Dapsone Hypersensitivity Syndrome with Myocarditis

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Abstract

Drug hypersensitivity with myocarditis is known to occur with many drugs especially with antiepileptics, sulpha-compounds and dapsone. Dapsone (4, 4 diamino diphenyl sulphone) induced hypersensitivity is known to occur in about 2% of leprosy patients on treatment and an incidence of 1.66% in non-leprosy patients. We report this rare case of dapsone hypersensitivity syndrome in a girl on dapsone who presented with fever, anaemia, jaundice, skin rash, lymphadenopathy, and hepatomegaly and later developed myocarditis. The drug was withdrawn and the patient was treated with steroids. She improved and was discharged. She relapsed after the corticosteroids were discontinued at home.

Introduction

The DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome is characterised by fever, eruptive rash and systemic symptoms including lymphadenopathy, hepatotoxicity, cardiac involvement and haematological abnormalities with anaemia and eosinophilia. It is a rare but potentially fatal complication of a number of drugs.

Hypersensitivity myocarditis is a rare condition characterised by inflammation of the myocardium secondary to a reaction. It is not frequently reported since the diagnosis is usually made on post mortem examination. Although rare, it has significant mortality.

Dapsone has been used for treatment of leprosy as well as many inflammatory skin conditions. Dapsone induced DRESS syndrome with hypersensitivity myocarditis is an unusual compication of treatment with high mortality. Symptoms generally begin between 3-8 weeks of commencing treatment but can occur after longer duration up to 6 months. In this article we present a case of dapsone induced DRESS syndrome with hypersensitivity myocarditis and review the literature concerning such cases.

Case Report

A 14 year old girl presented with history of moderate to high grade fever, erythematous rash over trunk and arms, noticing multiple swellings in the neck, yellowish discolouration of eyes, generalised weakness and easy fatigue. Patient gave history of taking dapsone for 10 weeks prior to admission which was started by her family physician for rash over her body which he clinically diagnosed as chronic urticaria. There was no histopathological confirmation of urticarial vasculitis.

On physical examination patient had fever of 102°F, tachycardia, normal blood pressure, icterus, cervical lymphadenopathy and hepatomegaly.

Lab results showed haemoglobin of 8.5 gm%, TLC of 7500 cells/cmm (61% lymphocytes, 39% neutrophils), serum bilirubin 5.6 mg%, direct fraction 4.8%, aspartate aminotransferase 392 U/L, alanine aminotransferase 501 U/L, alkaline phosphatase 242 U/L, a prolonged prothrombin time with INR 6.1 and hypoalbuminaemia. Blood tests were negative for hepatitis A, B, C, E, leptospirosis, dengue, malaria, typhoid and HIV. Routine urine examination was not suggestive of infection. Blood and urine cultures were sterile. Antinuclear antibody was negative. Mantoux test was negative. Abdominal ultrasound revealed mild hepatomegaly with bright echotexture. FNAC of cervical lymph node revealed reactive hyperplasia.
Provisional diagnosis of dapsone hypersensitivity syndrome was made based on history of taking dapsone, fever, rash, jaundice, anaemia, lymphadenopathy and hepatomegaly. Patient was started on treatment with intravenous methylprednisolone 1 gm daily for 3 days and showed a dramatic improvement. Later patient was put on oral steroids (wysolone) 1 mg/kg/day and was discharged after 4 days. She was told to continue her steroids and follow up at OPD level after 8 days.

About two weeks later patient presented to the emergency with acute onset fever, giddiness and breathlessness (grade 4 dyspnoea). Patient had taken oral steroids for one week and due to symptomatic improvement, stopped the steroids on her own. On physical examination, she was found to have desquamating rash and tachycardia of 170 beats/min with systolic blood pressure of 60 mmHg. Systemic examination revealed fine crepitations in bilateral infrascapular areas of the lung fields. ECG at admission showed a supraventricular tachycardia. ECHO revealed a mild pericardial effusion with a global LV systolic function of 40%. A provisional diagnosis of myocarditis with cardiogenic shock was made.

Patient did not revert to sinus rhythm even after two injections of adenosine and DC shock. She was started on dopamine infusion in view of hypotension. 1 g methylprednisolone was restarted intravenously in view of dapsone syndrome and myocarditis. Patient reverted to sinus rhythm the next day when systemic examination showed an S3 gallop. ECG showed sinus tachycardia with ST segment elevation in leads I, II, aVL, aVF and V2 to V6. Patient worsened over the next two days, developed multiple ventricular arrhythmias and a repeat ECHO revealed a 20% LV ejection fraction with global hypokinesia and clots in both ventricles.

Patient expired despite aggressive resuscitative measures. An endomyocardial biopsy could not be done as the relatives of the patient did not consent for the same. A final diagnosis of dapsone syndrome with myocarditis was made.

Discussion

Dapsone (4',4'-diaminodiphenylsulphone) is the parent compound of the sulphones. It has been used to treat a number of skin diseases including leprosy, dermatitis herpetiformis, erythema elevatum diutinum, linear immunoglobulin A dermatosis and the bullous eruption of systemic lupus erythematosus. It is an alternative treatment for urticarial vasculitis which is proven on biopsy. It is also used in the treatment of pneumocystis carinii pneumonia in HIV patients and in the prophylaxis of malaria along with pyrimethamine.

The anti inflammatory effects of dapsone are mainly associated with its interference with neutrophil chemotactic migration, adherence, and recruitment by inhibiting local production of toxic respiratory/secretory products and oxidants.

Dapsone is well absorbed from the gut and primarily metabolised through N-acetylation and N-hydroxylation. It is excreted by the kidney but has significant enterohepatic circulation. It has a long half life and may persist in the body for 30-35 days. This is important to keep in mind in case adverse reactions emerge after a long metabolite impact period.

Severe adverse reactions to dapsone and other sulphones include the characteristic hypersensitivity syndrome termed as ‘Dapsone Hypersensitivity Syndrome’. This syndrome has a frequency of 0.5 - 3%. It can be considered a manifestation of DRESS (drug rash with eosinophilia and systemic symptoms) syndrome and is an idiosyncratic multiorgan disease. Other drugs causing the DRESS syndrome include carbamazepine, phenobarbitone, phenytoin, sulphonamides, allopurinol, NSAIDs, ACE inhibitors, minocycline, penicillin, metronidazole and terbinafine.

This syndrome may begin as early as 7 to 10 days after administration of the drug or as late as six months in the case of therapy with dapsone. However, it normally occurs during the first 3 to 8 weeks of daily therapy. The syndrome presents with a combination of fever, exfoliative dermatitis, lymphadenopathy, jaundice secondary to hyperbiliarubinaemia which is due to haemolysis as well as hepatotoxicity, and eosinophilia. The severity of cutaneous changes does not necessarily reflect the severity of internal organ involvement; therefore careful assessment is necessary for patients with any drug associated eruptions associated with systemic symptoms.

Liver involvement displays mixed hepatocellular and cholestatic pattern hypoalbuninaemia seen in our patient is also a feature of dapsone hypersensitivity, which is probably due to binding of dapsone to circulating serum albumin. In addition there have been a few cases of dapsone hypersensitivity myocarditis, some of which were diagnosed on post mortem examination. The 10% mortality rate associated with DRESS syndrome is usually secondary to hepatotoxicity or myocarditis.

The underlying mechanisms causing dapsone syndrome are poorly understood. Defective detoxification of reactive oxidative metabolites and a genetic predisposition have been implicated in the pathophysiology of this syndrome, as has slow acetylator status. A role of viral co-infection is also suspected, specifically, a reactivation of the human herpes virus 6 (HHV 6).
Hypersensitivity myocarditis is a rare inflammatory disease of the myocardium resulting from an allergic reaction. Drugs that are most often implicated include alpha methylbopa, sulphonamides and penicillins, cefaclor, clozapine, anticonvulsants and allopurinol. It is a rare clinical entity as its diagnosis is usually made retrospectively or on post mortem. The pathogenesis is still not well understood. It is believed to be a hypersensitivity reaction to metabolites of the parent drug which serve as haptens. This elicits a complex immunological reaction that causes hypersensitivity myocarditis.

The diagnosis of hypersensitivity myocarditis is suggested by the presence of signs and symptoms of drug hypersensitivity (rash, fever, eosinophilia) associated with non specific cardiac findings. These may include ECG changes, unexplained tachycardia or serum cardiac enzyme elevations. Clinically the patient may present with symptoms of heart failure, ECG abnormalities such as non specific ST-T changes or sinus tachycardia, arrhythmias or even sudden death. An endomyocardial biopsy remains the gold standard for diagnosis of myocarditis. However this is a highly invasive procedure which is not routinely performed. Other non invasive strategies include antmyosin scintigraphy, contrast enhanced MRI and echocardiography. However, the diagnosis of myocarditis is still largely dependent on clinical suspicion rather than definitive diagnostic tests. In our patient the diagnosis of hypersensitivity myocarditis was made clinically based on the presence of drug hypersensitivity syndrome, associated with recent ECG changes and echocardiographic findings of global hypokinesia and clots in both ventricles.

Cardiac involvement is an unusual presentation of Dapsone induced DRESS syndrome. Very few cases have been reported in literature. The details of the cases are presented in Table 1.

DRESS syndrome and hypersensitivity myocarditis must be promptly recognised and all potential offending drugs should be withdrawn. Although there have been no controlled studies in the use of corticosteroids in dapsone hypersensitivity syndrome, its use has been recommended for patients with visceral involvement. When used corticosteroids should be slowly tapered over a period of one month, as abrupt cessation may cause a relapse. This is because dapsone persists for up to 35 days in organs via protein binding and enterohepatic circulation.

Supportive care is also the first line of treatment for hypersensitivity myocarditis. Diuretics and ACE-inhibitors may be used in heart failure.

The use of immunosuppressant therapy such as intravenous immunoglobulin or cyclosporine in myocarditis is controversial. Placebo- controlled trials have not shown such therapy to have beneficial effects.

### Conclusion

In summary we present this case of dapsone hypersensitivity syndrome who had fever, rash and multiorgan involvement. She was started on steroids but had a relapse of the syndrome with myocarditis when she stopped steroids on her own after 2 weeks. The myocarditis was diagnosed clinically based on presence of tachycardia, electrocardiography changes and echocardiography findings. Clinicians should be aware of this unusual but potentially fatal complication of dapsone therapy. There should be a clear justification for the use of dapsone in the treatment of various dermatological conditions. The diagnosis should always be confirmed histopathologically prior to commencement of treatment. In patients with urticaria, it should be used only as an alternative treatment in cases of urticarial vasculitis proven by biopsy.

### References

1. Wei-Hsuan Li, Han-Nan Liu, Ding-Dar Lee. Myocarditis in Dapsone induced drug reaction with eosinophilia and systemic symptoms. A


