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CLINICAL REPORT

Six-year Retrospective Review of Drug Reaction with Eosinophilia and Systemic Symptoms

Pranee WONGKITISOPHON, Kumutnart CHANPRAPAPH, Ploysyne RATTANAKAEMAKORN and Vasanop VACHIRAMON
Division of Dermatology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare, severe adverse drug reaction. The aim of this study was to characterize the aetiology, clinical features, laboratory findings, and management of patients with DRESS, diagnosed from January 2005 to April 2010 in a tertiary centre in Thailand. Twenty-seven patients were included in the study with a mean age of 52 years. Phenytoin, allopurinol, and nevirapine were the most commonly implicated medications. Mean duration of drug administration before the onset of symptoms was 34 days. The latent period was longer for allopurinol (103 days) and shorter for nevirapine (10 days). Skin rash was seen in all patients, while fever and lymphadenopathy were found in 88.9% and 22.2%, respectively. Hepatic and haematological involvement were the two most common systemic complications, occurring in 96.3% and 85.2%, respectively. Most patients were treated with systemic corticosteroids, for a mean duration of 49 days. The mortality rate in this study was 3.7%. Early detection and discontinuation of the suspected drug are the key steps of management. ***Key words: drug reaction with eosinophilia and systemic symptoms; drug hypersensitivity; adverse drug reaction.***

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Vasanop Vachiramon, Division of Dermatology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, 270 Rama VI Road, Rajthevi, Bangkok 10400, Thailand. E-mail: vasanop@gmail.com

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe idiosyncratic adverse drug reaction with multiple-organ involvement, which was first described by Bocquet et al. in 1996 (1). The onset of symptoms usually occurs 2–8 weeks after drug administration, which is longer than for other drug reactions. Common clinical manifestations and laboratory findings include fever, cutaneous eruption, facial oedema, lymphadenopathy, peripheral eosinophilia, atypical circulating lymphocytes, and abnormal results of liver function tests (2, 3). Other systemic manifestations include pneumonitis, pancreatitis, renal failure, and neurological symptoms. A number of studies have suggested a relationship between human herpes virus 6 (HHV-6) and the development of DRESS (4–8). Numerous medications have been described in case reports and case series to cause DRESS, including anticonvulsants (carbamazepine, phenytoin, phenobarbital), dapsone, mexiletine, salazosulfapyridine, allopurinol, and antimicrobials (anti-tuberculous drugs, minocycline, trimethoprim-sulfamethoxazole) (9). The aim of this study was to review the clinical presentations, laboratory and pathological findings, and prognosis of all patients with DRESS in a tertiary centre in Thailand.

METHODS

The medical records of 27 patients with DRESS treated at the Ramathibodi Hospital, Mahidol University from January 2005 to April 2010 were retrospectively reviewed. Diagnosis was based on clinical presentation, including skin rashes after starting the suspected drug, fever, lymphadenopathy and systemic involvement (e.g. hepatitis, eosinophilia, atypical lymphocytosis, pneumonitis, renal failure, etc.). We used the diagnostic criteria proposed by the European Registry of Severe Cutaneous Adverse Drug Reactions (RegiSCAR) (Table I) (10). The normal range of lymphocyte count was defined as 1,500/μl to 4,000/μl and the normal range of platelet count was $150–450 \times 10^3$/μl. Eosinophilia was defined as absolute eosinophil count more than 700/μl or above 10% if the leukocyte count was lower than 4,000/μl. Atypical lymphocytosis was considered if the atypical lymphocyte count was more than 5%. Hepatic involvement was defined as an elevated level of serum alanine aminotransferase (ALT) two times the upper normal limit, or two times the patients' baseline levels. Renal involvement was considered when patients experienced deterioration of renal function of more than twice the normal values or developed recent onset of haematuria or proteinuria. Pulmonary insult associated with drug reaction was anticipated when there was a new onset of dyspnoea or abnormal chest radiographs. In addition, the scoring system for classifying DRESS had been used (10). Laboratory investigations (e.g. antinuclear antibody, blood culture, hepatitis virus serology, and mycoplasma titre) had been carried out in doubtful cases in order to exclude other potential causes. For identification of

Table I. *Inclusion criteria for potential cases of drug reaction with eosinophilia and systemic symptoms (DRESS) by RegiSCAR (10)*

Hospitalization
Reaction suspected to be drug-related
Acute skin rash*
Fever above 38ºC*
Enlarged lymph nodes in at least two sites*
Involvement of at least one internal organ*
Blood count abnormalities
• Lymphocytes above or below the laboratory limits*
• Eosinophils above the laboratory limits*
• Platelets below the laboratory limits*

*3 or more required.

offending drugs, the criteria of Naranjo et al. (11) were used for determination of causality for DRESS. Moreover, patients were excluded if there were signs of epidermal necrosis.

RESULTS

Demographics

From January 2005 to April 2010, a total of 27 cases diagnosed as DRESS were identified (14 males, 13 females; age range 23–81 years, mean age 52 years) (Table II).

Aetiology

The criteria proposed by Naranjo et al. (11) were used to identify the culprit drugs. The most common culprits were phenytoin, allopurinol, and nevirapine (Fig. 1). Three cases were classified as uncertain because multiple medications (including isoniazid, rifampicin, ethambutol, pyrazinamide, and unknown herbal medicine) had been taken concurrently. The mean time of diagnosis of DRESS was 34 days (range 2–180 days) after commencement of the drug. The mean onset of nevirapine group was 10 days (range 5–25 days). There were 4 patients with allopurinol sensitivity, all of whom had been taking allopurinol consistently, the mean onset was 103 days (range 15–180 days), which was longer than for other drugs.

Clinical features and laboratory findings

According to the RegiSCAR score, all patients had a score of 5 or more. Regarding the rash morphology, all patients had maculopapular rash involving more than 50% of their body surface area (Fig. 2a). One patient had

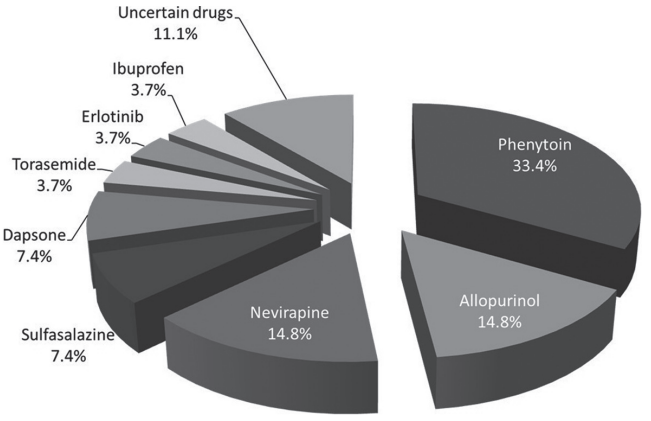

Fig. 1. Drugs causing DRESS in this study.

multiple pustules co-existing with maculopapular rash. Four patients (14.8%) later developed erythroderma. The rash usually began on the trunk and progressed to the extremities and the face. Facial oedema was observed in 20 patients (74.1%) and one patient had swelling of both hands. Itch was observed in 19 patients (70.4%). Five patients (18.5%) had at least one area (oral, ocular) of mucosal involvement. Fever and lymphadenopathy was present in 88.9% and 22.2% of patients, respectively. Hepatomegaly was present in 7.4% of patients.

Hepatic involvement was seen in 96.3% of patients; this is the most common systemic involvement. Among those with hepatic involvement, the mean serum alanine aminotransferase and aspartate aminotransferase are 188 IU/l (range 132–1708 IU/l) and 132 IU/l (range 89–857 IU/l), respectively. Hyperbilirubinaemia was found in 9 patients (33.3%) with a mean serum total bilirubin of 32.7 μmol/l (range 18.9–244.2 μmol/l).

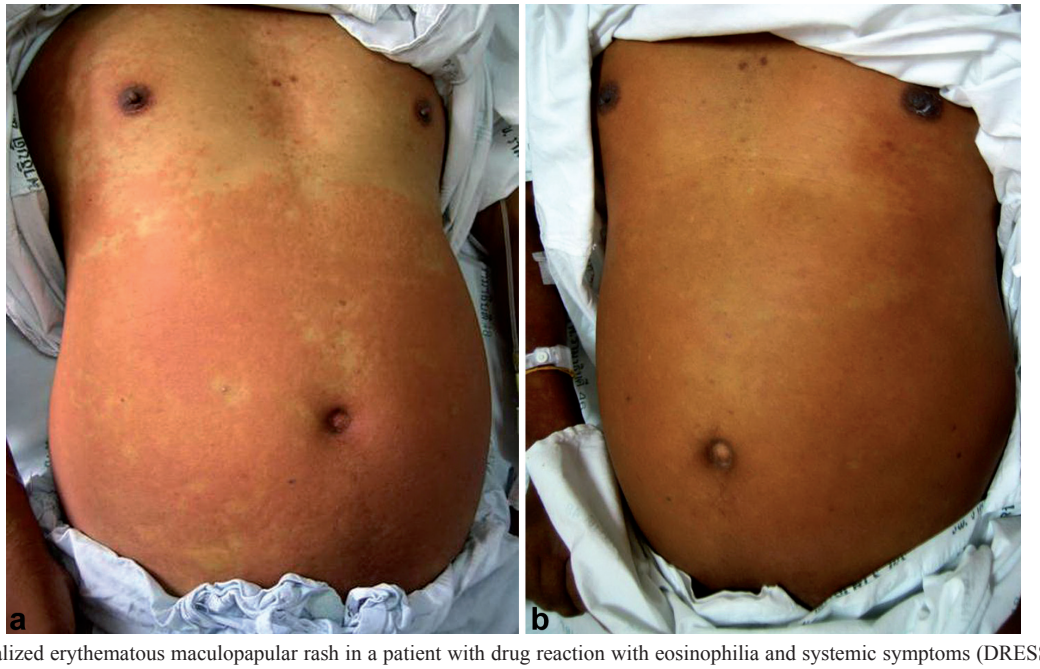

Fig. 2. (a) Generalized erythematous maculopapular rash in a patient with drug reaction with eosinophilia and systemic symptoms (DRESS). (b) Ten days after discontinuation of culprit drug, and administration of systemic corticosteroids.

Table II. *Patient data (demographics, underlying diseases, drug exposure, onset of symptoms, clinical and laboratory findings, and European Registry of Severe Cutaneous Adverse Drug Reactions (RegiSCAR) score)*

No.	Age (years) Sex	Underlying disease(s)	Medication(s) taken at the time of onset of DRESS and duration between initiation and DRESS	Clinical and laboratory findings	RegiSCAR score
1	66 F	Cerebral infarction, diabetes, hypertension	Phenytoin* (29 days) Aspirin (1.5 years) Enalapril (2 years) Glipizide (3.5 years) Metformin (4 years)	Fever, MP rash (80% BSA), hepatitis, eosinophilia, thrombocytopaenia	6
2	50 M	Rheumatoid arthritis	Sulfasalazine* (39 days) Methotrexate (6 months) Celecoxib (6 months)	Fever, MP rash (60% BSA), hepatitis, eosinophilia, lymphocytosis	6
3	39 F	Epilepsy	Phenytoin* (41 days)	Fever, MP rash, erythroderma (90% BSA), hepatitis, pancreatitis, atypical lymphocytosis	6
4	52 F	Epilepsy	Phenytoin* (7 days)	Fever, MP rash (70% BSA), hepatitis, eosinophilia, lymphopaenia	6
5	29 M	Viral meningitis	Phenytoin* (48 days)	Fever, MP rash (70% BSA), hepatitis, eosinophilia	6
6	66 F	No underlying disease	Chinese herbal medicine* for supplement (7 days)	MP rash (80% BSA), hepatitis, eosinophilia	5
7	61 M	Asymptomatic hyperuricaemia, Hypertension, dyslipidaemia	Allopurinol* (15 days) Losartan (3 years) Simvastatin (3 years)	Fever, MP rash, erythroderma (90% BSA), hepatitis, eosinophilia, lymphocytosis	6
8	41 M	Intracerebral haemorrhage, hypertension	Phenytoin* (16 days) Amlodipine (9 months)	Fever, MP rash (60% BSA), lymphadenopathy, hepatitis	5
9	56 M	Pulmonary tuberculosis	Anti-tuberculous drugs* (isoniazid, rifampicin, ethambutol, pyrazinamide) (19 days)	Fever, MP rash (60% BSA), hepatitis, pneumonitis, eosinophilia, lymphopaenia	6
10	23 M	Pulmonary tuberculosis	Anti-tuberculous drugs* (isoniazid, rifampicin, ethambutol, pyrazinamide) (33 days)	Fever, MP rash (70% BSA), hepatitis, eosinophilia, lymphopaenia	6
11	39 F	HIV infection	Zidovudine, lamivudine, nevirapine* (7 days)	Fever, MP rash (80% BSA), hepatitis, eosinophilia, lymphopaenia	6
12	63 M	Non-small cell lung cancer, hypertension	Erlotinib* (33 days) Atenolol (20 months)	Fever, MP rash, pustules, erythroderma (90% BSA), hepatitis, eosinophilia	6
13	49 M	Meningioma	Phenytoin* (30 days)	Fever, MP rash, erythroderma (90% BSA), hepatitis, eosinophilia, lymphopaenia	6
14	53 F	HIV infection	Zidovudine, lamivudine, nevirapine* (9 days)	Fever, MP rash (80% BSA), lymphadenopathy, hepatitis, nephritis	6
15	43 F	Carpal tunnel syndrome, History of skin rashes from over-the-counter analgesics	Ibuprofen* (2 days)	Fever, MP rash (60% BSA), lymphadenopathy, hepatitis, atypical lymphocytosis	6
16	81 M	Asymptomatic hyperuricaemia, hypertension	Allopurinol* (180 days) Amlodipine (5 years)	Fever, MP rash (70% BSA), hepatitis, eosinophilia, lymphopaenia	6
17	72 F	Intracerebral haemorrhage, hypertension, dyslipidaemia	Phenytoin* (19 days) Enalapril (3 years) Simvastatin (3 years)	Fever, MP rash (80% BSA), lymphadenopathy, hepatitis	5
18	54 M	Gouty arthritis, dyslipidaemia	Allopurinol* (38 days) Colchicine (3 months) Celecoxib (3 months), Rosuvastatin (14 months)	Fever, MP rash (70% BSA), hepatitis, pneumonitis, atypical lymphocytosis, lymphopaenia	6
19	71 M	Gouty arthritis, hypertension	Allopurinol* (180 days) Diltiazem (2.5 years)	MP rash (60% BSA), hepatitis, eosinophilia, lymphopaenia	5
20	32 F	HIV infection	Zidovudine, lamivudine, nevirapine* (20 days)	Fever, MP rash (80% BSA), hepatitis, eosinophilia, lymphopaenia	6
21	75 F	Subarachnoid haemorrhage	Phenytoin* (36 days)	Fever, MP rash (70% BSA), hepatitis, eosinophilia, lymphopaenia	6

Table II contd.

22	29 M	HIV infection	Zidovudine, lamivudine, nevirapine* (5 days)	Fever, MP rash (60% BSA), eosinophilia, atypical lymphocytosis, lymphopaenia	6
23	36 F	SLE, cutaneous vasculitis	Dapsone* (11 days) Hydroxychloroquine (8 months) Prednisolone (8 months)	Fever, MP rash (70% BSA), lymphadenopathy, hepatitis, atypical lymphocytosis	5
24	56 M	Rheumatoid arthritis, dyslipidaemia	Sulfasalazine* (29 days) Methotrexate (6 months) Celecoxib (6 months) Rosuvastatin (3.5 years)	Fever, MP rash (70% BSA), lymphadenopathy, hepatitis, nephritis	6
25	56 M	Cirrhosis, furosemide and spironolactone allergy	Torasemide* (3 days) Lactulose (1.5 years)	MP rash (60% BSA), hepatitis, eosinophilia, lymphopaenia	5
26	32 F	SLE with cutaneous vasculitis	Dapsone* (69 days) Hydroxychloroquine (4 months) Prednisolone (6 months) Azathioprine (6 months)	Fever, MP rash (80% BSA), hepatitis, eosinophilia, lymphopaenia	5
27	71 F	Primary brain lymphoma	Phenytoin* (49 days)	Fever, MP rash (70% BSA), hepatitis, eosinophilia, lymphopaenia	6

*Culprit drug.
BSA: body surface area; HIV: human immunodeficiency virus; SLE: systemic lupus erythematosus; F: female; M: male; DRESS: drug reaction with eosinophilia and systemic symptoms; MP rash: macolupapular rash.

Haematological abnormalities were found in 85.2% of cases (eosinophilia 70.4%, lymphocytosis 7.4%, lymphopaenia 51.9%, atypical lymphocytosis 18.5%, and thrombocytopaenia 3.7%). Renal and pulmonary involvement were both seen in 7.4% of cases. One patient was screened for HHV-6 reactivation in serum, the result was negative.

Skin biopsy was carried out in three patients. All specimens showed various degrees of superficial and deep perivascular infiltration with lymphocytes and eosinophils without evidence of vasculitis. Epidermal changes include focal spongiosis and focal vacuolar change.

Treatment and outcome

In all patients, the causative drug was discontinued. Twenty-three patients (85.2%) were treated with systemic corticosteroids, whereas the remaining 4 received supportive therapy. Among those who were treated with systemic steroids, either intravenous dexamethasone (15–20 mg/day) or oral prednisolone (0.5–0.7 mg/kg/day) was administered. Twelve patients were commenced on a regimen of intravenous dexamethasone with subsequent switch to oral prednisolone once the clinical picture improved. Overall, the mean duration of treatment was 49 days (range 3–520 days). After discontinuation of causative agents and treatment with systemic corticosteroids, the fever usually subsided within 2 days (1–10), the rash lasted for a mean of 10 days (range 2–117 days) (Fig. 2b) and the abnormal liver function test persisted for a mean of 33 days (range 20–65 days).

Five patients (18.5%) experienced a flare of DRESS during tapering of systemic steroids. All patients experienced recurrence of the rash, which responded to an increase in the dose of systemic steroids. Twenty-one patients (77.8%) recovered without complications. Five patients developed late complications (2 telogen effluvium, 1 adrenal insufficiency, 1 renal failure, and 1 respiratory insufficiency), with complete recovery during 6 months follow-up. One patient, who was allergic to sulfasalazine, died from multi-organ failure and sepsis. The mortality rate in this study was 3.7%.

DISCUSSION

DRESS is an uncommon idiosyncratic adverse drug reaction characterized by skin rash, fever, lymphadenopathy, and multisystemic involvement (e.g. hepatic, pulmonary, renal, and haematological abnormalities) (2). The incidence of DRESS is estimated as 1:1000 to 1:10,000 exposures to drugs (12).

We present here the largest case series of DRESS in Thailand. The most common causative drug in our study was phenytoin (33.4%), which is consistent with an earlier report (2). An inability to detoxify the toxic arene oxide metabolites has been implicated in the pathoge-

nesis of DRESS induced by anti-epileptic drugs. Cross-reactivity among aromatic anticonvulsants (phenytoin, phenobarbital, and carbamazepine) is well documented (13). Thus, avoidance of all aromatic anticonvulsants is highly recommended in cases with hypersensitivity to any particular agent. After the resolution of DRESS, levetiracetam or valproic acid were substituted for phenytoin without recurrence.

The second most common causes of DRESS in our study were allopurinol (14.8%) and nevirapine (14.8%). The high incidence of allopurinol-induced DRESS is similar to previous reports from Taiwan (14). This may be due to a common practice of giving allopurinol for asymptomatic hyperuricaemia in Thailand and a higher prevalence of HLA-B*5801 among Asians, which is associated with allopurinol-induced severe cutaneous adverse reactions (15, 16). Interestingly, nevirapine was another common cause of DRESS in our study. Four patients diagnosed with nevirapine-induced DRESS initially received three combined antiretroviral drugs; zidovudine, lamivudine and nevirapine. Patch-testing and the lymphocyte transformation test were not performed herein; thus, it was difficult to determine the exact culprit drug. Nevertheless, after discharging all drugs, each patient returned to their normal status. Despite zidovudine and lamivudine re-administration together with the addition of efavirenz as a substitution for nevirapine, patients did not develop recurrence. Thus, we made an assumption that nevirapine was the offending drug. A predisposition to nevirapine hypersensitivity is associated with HLA-DRB1*0101 (17). However, we did not perform HLA screening in these patients. There were two patients who had allergy to anti-tuberculous drugs (isoniazid, rifampicin, ethambutol, and pyrazinamide). However, it is difficult to determine the culprit drug, because all of them had been taken at the same time. After DRESS subsided, these two patients were treated with second-line anti-tuberculous drugs (levofloxacin, amikacin, and ethionamide) without recurrence of DRESS.

The mean onset of DRESS in our study was 34 days (range 2–180 days). Interestingly, this was longer than anticipated due to the delay onset of allopurinol hypersensitivity (mean 103 days). Therefore, elderly patients with multiple comorbidity should receive a complete assessment and review of medical records for up to 6 months to avoid overlooking any drug reaction to allopurinol. On the other hand, nevirapine causes rapid induction of DRESS, mean 10 days. Thus, careful and close monitoring during drug initiation is mandatory for nevirapine prescription. To the best of our knowledge, these characteristics have never been described. Further comparative study between each drug is needed to support these preliminary findings. In this study, two patients had early onset of DRESS; 2 days with ibuprofen and 3 days with torasemide. The prompt development of DRESS could be explained in one patient by having had a history of skin rashes to unknown over-the-counter analgesics and, in another patient, to furosemide and spironolactone. This emphasizes that rapid onset of DRESS can occur in individuals with prior exposure to a similar group of drugs.

The pathogenesis of DRESS is related to multiple factors, including host, drug, and virus. Human leucocyte antigen-related genes have been identified as predictors for severe cutaneous adverse drug reactions (16). Accumulation of toxic metabolites due to a failure of the drug detoxification pathway has been hypothesized to explain anticonvulsant and sulphonamide hypersensitivity (18). HHV-6 reactivation during the acute phase of DRESS has been found to relate to the pathogenesis of DRESS, and is considered a prognostic factor (4–8). A transient drug-induced hypogammaglobulinaemia creates an immunological environment that permits viral reactivation (19). Increased level of interleukin-5 release from drug-specific $CD4^+$ and $CD8^+$ T cells is associated with eosinophil activation and the generation of eosinophilia (20).

All patients in this study presented with maculopapular rash. There were co-existing pustular lesions in one patient. The reported cutaneous findings include maculopapular rash, vesicles, bullae, target lesions, purpura, and erythroderma (14, 21). However, pustules have rarely been reported. Facial oedema was the common presentation, seen in 74.1%. This finding is an important clue to the diagnosis of DRESS, because it is not commonly seen in exanthematous drug eruption. The histopathological finding is non-diagnostic for DRESS. The consistent finding in our cases was perivascular infiltration with lymphocytes and eosinophils. Lichenoid dermatitis, pseudolymphoma and erythema multiforme patterns have been described by Chiou et al. (14); however, they were not seen in our study. Mucosal involvement (oral mucositis, conjunctivitis) was seen in 18.5% and was milder than those seen in toxic epidermal necrolysis.

Hepatic and haematological involvements were the two most common systemic involvements. The severity ranged from mild elevation of serum transaminase to fulminant hepatitis. In our study, the abnormal liver function test usually persists for 33 days after discontinuation of the culprit drugs. Haematological abnormalities included lymphocytosis, lymphopaenia, eosinophilia, atypical lymphocytosis, and thrombocytopaenia. There was one patient who was allergic to sulfasalazine, who died from multi-organ failure and sepsis. In this case, the degree of eosinophilia was highest (eosinophil count 3240/μl) compared with the rest of our patients. This finding supports the idea of a previous study, in that a high level of eosinophilia corresponds to cytokine storms in patients' bodies and may correlate with the internal organ involvement. In addition, a high degree of eosinophilia may further disturb

the defence immune system, resulting in susceptible to infectious complication (14).

Identification and withdrawal of the culprit drug/s is the most important step in the treatment of DRESS. Systemic corticosteroids are the mainstay of treatment. Twenty-three patients (85.2%) were treated with systemic corticosteroids. There were four patients who did not receive systemic corticosteroids due to HIV infection. Fever was the first sign of response to treatment within 2 days of corticosteroid administration. However, 18.5% of cases experienced a flare of symptoms during tapering of the prednisolone dose. Thus, gradual tapering of systemic corticosteroids is necessary to avoid flaring of skin rash and worsening of hepatitis. In a case of renal involvement, a short course of ciclosporin has been reported to improve skin eruption and renal function (22). In this study, the mortality rate was 3.7%, which is lower than previous reports (2, 14). The lower mortality rate may be due to an early diagnosis and withdrawal of the culprit drug. To date, there is no defining prognostic factor for DRESS, in contrast to toxic epidermal necrolysis, but allopurinol, minocycline, high eosinophil count, and multiple underlying diseases are proposed to be poor prognostic factors (14, 21).

The limitations of this study are its retrospective nature and small number of subjects. However, owing to the rarity of DRESS, large-scale studies are limited. We did not measure HHV-6 serology and HLA screening as part of the work-up for DRESS.

In conclusion, DRESS is potentially life-threatening, with significant morbidity and mortality. Our analysis shows that anticonvulsants are still the major cause of DRESS, followed by allopurinol and nevirapine. Early detection, discontinuation of the suspected drug, and administration of systemic corticosteroids, are the key steps in management of DRESS.

The authors declare no conflict of interest.

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