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Review Article

# Drug reaction with eosinophilia and systemic symptoms (DRESS)

# 系統症狀伴隨嗜酸性粒細胞增多的藥物反應

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Drug reaction with eosinophilia and systemic symptoms (DRESS) is a unique, potentially lethal drug-induced idiosyncratic hypersensitivity reaction. Alongside Stevens-Johnson syndrome (SJS) / toxic epidermal necrolysis (TEN) and acute generalised exanthematous pustulosis (AGEP), DRESS is categorised as one of the few severe cutaneous adverse reactions (SCARs). The syndrome is characterised by its heterogeneous clinical, laboratory and histopathological features. In this review article, we will discuss on the pathogenesis, diagnosis, clinical and biochemical presentations, treatment and prognosis of this peculiar entity.

系統症狀伴隨嗜酸性粒細胞增多的藥物反應是一種獨特的，可致命的特殊藥物過敏反應。系統症狀伴隨嗜酸性粒細胞增多的藥物反應與史蒂芬斯－強森症候群、毒性表皮溶解症和急性廣泛性發疹性膿皰症等，一同歸屬爲小數的嚴重型皮膚藥物過敏反應。此綜合徵的特別處爲其多樣性的臨床、化驗及組織病理學特徵。本文將探討此獨特藥疹的發病、診斷、臨床及生化表現、治療及預後等事項。

**Keywords:** DRESS, pharmacogenetics, SCARs, treatment

**關鍵詞**：系統症狀伴隨嗜酸性粒細胞增多的藥物反應、藥物基因研究學、嚴重型皮膚藥物過敏反應、治療

## Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) is an acute, distinct and potentially fatal idiosyncratic drug-induced hypersensitivity reaction. The incidence of DRESS was estimated between 1 in 1000 to 1 in 10,000 drug exposures.[1] It carries a mortality of around 10%. Lethal events are often due to myocarditis and fulminant hepatitis.[2] DRESS is associated with autoimmune sequelae in the long-term, which includes insulin-dependent diabetes, autoimmune thyroiditis and systemic lupus erythematosus.

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### *Clinical features*

DRESS is characterised by a delayed onset, usually two to six weeks after initiating the offending drug.[3] Fever, rash and visceral involvement are the classic

triad of the syndrome. Lymphadenopathy is typically present. Cutaneous manifestations are highly heterogeneous in DRESS. Common findings include maculopapular eruption, lichenoid eruption, erythroderma, facial oedema and sterile pustulosis (Figure 1).

### *Haematological and biochemical features*

Peripheral eosinophilia is encountered more than half of the cases (>50%),[2] and atypical lymphocytosis (presence of activated, large lymphocytes in peripheral blood smear) is a typical haematological feature. Other well-reported haematological abnormalities include lymphopenia, lymphocytosis, neutropenia, thrombocytopenia and pancytopenia.

Internal organ involvement is the main cause of morbidity and mortality in DRESS. Hepatic damage, either in the form of hepatitis or cholestasis (less common), occurs in a majority of patients with DRESS. Some patients may present with hepatomegaly alone without significant liver function derangement. Hepatic failure may complicate fulminant hepatitis and result in death. Isolated proteinuria without renal function derangement is the most common pattern of kidney involvement in DRESS.[2] Interstitial nephritis is not uncommon and may result in marked deterioration in renal excretory function. A higher incidence of renal function impairment is associated with allopurinol-induced DRESS.[4] Renal failure requiring dialysis has been reported due to acute tubular necrosis. Cardiac involvement is rare but may lead to rapid deterioration and death. Myocarditis and pericarditis have been described in DRESS cases caused by minocycline.[2] Pneumonitis, myositis and pancreatitis have also been reported in the literature.

### *Histopathological features*

There are no pathognomonic histological features in DRESS. An interface mononuclear infiltrate with basal vacuolar degeneration is often seen. Superficial perivascular lymphocytic infiltrates are often seen as well but is a rather non-specific feature. Dense band-like epidermal lymphocytic infiltrates which can be confused with lymphoma may be seen in certain patients and is sometimes considered by some authors to be pseudolymphoma. Other reported histological findings include lymphocytic and leukocytoclastic vasculitis. Some authors have isolated human herpesvirus 6 (HHV-6) genome in the cellular infiltrates of early lesions.[5] Nevertheless, the detection of lesional HHV-6 genome cannot be taken as proof to a viral causation of DRESS. It is possible that the positive detection of HHV-6 DNA merely represent a propensity of viral reactivation during the course of DRESS.

### *Culprit agents*

To date, more than 40 drugs have been reported to be associated with DRESS (Table 1). Aromatic anti-convulsants (phenytoin, phenobarbital and carbamazepine), sulphonamides and allopurinol are the most important causative drugs. Anti-retroviral agents (particularly abacavir and nevirapine) and minocycline are also frequently reported.[2]

### *Pathophysiology*

The exact pathogenic mechanism of DRESS is unknown. Slow acetylator phenotype was thought to be implicated, with the observation of a high incidence of sulfonamide hypersensitivity in the slow acetylators.[7] Shear and Spielberg hypothesised that an intrinsic defect of detoxification would be the key in the pathogenesis of DRESS. The defective formation of certain drug metabolites was proposed to trigger off a series of immunological events observed in DRESS.[8] Viral reactivation has been a topic of interest in the research of DRESS. A transient hypogammaglobulinaemia due to drug hypersensitivity reaction was thought to have promoted viral reactivation. As a result, T-cell expansion was stimulated and may lead to the resultant skin and visceral injury.[9,10] In the literature, reactivation of HHV-6 has been extensively reported to be correlated with DRESS.[11-13] HHV-6 reactivation has even been

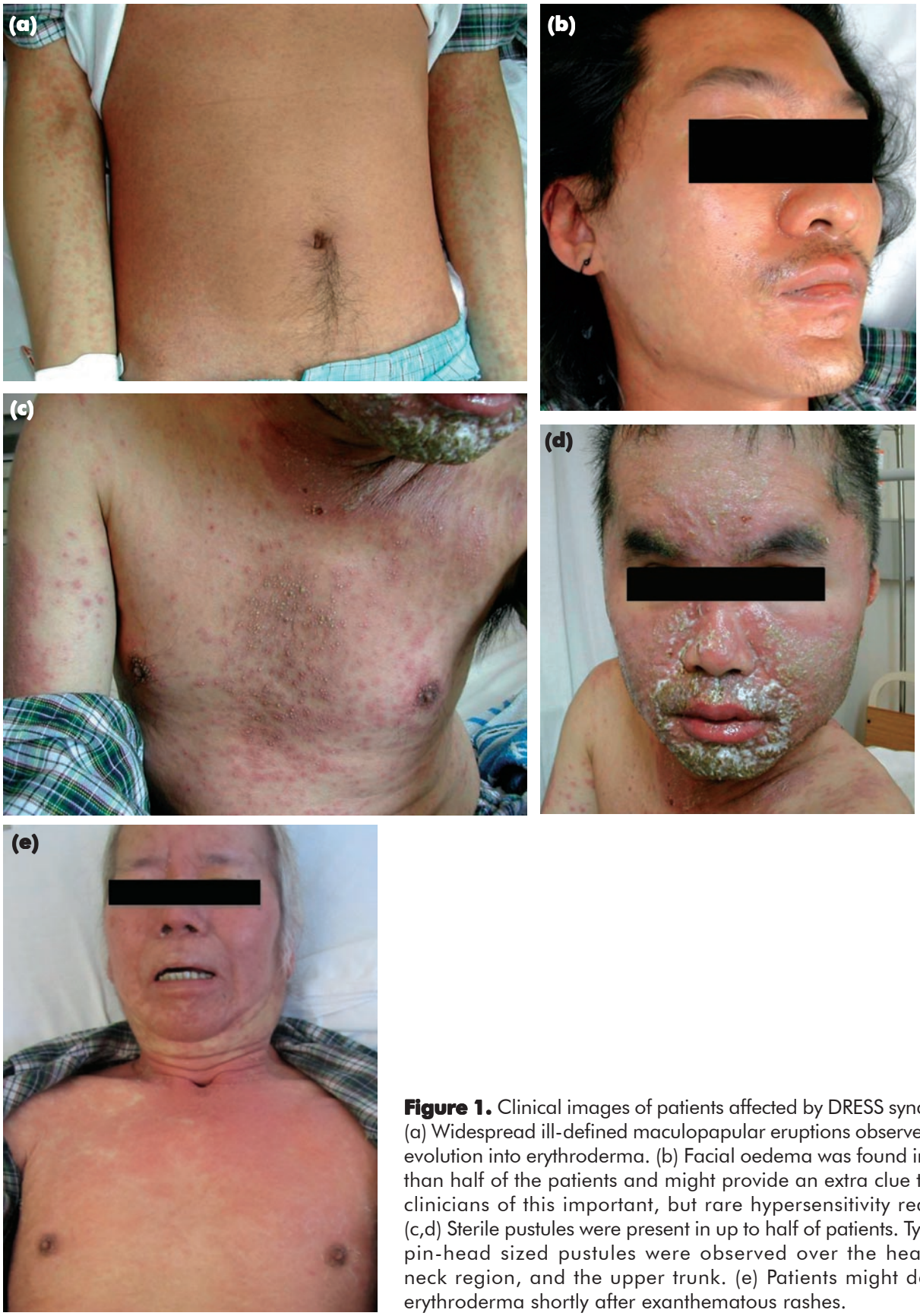


**Figure 1.** Clinical images of patients affected by DRESS syndrome. (a) Widespread ill-defined maculopapular eruptions observed, with evolution into erythroderma. (b) Facial oedema was found in more than half of the patients and might provide an extra clue to alert clinicians of this important, but rare hypersensitivity reaction. (c,d) Sterile pustules were present in up to half of patients. Typically, pin-head sized pustules were observed over the head and neck region, and the upper trunk. (e) Patients might develop erythroderma shortly after exanthematous rashes.

**Table 1.** Reported causative agents in DRESS syndrome[6]

**Common**

Allopurinol
Aromatic anti-convulsants
(carbazepine, pheytoin, phenobarbital)
Sulphonamides
(sulphaslazine, salazosulfapyridine, cotrimoxazole, dapsone)
Lamotrigine
Minocycline
Anti-retroviral drugs
(abacavir, nevirapine)

**Uncommon**

Amitriptyline
Amoxicillin plus clavulanic acid
Aspirin
Atovarstatin
Cefadroxil
Captopril
Celecoxib
Chlorambucil
Clomipramine
Clopidogrel
Codeine phosphate
Cyanamide
Diaphenylsulfone
Efalizumab
Esomeprazole
Hydroxychloroquine
Ibruprofen
Imatinib
Mexiletine
Olanzapine
Phenylbutazone
Quinine and thiamine
Sodium meglumine ioxitalamate
Sodium valproate/ethosuximide
Spironolactone
Streptomycin
Strontium ranelate
Tribenoside
Vancomycin
Zonisamide

included as one of the diagnostic criteria of DRESS.[14] Other members of the human herpesvirus family, namely Epstein-Barr virus (EBV), cytomegalovirus (CMV) and human herpesvirus 7 (HHV-7) have also been widely reported to be implicated. In a small longitudinal study, sequential reactivation of herpesviruses (HHV-6 and EBV in early phase, HHV-7 and CMV in late phase) was observed during the course of DRESS.[15] Other viruses including hepatitis E and paramyxovirus have also been suggested to be involved in the development of DRESS.[16,17]

### *Pharmacogenetics*

Table 2 summarises the reported HLA associations with DRESS. HLA-B*58:01 was recently identified as a genetic marker for both allopurinol-induced DRESS and Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) in the Han-Chinese population.[18] In a case-control study conducted by Hung et al., HLA-B*58:01 was strongly associated with allopurinol-induced severe cutaneous adverse reactions (SCARs) in the Han-Chinese population (odds ratio: 580). Other HLA associations have also been identified in abacavir-and nevirapine-induced DRESS. It has been suggested that certain HLA proteins might have high binding affinity toward certain drugs and/or their metabolites. They may incidentally provide antigen-presenting functions for the drugs and trigger certain HLA-restricted T-cell activation, and hence induction of the subsequent immunological reactions.[18,19]

## Diagnostic criteria

Two sets of diagnostic criteria have been established for DRESS.[14,20] The RegiSCAR study group has undergone a multi-national prospective study on various SCARs in six European countries since 2007. The authors established a set of inclusion criteria (Table 3) and a scoring system (Table 4) for DRESS. The

**Table 2.** HLA associations with DRESS syndrome induced by specific drugs

| Culprit drug | Allele | Ethnicity | References |
|---|---|---|---|
| Allopurinol | HLA-B*58:01 | Han Chinese | 18 |
| Abacavir | HLA-B*57:01 | Caucasian (highest risk); generalised across ethnicity | 26-29 |
| Nevirapine | HLA-Cw8 | Japanese | 30 |
| | HLA-Cw8-B14 haplotype | Sardinian | 31 |
| | HLA-B*35:05 | Thai | 32 |
| | HLA-B*35:01 | White Caucasian | 33 |

**Table 3.** Inclusion criteria of DRESS published by RegiSCAR[20]

**Criteria must be fulfilled**

1. Hospitalisation
2. Reaction suspected to be drug-related
3. Acute rash

**Three of the following four criteria are required for diagnosis**

1. Fever >38°C
2. Enlarged lymph nodes at a minimum of two sites
3. Involvement of at least one internal organ
4. Blood count abnormalities; defined either by:
   - Lymphocytes above or below normal limits; or
   - Eosinophils above the laboratory limits; or
   - Platelets below the laboratory limits.

major difference of the Japanese criteria (Table 5) is the inclusion of HHV-6 reactivation as part of the criteria. The Japanese group supported their view with an observational study of 100 patients, in which HHV-6 reactivation was detected in more than 60% of the cases.[21] Nethertheless, the use of detection of viral reactivation in defining DRESS remains controversial. To date, definite evidence of the causative role of herpesviruses in DRESS is lacking. Moreover, the low availability of relevant assay to detect the virus renders the Japanese criteria less practical in routine clinical services.

## Treatment

Early identification and prompt withdrawal of the offending agent is central to a successful clinical outcome. Patients are often hospitalised for careful monitoring of the vital signs and organ function. In patients with a milder presentation, complete resolution of the skin eruption and full recovery of visceral injury can be achieved in over a period of weeks by appropriate supportive care alone. Specific blood tests and imaging should be employed to exclude the uncommon occurrence of myositis, myocarditis, pneumonitis and pancreatitis in DRESS patients if clinically indicated.

Unlike the controversy in SJS/TEN, systemic corticosteroid is regarded as the mainstay of treatment in DRESS. It is widely accepted that moderate to high dose corticosteroids should be commenced in cases with internal organ involvement. Infection should be carefully sought out before the initiation of systemic corticosteroids. The usual dose of oral corticosteroid is prednisolone 1 mg/kg/day. Corticosteroid should be gradually tapered over a period of 6-8 weeks in order to prevent relapse of organ impairment. Relapse of rashes or liver function derangement may occur with rapid tailing or abrupt discontinuation of corticosteroid. Other treatments with reported success include pulsed intravenous methylprednisolone, intravenous immunoglobulin

**Table 4.** Scoring system for definite, probable, possible or no case of DRESS[20]

| Score (minimal score to maximal score) | -1 | 0 | 1 | 2 |
|---|---|---|---|---|
| 1. Fever ≧38.5°C (-1 to 0) | No/Unknown | Yes | | |
| 2. Enlarged lymph nodes (0 to 1) | | No/Unknown | Yes | |
| 3. Eosinophilia (0 to 2) | | | | |
| - Eos. count; OR | | | 0.7-1.499x10$^9$/L | ≧1.5x10$^9$/L |
| - Eos. %, if leucocyte <4.0x10$^9$/L | | | 10-19.9% | ≧20% |
| 4. Atypical lymphocytes (0 to 1) | | No/Unknown | Yes | |
| 5. Skin involvement (-2 to 2) | | | | |
| - Extent (% of BSA) | | No/Unknown | ≧50% | |
| - Suggestive skin rash | No | Unknown | Yes | |
| - Suggestive skin biopsy | No | Yes/Unknown | | |
| 6. Organ involvement (0 to 2) | | | | |
| - Liver | | No/Unknown | Yes | |
| - Kidney | | No/Unknown | Yes | |
| - Lung | | No/Unknown | Yes | |
| - Muscle/Heart | | No/Unknown | Yes | |
| - Pancreas | | No/Unknown | Yes | |
| - Other organ | | No/Unknown | Yes | |
| 7. Resolution ≧15 days (-1 to 0) | No/Unknown | Yes | | |
| 8. Evaluation of other potential causes (0 to 1) | | | | |
| - Antinuclear antibody | | | | |
| - Blood culture | | | | |
| - Serology for HAV/HBV/HCV | | | | |
| - Chlamydia/Mycoplasma | | | | |
| - ≧3 of above conditions -ve | | Yes | | |

**Total score ranges from -4 to 9**

| *Final score* | *Classification* |
|---|---|
| >5 | Definite case |
| 4-5 | Probable case |
| 2-3 | Possible case |
| <2 | No case |

Eos: eosinophil; BSA: body surface area; HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus.

**Table 5.** Diagnostic criteria for drug-induced hypersensitivity syndrome (DIHS) established by the Japanese consensus group[14]

**Criteria**

1. Maculopapular rash developing >three weeks after starting with the suspected drug
2. Prolonged clinical symptoms two weeks after discontinuation of the suspected drug
3. Fever (>38°C)
4. Liver abnormalities (alanine aminotransferase >100 U/L) / Renal involvement
5. Leucocyte abnormalities; defined by
   - Leucocytosis (>11x10$^9$/L); or
   - Atypical lymphocytosis (>5%); or
   - Eosinophilia (>1.5x10$^9$/L).
6. Lymphadenopathy
7. Human herpesvirus 6 reactivation

**Definitions**

Typical DIHS: Presence of all seven criteria
Atypical DIHS: Presence of the first five criteria

G (IVIG) and plasmapheresis.[22,23] Cyclosporine A and cyclophosphamide have also been reported to be effective in corticosteroid-resistant cases.[24,25]

## Prognosis and complications

The mortality of DRESS syndrome was reported to be between 10 to 20%. Fatality was mostly due to liver failure and myocarditis. With the use of high-dose corticosteroid, lethal opportunistic infection may be encountered during the course of treatment. Death resulted from bacteraemia and fungaemia has been reported in the literature.[9]

The DRESS syndrome is well-known to be associated with certain autoimmune diseases in the long-term. Hypothyroidism due to autoimmune thyroiditis can develop months after DRESS. Insulin-dependent diabetes is also associated with DRESS. It has been hypothesised that pancreatic islet cell may be injured by the ongoing immune phenomenon. Systemic lupus erythematosus has been described complicating DRESS, in which EBV reactivation was thought to be responsible.

## Conclusion

Drug reaction with eosinophilia and systemic symptoms (DRESS) is one of the most important severe cutaneous adverse drug reactions. A high level of suspicion is required to identify this peculiar entity in time in order to minimise morbidity and fatal outcome. Immediate cessation of the implicated drug is essential to successful management of DRESS syndrome. Long-term monitoring is necessary to screen for potential autoimmune complications.

## References


1. Fiszenson-Albala F, Auzerie V, Mahe E, Farinotti R, Durand-Stocco C, Crickx B, et al. A 6-month prospective survey of cutaneous drug reactions in a hospital setting. Br J Dermatol 2003;149:1018-22.
2. Peyriere H, Dereure O, Breton H, Demoly P, Cociglio M, Blayac JP,, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol 2006;155:422-8.
3. Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (Drug Rash with Eosinophilia and Systemic Symptoms: DRESS). Semin Cutan Med Surg 1996;15:250-7.
4. Chen YC, Chiu HC, Chu CY. Drug reaction with eosinophilia and systemic symptoms: a retrospective study of 60 cases. Arch Dermatol 2010;146:1373-9.
5. Suzuki Y, Inagi R, Aono T, Yamanishi K, Shiohara T. Human herpesvirus 6 infection as a risk factor for the development of severe drug-induced hypersensitivity syndrome. Arch Dermatol 1998;134:1108-12.
6. Cacoub P, Musette P, Descamps V, Meyer O, Speirs C, Finzi L, et al. The DRESS syndrome: a literature review. Am J Med 2011;124:588-97.
7. Shear NH, Spielberg SP, Grant DM, Tang BK, Kalow W. Differences in metabolism of sulfonamides predisposing to idiosyncratic toxicity. Ann Intern Med 1986;105:179-84.
8. Shear NH, Spielberg SP. Anticonvulsant hypersensitivity syndrome: In vitro assessment of risk. J Clin Invest 1988; 82:1826-32.
9. Aihara Y, Ito SI, Kobayashi Y, Yamakawa Y, Aihara M, Yokota S. Carbemazepine-induced hypogammaglobulinaemia and reactivation of human herpesvirus 6 infection demonstrated by real-time quantitative polymerase chain reaction. Br J Dermatol 2003;149:165-9.
10. Kano Y, Inaoka M, Shiohara T. Association between human herpesvirus 6 reactivation and hypogammaglobulinaemia. Arch Dermatol 2004;140: 183-8.
11. Descamps V, Bouscarat F, Laglenne S, Aslangul E, Veber B, Descamps D, et al. Human herpesvirus 6 infection associated with anticonvulsant hypersensitivity syndrome and reactive haemophagocytic syndrome. Br J Dermatol 1997;137:605-8.
12. Descamps V, Valance A, Edlinger C, Fillet AM, Grossin M, Lebrun-Vignes B, et al. Association of human herpesvirus 6 infection with drug reaction with eosinophilia and systemic symptoms. Arch Dermatol 2001;137:301-30.
13. Tohyama M, Yahata Y, Yasukawa M, Inagi R, Urano Y, Yamanishi K, et al. Severe hypersensitivity syndrome due to sulfasalazine associated with reactivation of human herpesvirus 6. Arch Dermatol 1998;134:1113-7.
14. Shiohara T, Iijima M, Ikezawa Z, Hashimoto K. The diagnosis of DRESS syndrome has been sufficiently established on the basis of typical clinical features and viral reactivation. Br J Dermatol 2007;156:1083-4.
15. Kano Y, Hiraharas K, Sakuma K, Shiohara T. Several herpesviruses can reactivate in a severe drug-induced multiorgan reaction in the same sequential order as in graft-versus-host disease. Br J Dermatol 2006;155:

301-6.
16. Naniwa T, Maeda S, Sawada H, Watanabe Y, Osawa T, Hayami Y, et al., Drug-induced hypersensitivity syndrome associated with a marked increase in anti-paramyxovirus antibody titers in a scleroderma patient. Allergol Int 2007;56:303-8.
17. Chogle A, Nagral A, Soni A, Agale S, Jamadar Z. Dapsone hypersensitivity syndrome with coexisting acute hepatitis E. Indian J Gastroenterol 2000;19:85-6.
18. Hung SI, Chung WH, Liou LB, Chu CC, Lin M, Huang HP, et al. HLA-B* 5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. Proc Natl Acad Sci U S A 2005;102:4134-9.
19. Aihara M. Pharmacogenetics of cutaneous adverse drug reactions. J Dermatol. 2011;38:246-54.
20. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, et al., Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol 2007;156:609-11.
21. Tohyama M, Hashimoto K, Yasukawa M, Kimura H, Horikawa T, Nakajima K, et al. Association of human herpesvirus 6 reactivation with the flaring and severity of drug-induced hypersensitivity syndrome. Br J Dermatol 2007;157:934-40.
22. Fields KS, Petersen MJ, Chiao E, Tristani-Firouzi P. Case reports: treatment of nevirapine-associated DRESS syndrome with intravenous immune globulin (IVIG). J Drugs Dermatol 2005;4:510-3.
23. Shaughnessy KK, Bouchard SM, Mohr MR, Herre JM, Salkey KS. Minocycline-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome with persistent myocarditis. J Am Acad Dermatol 2010; 62:315-8.
24. Zuliani E, Zwahlen H, Gilliet F, Marone C. Vancomycin-induced hypersensitivity reaction with acute renal failure: resolution following cyclosporine treatment. Clin Nephrol 2005;64:155-8.
25. Laban E, Hainaut-Wierzbicka E, Pourreau F, Yacoub M, Sztermer E, Guillet G, et al. Cyclophosphamide therapy cortico-resistant drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome in a patient with severe kidney and eye involvement and Epstein-Barr virus reactivation Am J Kidney Dis 2010;55: e11-4.
26. Mallal S, Nolan D, Witt C, Masel G, Martin AM, Moore C, et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. Lancet 2002;359:727-32.
27. Hetherington S, Hughes AR, Mosteller M, Shortino D, Baker KL, Spreen W, et al. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. Lancet 2002;359:1121-2.
28. Mallal S, Phillips E, Carosi G, Molina JM, Workman C, Tomazic J, et al. HLAB* 5701 screening for hypersensitivity to abacavir. N Engl J Med 2008;358:568-79.
29. Saag M, Balu R, Phillips E, Brachman P, Martorell C, Burman W, et al. High sensitivity of human leukocyte antigen-B*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. Clin Infect Dis 2008;46:1111-8.
30. Gatanaga H, Yazaki H, Tanuma J, Honda M, Genka I, Teruya K, et al. HLA-Cw8 primarily associated with hypersensitivity to nevirapine. AIDS 2007;21:264-5.
31. Littera R, Carcassi C, Masala A, Piano P, Serra P, Ortu F, et al. HLA-dependent hypersensitivity to nevirapine in Sardinian HIV patients. AIDS 2006;20: 1621-6.
32. Chantarangsu S, Mushiroda T, Mahasirimongkol S, Kiertiburanakul S, Sungkanuparph S, Manosuthi W, et al. HLA-B* 3505 allele is a strong predictor for nevirapine-induced skin adverse drug reactions in HIV-infected Thai patients. Pharmacogenet Genomics 2009; 19:139-46.
33. Phillips E, Lucas M, Kean N, Lucas A, McKinnon E, Mallal S. HLA-B* 35 is associated with nevirapine hypersensitivity in the contemporary Western Australian HIV cohort study. Eur Ann Allergy Clin Immunol 2010; 42:48.