case report and review of the literature

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A B S T R A C T
Dapsone (4,4′-diaminodiphenylsulfone) has been used for a variety of dermatological conditions. Dapsone-induced drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare but severe drug reaction characterized by fever, cutaneous eruption, and systemic involvement. We present a case of dapsone-induced DRESS, which resulted in fever, maculopapular eruptions progressing to exfoliative dermatitis, cervical lymphadenopathy, transaminitis, and hypersensitivity myocarditis resulting in congestive heart failure. This patient was withdrawn from dapsone and treated with systemic corticosteroids, but he finally passed away despite aggressive intensive care. We report this rare case and review the literature concerning DRESS with cardiac involvement.

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Introduction
Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare but severe drug reaction characterized by fever, skin eruption, and systemic involvement, including lymphadenopathy, abnormal liver function, renal impairment, pulmonary or pericardial infiltrates, and hematologic abnormalities, mainly hyper-eosinophilia and lymphocytosis. Symptoms typically begin between 2 weeks and 6 weeks after initiation of drug therapy and mostly subside after discontinuing the drug.1 However, potentially life-threatening events have been reported. The 10% mortality rate associated with DRESS is usually secondary to hepatotoxicity or myocarditis.2

Dapsone is the drug of choice for treatment of leprosy and dermatitis herpetiformis and can be used for various kinds of inflammatory skin diseases. Dapsone-induced DRESS with myocarditis is a rare but potentially fatal complication. In this article, we present a case of dapsone-induced DRESS with hypersensitivity myocarditis and review previous reports of dapsone-induced DRESS with cardiac involvement.

Case report
A 33-year-old man presented with fever, malaise, multiple oral ulcers, and generalized itchy erythematous maculopapular rash with scaling on the face, trunk, and limbs for 3 weeks (Figure 1). He had received dapsone 100 mg daily for 6 weeks because of chronic refractory urticaria. Dapsone-related drug eruption was suspected, and dapsone was therefore discontinued. Topical clobetasol cream and oral prednisolone (30 mg/d) were given in another medical setting but did not alleviate his symptoms. Then, he was transferred to our hospital.

On admission, his body temperature was 38.7°C, blood pressure 86/52 mmHg, and heart rate 135 beats/min. Other physical examinations of cardiovascular and respiratory system were unremarkable. Bilateral cervical lymphadenopathy was palpable. His skin biopsy showed spongiosis, necrotic keratinocytes, and a dense perivascular inflammatory infiltrate of lymphohistiocytes and eosinophils (Figure 2). Laboratory investigations revealed hemoglobin, 13.9 g/dl (normal range: 14–18 g/dl); platelet count, 495,000/μL (normal range: 150,000–450,000/μL); leukocyte count, 17,700/μL (eosinophil, 10%); total serum bilirubin, 0.3 mg/dl (normal range: 0.2–1.6 mg/dl); aspartate aminotransferase, 226 U/L (normal range: 0–40 U/L); and alanine aminotransferase, 252 U/L (normal range: 5–45 U/L). Hepatitis B surface antigen, hepatitis C virus antibody, anti-dsDNA, antimitochondrial antibody, anti-Jo-1 antibody, and extractable nuclear antigen were tested to rule out viral and autoimmune hepatitis. The workup was all negative. Subsequent laboratory studies for systemic infection, including cytomegalovirus (CMV), Epstein-Barr virus (EBV), toxoplasma, herpes simplex virus, and HIV, were all negative. Intravascular hydrocortisone 150 mg daily was then given under the impression of DRESS. However, the patient developed chest pain and dyspnea 1 week after admission. Cardiac ischemic change was detected by
abnormal electrocardiogram (ST elevation in leads V1, V2, and T-wave inversion in V3–V6) and elevated cardiac enzyme (creatinine kinase, 1074 U/L (normal range: 40–210 U/L)). Troponin-I level was 13.43 ng/mL (<1.5 ng/mL). The echocardiography revealed generalized hypokinesia and markedly declined left ventricular ejection fraction (from 64% to 11%). The patient’s coronary angiography demonstrated patent coronary arteries. The endomyocardial biopsy revealed organizing endomyocarditis with eosinophilic infiltration (Figure 3). His condition deteriorated rapidly, and he passed away despite aggressive intensive care and extracorporeal membrane oxygenation support.

Discussion

Dapsone (4,4′-diaminodiphenylsulfone) is the parent compound of the sulfones. It has a history of more than a century and remains a powerful therapeutic tool for many 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 chronic idiopathic urticaria.

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. There have been reported dapsone-induced adverse effects, including hemolysis, agranulocytosis, methemoglobinemia, hepatobiliary damage, and cutaneous involvement (morbilliform eruptions, erythema multiforme, exfoliative dermatitis, or toxic epidermal necrolysis). The definition of DRESS was proposed by Bocquet et al as fever with eosinophilia, skin rash, and multisystemic involvement in 1996. It is a rare but serious drug reaction with delayed onset, variable clinical presentation, and prolonged course. Various groups of drugs are emerging as culprits of DRESS, including aromatic anticonvulsants, antidepressants, sulfones, sulfonamides, allopurinol, nonsteroidal anti-inflammatory drugs, anti-infective agents (minocycline, penicillin, metronidazole, terbinafine), angiotensin-converting enzyme inhibitors, and β-blockers. Aromatic anticonvulsants and sulfonamides are the most common culprit drugs inducing DRESS. The interval between first drug exposure and symptoms is usually 2–4 weeks but has been reported in individuals receiving anticonvulsants for 3 months. Cutaneous manifestations in DRESS can be presented as facial edema, maculopapular eruptions, or exfoliative dermatitis. Multivisceral involvement may be manifested as lymphadenopathy, hepatitis, cholangitis, renal toxicity, pneumonitis, myoccarditis, pericardial effusion, thyroiditis, and cerebral edema. Hematological abnormalities include hypereosinophilia and lymphocytosis with large, activated, and sometimes atypical, circulating lymphocytes.

DRESS has been associated with considerable morbidity and mortality, which is 10% if unrecognized and untreated. The pathogenesis of DRESS still remains unclear, but it is likely to involve a complex interaction of many factors, including genetics, immunology, individual metabolic difference in the production and detoxification of reactive metabolites, and reactivation of latent viruses of the human herpes virus (HHV) family, including HHV-6, CMV, EBV, and HHV-7. Our patient had negative serologies for CMV and EBV. HHV-6 and HHV-7 serologies were not tested.

DRESS with myocardial involvement has been induced by various drugs, such as antibiotics (sulfonamides and penicillins), anticonvulsants, diuretics, allopurinol, and antipsychotic agents. Cardiac involvement is an unusual presentation of dapsone-induced DRESS. To date, only three cases of DRESS with cardiac involvement were documented at the time of this literature review (Table 1). The total four cases, including our case, were Asians (3 Chinese and 1 Malaysian). Including our patient, there were three cases manifested as hypersensitivity myocarditis combined with fever, skin rash, and transaminitis. The other one case presented as complete atrial-ventricular block and had episodes of syncope. One case of myocarditis was diagnosed with postmortem histological examination. Despite systemic corticosteroids treatment, intensive care, and immediate withdrawal of dapsone, two of them eventually died. Clinicians should be vigilant for the possibilities of hypersensitivity myocarditis when the signs and symptoms of drug hypersensitivity coexist with nonspecific cardiac findings, such as unexplained tachycardia, electrocardiographic changes, and elevations of cardiac enzymes. An endomyocardial biopsy remains the golden standard for diagnosis of myocarditis. Many factors, including delayed endomyocardial biopsy and inadequate sampling, contributed to underestimation of hypersensitivity myocarditis.

DRESS must be promptly recognized and all potential culprit drugs should be withdrawn. Although controlled clinical trials regarding the effectiveness of corticosteroids in DRESS are lacking, it is recommended for patients with life-threatening visceral manifestations. The recommended dose of corticosteroids is 0.5–1 mg/kg/d. Because dapsone is found to persist in the body for up to 35 days because of protein binding and enterohepatic recirculation, slow tapering of corticosteroids over at least 1 month with close monitoring of organ function is required. When the skin rash results in exfoliative dermatitis, supportive care consists of warming the environmental temperature and using local antiseptics and topical corticosteroids. If the erythroderma is severe, clinicians should be vigilant for the development of cardiac failure in elderly patients or those with prior cardiac disease.

Dapsone-induced DRESS with hypersensitivity myocarditis is a rare but potentially fatal adverse reaction. Patients treated with

![Figure 3](Image 48x546 to 289x727)

**Figure 3** Endomyocardial biopsy demonstrates endocardial fibrosis with infiltrate of lymphohistiocytes and eosinophils (hematoxylin and eosin, original magnification ×400).

### Table 1: Cases of dapsone-induced DRESS syndrome with cardiac involvement in the literature.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/sex</th>
<th>Race</th>
<th>Interval (wk)</th>
<th>Clinical presentations</th>
<th>Management</th>
<th>Outcomes</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>71/M</td>
<td>Chinese</td>
<td>8</td>
<td>Fever, jaundice, hepatomegaly, transaminitis, acute renal failure, pleural effusion, myocarditis, and hypereosinophilia</td>
<td>Withdraw dapsone, intensive care</td>
<td>Expired</td>
<td>Lau et al.1</td>
</tr>
<tr>
<td>2</td>
<td>22/M</td>
<td>Malaysian</td>
<td>12</td>
<td>Fever, rash, lymphadenopathy, hypereosinophilia, thyroiditis, serratosis, hepatitis, hypersensitivity myocarditis, and congestive heart failure</td>
<td>Withdraw dapsone, prednisolone 40 mg/d, intensive care</td>
<td>Recovery</td>
<td>Teo et al.18</td>
</tr>
<tr>
<td>3</td>
<td>45/F</td>
<td>Chinese</td>
<td>5</td>
<td>High fever, generalized maculopapular rash, complete atrial-ventricular block, two episodes of syncope</td>
<td>Methylprednisolone 320 mg/d</td>
<td>Recovery</td>
<td>Zhu et al.19</td>
</tr>
<tr>
<td>Our case</td>
<td>33/M</td>
<td>Chinese</td>
<td>6</td>
<td>Fever, exfoliative dermatitis, lymphadenopathy, transaminitis, hypersensitivity myocarditis, and congestive heart failure</td>
<td>Withdraw dapsone, prednisolone 30 mg/d, then hydrocortisone 150 mg/d, intensive care</td>
<td>Expired</td>
<td>Present study</td>
</tr>
</tbody>
</table>
dapsone for various indications are required to be monitored carefully for the development of DRESS.

References