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ORIGINAL RESEARCH

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): A Retrospective Study of 51 Chinese Patients

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Background: Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe and potentially lethal adverse drug reaction. Its clinical complexity and heterogeneity pose challenges for diagnosis and management.

Methods: We retrospectively reviewed the medical records of patients with DRESS who were admitted to our hospital between 2013 and 2022. Data on demographics, culprit drugs, clinical manifestations, laboratory findings, and treatments were collected.

Results: Fifty-one patients were included in the final analysis, with 16 probable and 35 definite cases. The most common causative drugs were antiepileptic drugs (15.7%), anti-tuberculosis drugs (15.7%), and Chinese herbs (9.8%). Common skin manifestations included extensive skin involvement (76.5%), facial edema (66.7%), polymorphic maculopapular lesions (66.7%), and exfoliation (56.9%). Eosinophilia and atypical lymphocytes were noted in 96.1% and 68.6% of the patients, respectively. The liver is the most frequently affected organ. Facial edema, extensive skin involvement, and atypical lymphocytes were correlated with higher Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) scores ($P<0.05$). DRESS induced by antiepileptic drugs, antituberculosis drugs, and Chinese herbs exhibited significant differences in platelet and lymphocyte counts, C-reactive protein (CRP) levels, and transaminase levels ($P<0.05$).

Conclusion: Clinical manifestations of DRESS are complex. Facial edema, extensive skin involvement, and atypical lymphocytes have emerged as significant diagnostic indicators.

Keywords: drug reaction with eosinophilia and systemic symptoms, DRESS, antituberculosis drugs, antiepileptic drugs, Chinese herbs

Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS), or drug-induced hypersensitivity syndrome (DIHS), is a severe delayed T cell-mediated adverse drug reaction characterized by fever, skin rash, lymphadenopathy, hematologic abnormalities, and organ involvement. DRESS is potential lethal, with a mortality of approximately 9%.[1] Additionally, autoimmune complications such as autoimmune thyroiditis, type 1 diabetes, hemolytic anemia and systemic lupus erythematosus have been observed months to years after the onset of DRESS.[2] Multiple factors contribute to the pathogenesis of DRESS. Drugs and viruses, including human herpes virus 6 (HHV-6), Epstein–Barr virus (EBV), and cytomegalovirus (CMV), are inciting stimuli of deranged immune response. Viral reactivation causes direct tissue damage, amplifies systemic inflammation, and is correlated with worse prognosis. Genetic predisposition also plays an important role in the pathogenesis of DRESS. Several HLA haplotypes were associated with DRESS, including HLA-B*58:01 for allopurinol, HLA-B*31:01 for carbamazepine, HLA-B*32:01 for vancomycin, and HLA-B*13:01 for dapsone.[3]

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The Japanese SCAR (J-SCAR) diagnostic criteria for DIHS and the European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) criteria for DRESS are most commonly used in clinical practice.[4,5] HHV-6 reactivation is included in the J-SCAR criteria as a defining criterion but not in RegiSCAR. DRESS may be confused with other severe drug eruptions and autoimmune diseases. Skin rash often starts as maculopapular exanthema, which may progress to confluent erythema and erythroderma, accompanied by additional lesions, including facial edema, scaling, purpura, infiltrated plaques, pustules, and targetoid lesions.

To better understand DRESS, we performed this retrospective study to describe the clinical features of patients in our center, with a focus on exploring the clinical features of diagnostic values.

Materials and Methods

We conducted a retrospective study by reviewing the medical records of inpatients diagnosed with DRESS between 2013 and 2022 at the West China Hospital. This study was approved by the Biomedical Ethics Committee of West China Hospital, Sichuan University (No. 2020-1829) and conducted in accordance with the 1964 helsinki Declaration. Due to the retrospective nature of the study and the use of de-identified patient data, informed consent was waived. "Drug reaction with eosinophilia and systemic symptoms" and "DRESS" and "drug-induced hypersensitivity syndrome" and "DIHS" were used to search potential cases in the medical database. The RegiSCAR score was calculated to grade possible (score of 2–3), probable (score of 4–5) and definite (score ≥6) cases. Patients with a RegiSCAR score of <4 or without a detailed skin lesion description were excluded.

We collected data on demographics, culprit drugs, clinical manifestations, laboratory and biopsy results, and treatments. Culprit drugs were identified by two dermatology specialists in following steps. First, drugs taken within three months prior to the onset (appearance of rash) of DRESS were screened. Next, drugs with highest probability were identified according to the Adverse Reaction Probability Scale proposed by Naranjo et al.[6] Eosinophilia was defined as an absolute eosinophil count > 0.7 $\times 10^9$/L. Lymphadenopathy was defined as enlarged lymph nodes at two different anatomical sites on physical examination or ultrasonography. Liver injury was defined as a more than two-fold elevation in transaminase levels on two different days. Renal involvement was defined as the presence of proteinuria, hematuria, or elevated creatinine levels. Patients showing interstitial changes on chest CT were considered to have pulmonary involvement after excluding other causes. Either elevated cardiac enzymes (creatine kinase-MB, CK-MB, or troponin), abnormal echocardiogram findings, or cardiac manifestations were considered indicative of cardiac involvement. The skin biopsies were reviewed when available.

Statistical analyses were performed using SPSS 26.0 (IBM Corp., Armonk, NY, USA). Differences were tested by *t*-test or nonparametric test, including the Mann–Whitney *U*-test, Kruskal–Wallis *H*-test, and Chi-square test. $P<0.05$ was considered statistically significant.

Results

Demographics and Clinical Characteristics

A total of 64 potential DRESS patients were identified from the medical database. Thirteen patients were excluded: one was diagnosed with angioimmunoblastic T-cell lymphoma and 12 with RegiSCAR scores less than 4. In the end, 51 patients with a mean age of 41.7±15.8 years including 16 probable cases and 35 definite cases were analyzed. As shown in Table 1, the predominant culprit drugs were antiepileptic drugs (15.7%), antituberculosis drugs (15.7%), and Chinese herbs (9.8%). The average latent period was 21.5 days and the average hospital stay was 19.5 days. Forty-five (88.2%) patients received systemic corticosteroids (SCs). Additional treatments included: twenty-two with intravenous immunoglobulin (IVIG), six with both IVIG and cyclosporine, two with both IVIG and tumor necrosis factor α (TNF-α) inhibitor, and one with cyclosporine. Patients initiated SCs at a prednisone dose of 0.6 to 1.14 mg/kg/d. Maximum prednisone doses ranging from 0.6 mg/kg/d to 2.9 mg/kg/d. Corticosteroid was reduced by 10–20% over 3–5 days following improvement.

Two patients experienced relapse: one during corticosteroids tapering, and the other without an under-recognized precipitant. One patient died: the 54-year-old female with underlying pulmonary infection and sepsis, developed DRESS

Table 1 Demographics and Characteristics of DRESS Patients

Demographics and Characteristics	
Age, mean ± SD, years	41.7±15.8
Gender, n (%)	
Male	23 (45.1)
Female	28 (54.9)
Comorbidity, n (%)	
Tuberculosis	8 (15.7)
Epilepsy	7 (13.7)
Infection	6 (11.8)
Pain	5 (9.8)
Autoimmune diseases	4 (7.8)
Mental disorders	4 (7.8)
Others (including digestive ulcer, gout, malignancy, and liver failure)	7 (13.7)
None	10 (19.6)
RegiSCAR score, n (%)	
Probable (4–5)	16 (31.4)
Definite (≥6)	35 (68.6)
Culprit drugs, n (%)	
Antiepileptic drugs	8 (15.7)
Carbamazepine	4 (7.8)
Lamotrigine	2 (3.9)
Phenobarbital	1 (2.0)
Phenytoin	1 (2.0)
Antituberculosis drugs*	8 (15.7)
Chinese herbs	5 (9.8)
Antibiotics	4 (7.8)
Penicillins	1 (2.0)
Penicillins or quinolones	1 (2.0)
Vancomycin	1 (2.0)
Cephalosporin or quinolones	1 (2.0)
Allopurinol	3 (5.9)
Sulfasalazine	3 (5.9)
Mixture (Chinese herbs/ NSAIDS/ Antibiotics)	3 (5.9)
Others	8 (15.7)
Unknown	9 (17.6)
Latent period, median (range), days, N=34	21.5 (5–90)
Hospital stays, median (range), days	19.5 (4–68)
Treatment	
Topical corticosteroids	6 (11.8)
Systemic corticosteroids	45 (88.2)
Cyclosporine	7 (13.7)
TNF-α inhibitor	2 (3.9)
Intravenous immunoglobulin	30 (58.8)
Relapse, n (%)	2 (3.9)
Death, n (%)	1 (1.9)

Note: *Antituberculosis drugs include isoniazid, rifampicin, rifapentine, ethambutol, pyrazinamide, and moxifloxacin.

suspected to be caused by piperacillin-tazobactam. SC and IVIG was given to treat DRESS but she ultimately succumbed to septic shock.

Skin rashes were observed in all patients with DRESS, and systemic involvement was observed in 98.0% of patients. Extensive skin rash, defined as more than half of the body surface area affected, was observed in 76.5% of the patients,

and 9.8% of the patients developed erythroderma. Facial edema and polymorphic maculopapular exanthema were present in two-thirds of patients. Among polymorphic maculopapular exanthema, scaling (56.9%), purpura (25.5%), and targetoid lesions (19.6%) were most common. Infiltration, urticaria, and blisters were rarely observed. Notably, mucosal involvement was frequently observed, occurring in 13.7% of cases (Table 2). Skin biopsy was performed in 11 patients. The epidermal findings included hyperkeratosis, parakeratosis, and microabscesses. The liquefaction of the basal cells

Table 2 Clinical Features of DRESS Patients

Clinical Manifestation, n (%)	
Skin rash	
Widespread skin involvement*	39 (76.5)
Facial edema	34 (66.7)
Monomorphic maculopapular	12 (23.5)
Polymorphic maculopapular	34 (66.7)
Scaling	29 (56.9)
Purpura	13 (25.5)
Targetoid lesion	10 (19.6)
Pustules	7 (13.7)
Exudation	5 (9.8)
Infiltration	1 (2.0)
Urticaria	2 (3.9)
Blister	2 (3.9)
Erythroderma	5 (9.8)
Mucosal involvement	7 (13.7)
Pruritis	35 (68.6)
Pain	3 (5.9)
Fever≥38.5°C	46 (90.2)
Hematologic System	
Leukocytosis	39 (76.5)
Thrombocytopenia	16 (31.4)
Eosinophilia	49 (96.1)
Atypical lymphocyte	35 (68.6)
Lymphadenopathy	30 (58.8)
Liver involvement	44 (86.3)
Elevated ALT	44 (86.3)
Elevated AST	44 (86.3)
Kidney involvement	20 (39.2)
Proteinuria	12 (23.5)
Hematuria	6 (11.8)
Creatinine	7 (13.7)
Heart involvement, N=25	7 (28)[#]
Elevated CK-MB	2 (8)
Elevated troponin	5 (2)
Lung involvement	2 (3.9)
Interstitial changes	2 (3.9)

Notes: *Defined as more than half of the affected body surface area. [#]Chinese herbs (1 patient), piperacillin-tazobactam (1 patient), icotinib (1 patient), mixture of NSAIDS and antibiotics (2 patients), unknown (2 patients).
Abbreviations: ALT, alanine transaminase; AST, aspartate transferase; CK-MB, creatine kinase-MB.

was observed in five specimens. Perivascular lymphocytic infiltrates were consistently found in all specimens, and perivascular eosinophilic infiltrate in four specimens.

Forty-six patients (90.2%) developed a fever of ≥ 38.5 °C. Blood tests revealed leukocytosis, thrombocytopenia, eosinophilia, and atypical lymphocytes in 76.5%, 31.4%, 96.1%, and 68.6% of patients, respectively. Lymphadenopathy occurred in 58.8% of patients. Six lymph node biopsies were performed, all of which revealed reactive lymphoid hyperplasias. Regarding internal organ involvement, the liver and kidneys were the most commonly affected targets (86.3% and 39.2%, respectively). Seven of twenty-five patients (28%) showed abnormalities in cardiac enzymes but were asymptomatic (Table 2). The HHV-6 test was not available at our hospital. EBV infection was common with positivity in 37.0% of the tested patients. Inflammatory markers including interleukin 6 (IL-6), interleukin 2 receptor (IL-2R), TNF-α, Ferritin and C-reactive protein (CRP) were high in majority. Eleven of the 16 patients (68.8%) had euthyroid sick syndrome (ESS) and most had low triiodothyronine syndrome (LT3S). Intriguingly, hyponatremia was observed in 64.7% cases (Supplementary Table 1), although most cases were temporary. One patient was further diagnosed with syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Three patients met the diagnostic criteria for hemophagocytic lymphohistiocytosis (HLH).

Comparison of Clinical Characteristics Between Probable and Definite Cases

Comparisons of skin and biological features between possible and probable cases are shown in Table 3. Facial edema, extensive skin involvement, and atypical lymphocytes were significantly more common in definite cases ($P<0.05$).

Comparison of Clinical Characteristics Among Different Causative Drugs

The clinical characteristics of antiepileptic drugs, antituberculosis drugs, and Chinese herbs were also analyzed. There were no statistically significant differences among the three groups regarding the latent period, hospital stay, and main lesion type. As for biological features, patients with DRESS induced by antituberculosis drugs had the lowest platelet counts ($P<0.05$). Compared to those affected by antiepileptic drugs, patients exposed to antituberculosis drugs exhibited significantly lower lymphocyte counts and higher CRP levels ($P<0.05$). In addition, anti-tuberculosis drugs were associated with a significant increase in transaminase levels compared with Chinese herbs ($P<0.05$) (Table 4).

Table 3 Comparison of Clinical Characteristics Between Probable and Definite Cases

	Probable Cases (n=16)	**Definite Cases (n=35)**	***P***
Age, mean ±SD, years	48.50±11.34	39.54±16.16	0.051
Skin lesions, n (%)			
Infiltration	0	1 (2.9)	1.000
Scaling	8 (50)	21 (60.0)	0.503
Purpura	3 (18.8)	10 (28.6)	0.689
Facial edema	7 (43.8)	26 (76.5)	0.023
Widespread skin involvement	9 (56.3)	30 (85.7)	0.021
Fever ≥ 38.5, n (%)	14 (87.5)	32 (91.4)	1.000
Leukocytosis, n (%)	10 (19.6)	29 (56.9)	0.112
Thrombocytopenia, n (%)	5 (9.8)	11 (21.6)	0.990
Peak Eosinophilia ($\times 10^9$/L), median (range)	1.67 (0.42–15.97)	2.41 (0.53–12.07)	0.417
Atypical lymphocytes, n (%)	7 (43.8)	28 (80.0)	0.010
Liver injury, n (%)*	12 (75.0)	32 (91.4)	0.253
Kidney injury, n (%)[#]	7 (43.8)	21 (60.0)	0.279

Notes: *Defined as more than two-fold elevation of transaminase levels on two different days. [#]Defined as proteinuria, hematuria, or elevated creatinine levels.

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Table 4 Comparison of Clinical Characteristics Among Different Culprit Drugs

	Antiepileptic Drugs (n=8)	Antituberculosis Drugs (n=8)	Chinese Herbs (n=5)	*P*
Age, median (range), years	29 (17–61)	42.5 (23–59)	43 (23–49)	0.385
Latent period, median (range), days	29 (10–90)	20 (10–50)	8 (6–30)	0.371
Hospital stays, median (range), days	19.5 (8–64)	18 (10–39)	18 (11–68)	0.957
Skin lesions, n (%)				
Scaling	6 (75.0)	2 (25.0)	3 (60.0)	0.125
Purpura	4 (50.0)	2 (25.0)	2 (40.0)	0.586
Facial edema	6 (75.0)	4 (50.0)	4 (80.0)	0.438
Widespread skin involvement	8 (100)	6 (75.0)	3 (60.0)	0.175
Fever≥38.5°C, n (%)	8 (100)	8 (100)	4 (80.0)	0.186
Leukocytosis	6 (75.0)	5 (62.5)	4 (80.0)	0.762
Thrombocytopenia	2 (25.0)	3 (37.5)	1 (20.0)	0.762
Platelet ($\times10^{12}$/L), median (range)	239 (143–421)*	149.5 (38–198)	206 (154–418)*	0.033
Peak Eosinophilia ($\times10^{9}$/L), median (range)	2.305 (1.02–12.07)	4.185 (0.53–15.97)	6.29 (0.47–11.16)	0.899
Lymphocytes ($\times10^{9}$/L), median (range)	4.115 (1.97–10.06)*	1.825 (0.15–3.14)	2.925 (2.01–3.66)	0.009
Atypical lymphocytes, n (%)	8 (100)	7 (87.5)	3 (60.0)	0.132
CRP (mg/L), median (range)	13.6 (3.89–77.8)*	90 (69.9–102)	33.9 (20.4–44.8)	0.025
ALT (U/L), median (range)	351 (166–2003)	431 (224–905)	131 (125–273)*	0.040
AST (U/L), median (range)	164 (42–1702)	463.5 (184–873)	104.5 (79–232)*	0.031
RegiSCAR score, median (range)	8 (6–10)	6 (4–8)	8 (4–9)	0.085

Note: *Compared with antituberculosis drugs: $P<0.05$.
Abbreviations: CRP, C-reactive protein; ALT, alanine transaminase; AST, aspartate transferase.

Discussion

This retrospective study analyzed the clinical features and laboratory findings of 51 patients with DRESS admitted to a Chinese tertiary hospital over the past decade. Our findings underscore the clinical complexity and heterogeneity of DRESS. We further explored the correlations between disease features and RegiSCAR scores, as well as between different causative drugs, to better understand the disease.

Our results identified a diverse range of drugs responsible for DRESS, including antiepileptic drugs (15.7%), antituberculosis drugs (15.7%), Chinese herbs (9.8%), and antibiotics (7.8%), accounting for nearly half of the cases. Antiepileptic drugs, particularly carbamazepine and lamotrigine, have been consistently reported to be closely related to DRESS.[5,7] Although some HLA class I risk alleles have a strong association with DRESS, their low predictive value limits their utility in routine clinical work.[8] For example, the positive predictive value (PPV) of HLA-B*5801 for allopurinol DRESS was reported to be only 3%, and the total number of individuals needed to test to prevent one case was calculated to be 250.[3] Nevertheless, identification of these HLA risk alleles facilitated pre-treatment screening to an extent. One study reviewed 1253 patients receiving antituberculosis drugs and found the prevalence of DRESS to be 1.2%.[9] As multiple antituberculosis drugs might be initiated simultaneously, identifying the specific causative drug is difficult. Rifampin and ethambutol have been reported to be the most frequent causative drugs.[9,10] In the case of Chinese herbs, it is even more challenging to identify the specific causative agent, owing to their complex composition. Public education on the use of Chinese herbs under medical guidance is necessary. Additionally, we compared clinical and laboratory features among the three causative drugs and found some distinct features in DRESS associated with antituberculosis drugs, including platelet and lymphocyte counts, CRP, and transaminase levels, indicating that antituberculosis drugs might be associated with a severe phenotype. However, these differences may also be caused by underlying diseases.

Skin manifestations can provide clues for diagnosis and prognosis. Facial edema and widespread skin involvement were observed in more than half of the cases in our study, as well as in previous reports.[7,11] Meanwhile, they were found to be associated with higher RegiSCAR scores. A previous study also associated purpura with a high RegiSCAR score.[7] Besides, Facial edema and purpura have been reported to be indicators of a severe phenotype.[12–14]

DRESS can involve multiple systems, most commonly hematologic, hepatic, renal, cardiac, and pulmonary. Common hematological manifestations of DRESS include eosinophilia, atypical lymphocytes, thrombocytopenia, and anemia. Although only eosinophilia and atypical lymphocytes were included in the RegiSCAR system, significant differences in thrombocytopenia between definite and probable cases were found in a previous study[15] with the prevalence rate ranging from 7% to 25%.[5,16,17] In our study, 31.4% of patients developed thrombocytopenia, with no significant difference between definite and probable cases. DRESS may in rare cases develop HLH.[5] Three cases in our study met the diagnostic criteria of HLH (fever, splenomegaly, cytopenia, ferritin ≥ 500 μg/L, soluble CD25 (IL-2Ra) ≥ 2400 U/mL, hypertriglyceridemia, and/or hypofibrinogenemia).[18] However, the incidence of HLH among DRESS patients may be underestimated because only a few patients have undergone specialized diagnostic tests. Interestingly, there is a view that HLH and DRESS may be diseases on the same spectrum of immune overactivation, sharing same features of notably fever, rash, and several organ involvements.[19]

Hepatic involvement is very common, with reported rates ranging from 75.0% to 94.2%. Phenytoin, antitubercular antibiotics, and allopurinol have been reported to be closely associated with hepatic involvement.[20] Renal involvement occurred in 39.2% of the patients, comparable to 15–35% in most retrospective studies. Drugs that frequently cause kidney involvement include antibiotics (vancomycin being the most common), xanthine oxidase inhibitors and anticonvulsants.[21] Cardiac injury is a relatively rare but high-mortality complication. All the patients with cardiac involvement in our study were asymptomatic. Minocycline and allopurinol are the most common reported medications that cause cardiac injury.[22]

Endocrine involvement in DRESS is generally considered rare and more of a concern as a long-term sequela, and the most common finding is thyroiditis.[2,23] Our data showed that ESS was not uncommon in the case of DRESS, but the mechanism is poorly understood. Although DRESS is generally considered a Th2-driven response, some studies have shown that Th1 cytokines are also overexpressed in DRESS and that elevated TNF-α and IL-6 levels precede HHV-6 infection.[24] ESS might be a part of the acute phase response mediated by proinflammatory cytokines, especially IL-6, IL-1β, and TNF-α.[25] Hyponatremia due to DRESS is an interesting phenomenon that has not been fully described in the current literature. Hyponatremia is a multifactorial condition. Proinflammatory cytokines such as IL-1β and IL-6 has been demonstrated to be involved in the development of hyponatremia, a condition related to SIADH.[26]

In conclusion, our study provides insights into the disease characteristics of patients with DRESS in China. Our results showed that antituberculosis drugs, antiepileptic drugs, and Chinese herbs were the most common causative agents. They cause similar skin manifestations, but exhibit differences in platelet counts, lymphocyte counts, CRP levels, and transaminase levels. We also compared the clinical characteristics between possible and definite DRESS cases cataloged by RegiSCAR scores. Facial edema, widespread skin involvement, and atypical lymphocytes are of diagnostic value. However, owing to the retrospective nature of the study, comprehensive and detailed data as well as clinical pictures were lacking. Therefore, these results should be cautiously interpreted.

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Disclosure

The authors report no conflicts of interest in this work.

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