^{1,2} but none of these previous patients had documented myocarditis. Thyroiditis manifesting as hypothyroidism has been reported, but is rare. This hypersensitivity reaction occurs in patients who are unable to detoxify reactive metabolites produced by thyroid peroxidase.³

Dapsone hypersensitivity syndrome (DHS) can be considered a manifestation of DRESS (drug rash with eosinophilia and systemic symptoms) syndrome and is an idiosyncratic multi-organ disease. It has a frequency of 0.2% to 0.5% in patients on dapsone therapy.⁴ Other drugs

frequently causing this syndrome include anticonvulsants, sulfonamide antibiotics, allopurinol and non-steroidal anti-inflammatory agents.⁵ It differs from other drug reactions in that it can begin after prolonged exposure to the offending agent, and can occur up to 6 months or more after exposure.⁵ However, it usually occurs during the first 3 to 8 weeks of daily therapy.¹

Clinical manifestations include a constellation of symptoms like fever, malaise, exfoliative dermatitis, hepatitis, haemolytic anaemia, lymphadenopathy and atypical lymphocytosis. Acute cholangitis,⁶ tonsillar membrane⁷ and Coombs' positive haemolytic anaemia¹ have also been reported. Although drug hypersensitivity-induced hypothyroidism has been reported,³ to our knowledge this is the first case of dapsone hypersensitivity thyroiditis manifesting as hyperthyroidism. In addition, there has only been one other reported case of dapsone hypersensitivity myocarditis, and this was diagnosed on post-mortem examination.⁸

Hypersensitivity myocarditis is a rare inflammatory disease of the myocardium resulting from an allergic reaction. Drugs that are most often implicated include alpha-methyldopa, sulfonamides and penicillins.^{9,10} In addition, cefaclor,¹¹ clozapine,¹² anticonvulsants¹³ and allopurinol¹⁴ have also been reported to cause hypersensitivity myocarditis. It is a rare clinical entity as its diagnosis is usually made retrospectively¹⁵ or post-mortem. The pathogenesis of drug-induced hypersensitivity myocarditis is still not well understood. It is believed to be a hypersensitivity reaction to the metabolites of the parent drug which serve as haptens. This elicits a complex immunological reaction that causes the hypersensitivity myocarditis.⁸

The diagnosis of hypersensitivity myocarditis is suggested in the presence of signs and symptoms of drug hypersensitivity (rash, fever and eosinophilia) associated with non-specific cardiac findings. These may include electrocardiographic changes, unexplained tachycardia or serum cardiac enzyme elevations.¹³ Clinically, the patient may present with symptoms of heart failure, electrocardiographic abnormalities such as non-specific ST-T changes or sinus tachycardia, arrhythmias or even sudden death.^{16,17}

An endomyocardial biopsy remains the gold standard for diagnosis of myocarditis.¹⁷ However, this is a highly invasive procedure which is not routinely performed. Other non-invasive strategies that may be used to identify myocarditis include antimyosin scintigraphy, contrast-enhanced magnetic resonance imaging and echocardiography. However, the diagnosis of myocarditis is still largely dependent on clinical suspicion rather than definitive diagnostic tests.¹⁷ In our patient, the diagnosis of

hypersensitivity myocarditis was made clinically, based on the presence of a drug hypersensitivity syndrome, associated with recent onset electrocardiogram changes, elevated serum cardiac enzymes and a structurally normal heart and normal coronaries with severe global hypokinesia.

The treatment of patients with DHS and hypersensitivity myocarditis is largely supportive. Early diagnosis and prompt withdrawal of the offending drug is essential. Although there have been no controlled studies on the use of corticosteroids in DHS, its use is recommended for patients with visceral involvement.¹⁸ If it is used, weaning doses over a period of 1 month are essential, as abrupt discontinuation may cause a relapse. This is because dapsone persists up to 35 days in organs via protein binding and enterohepatic circulation.⁵

Supportive care is also the first line of treatment for hypersensitivity myocarditis. Diuretics and angiotensin-converting-enzyme inhibitors may be used in heart failure, as well as a beta-blocker once the patient's cardiac status has stabilised. Digoxin should be used cautiously as it has been shown in a murine model of viral myocarditis to increase expression of proinflammatory cytokines and mortality.¹⁹ In severe cases, inotropic therapy or a ventricular assist device may be required.

The use of immunosuppressant therapy such as intravenous immunoglobulin or cyclosporin in myocarditis is controversial. Placebo-controlled trials have not shown such therapy to have beneficial effects.^{20,21} However, in some uncontrolled clinical studies, immunosuppressive agents have been shown to cause rapid resolution of the inflammatory component of cardiac disease.²²

Conclusion

In summary, we report a case of dapsone hypersensitivity syndrome with classical symptoms of fever, rash and multi-organ involvement including thyroiditis presenting as hyperthyroidism and a rare manifestation of myocarditis. To our knowledge, this is the first case of dapsone-related hypersensitivity myocarditis not diagnosed in a post-mortem setting. As maloprim is widely used for malaria prophylaxis, clinicians need to be aware of this unusual but potentially serious association.

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