Original Article

Drug Reaction with Eosinophilia and Systemic Symptoms: Retrospective Analysis of 104 Cases over One Decade

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Abstract

Background: Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe, life-threatening disorder caused by drugs. In the present study, we tried to explore the types of DRESS-inducing drugs, incubation period, features of skin rashes, accompanying visceral damage, and effectiveness of glucocorticoid therapy so as to inform clinical practice.

Methods: Patients diagnosed with a drug-induced rash, dermatitis, and DRESS admitted to our hospital from January 2006 to December 2015 were included in the study. The diagnosis followed the criteria and scoring system set by the European Registry of Severe Cutaneous Adverse Reactions. Statistical analyses were carried out using SPSS version 17.0 (IBM, Armonk, NY, USA), and a value of $P < 0.05$ was considered statistically significant.

Results: Among 104 patients, 38 were male and 66 female (aged 18–83 years). The latent period was 13 (interquartile range [IQR]: 10–17) days. The most common allergy-inducing drugs were antibiotics ($n = 37$, 35.6%), followed by antiepileptic drugs and traditional Chinese medicines (TCMs). Eighty-two cases (78.8%) had rash with area >50% body surface area (BSA). Liver damage occurred in 90% of cases. Patients were divided into oral antihistamine group and glucocorticoid/immunosuppressive agent/intravenous immunoglobulin (IVIG) group. Sex, age, incubation period, duration of hospital stay, and the number of patients with body temperature ≥38.5°C were not significantly different between the two groups. However, the number of patients meeting the criteria of "definite" and "probable" ($\chi^2 = 5.852$, $P = 0.016$), with an eosinophilic granulocyte count of $\geq 1.5 \times 10^9$/L ($\chi^2 = 7.129$, $P = 0.008$), and with rash area of >50% BSA ($\chi^2 = 4.750$, $P = 0.029$), was significantly different.

Conclusions: Antibiotics were associated with allergic reactions, but TCMs also had an important role. Allergy resulting from repeat use of the same drug was more severe with a shorter incubation period. The most typical rash was widespread erythematous papules. Liver damage accounted for >90% of cases.

Key words: Drug Reaction; Drug Reaction with Eosinophilia and Systemic Symptoms Syndrome; Hypersensitivity Reaction

Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS), also known as drug-induced hypersensitivity syndrome, was introduced first by Bocquet *et al*.[1] in 1996. DRESS is caused by medication exposure and characterized by rash, fever, and enlarged lymph nodes. Typically, the blood test for DRESS shows liver damage as well as other life-threatening symptoms, such as damage to the kidneys, lungs, heart, and pancreas.[2] The incidence of DRESS is between 1/1000 and 1/10,000 individuals.[3] It has an incubation period of 2–8 weeks and can last for weeks or months after the medication has been discontinued. Continuous deterioration after medication discontinuation distinguishes it from other common types of drug-induced dermatitis.[4] Mortality from DRESS is about 10% and causes include organ failure and sepsis.[5] Medications that commonly cause allergy are anticonvulsants (mostly, aromatase derivatives), antimicrobial agents (particularly, penicillin and sulfonamide-based agents), and antipyretic/anti-inflammatory analgesics.[4,6]

The pathogenic mechanisms of DRESS are not clear, but studies have demonstrated that genetic polymorphisms are

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.204104

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Received: 03-12-2016 **Edited by:** Peng Lyu
How to cite this article: Wang L, Mei XL. Drug Reaction with Eosinophilia and Systemic Symptoms: Retrospective Analysis of 104 Cases over One Decade. Chin Med J 2017;130:943-9.

associated with reactivation of human herpes viruses 6 and 7, Epstein-Barr virus, cytomegalovirus, and varicella-zoster virus and with DRESS pathogenesis.[7-9]

In Asian countries, DRESS may contribute to 10% of adverse drug reactions.[5,10] DRESS can have diverse clinical manifestations and systematic damage.[11-13] Thus, DRESS must be differentiated from bacterial infections, viral infections, cancer, autoimmune diseases, and other conditions. As a specific laboratory test is not available, its clinical diagnosis is particularly challenging.[14] The present study was carried out to investigate the causes, relevant medications, clinical manifestations, treatments, and prognosis of DRESS in a tertiary-care setting in China.

Methods

Patients

Patients diagnosed with drug rash, drug-induced dermatitis, or DRESS and admitted to the Allergy and Clinical Immunology Centre of Beijing Friendship Hospital (Capital Medical University, Beijing, China) from January 2006 to December 2015 were included in the study.

Definition of disease

The diagnosis was made according to the guidelines set by the European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR).[15] According the guideline, hospital stay was required, and clinical manifestations were related to drug use plus three of the following diagnostic criteria: rash eruption; body temperature >38°C; enlarged lymph nodes on at least two sites; involvement of at least one internal organ; abnormal blood tests (lymphocytes above or below the normal range [NR]; eosinophils above the NR [percentage or absolute count]; platelets below the NR). According to the RegiSCAR classification system, a score >5 was considered "definite" and score of 4–5 considered "probable" for DRESS.[12] This study included definite and probable cases in statistical analyses.

The World Health Organization-Uppsala Monitoring Centre causality categories system was used to ascertain if a drug causes an allergic reaction.[16] The "latent period" refered to the period from drug initiation to symptom onset. If a drug was used continuously for >3 months, withdrawn for >14 days, or had an incubation period <3 days, it would not be considered to cause an allergic reaction.[17]

Diagnostic criteria for organ damage

Organ damage was diagnosed by checking for increased levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and γ-glutamyltransferase (GTT, liver); blood urea nitrogen (BUN) and creatinine (Cr, kidney); and amylase (pancreas).

Organ involvement was diagnosed by checking for unexplained respiratory difficulty (lungs);[3] increased levels of cardiac troponin-T (cTnT) and creatine kinase (CK)-MB (heart); unexplained diarrhea, hemorrhage, perforation, and severe loss of appetite (gastrointestinal tract); various types of encephalopathy (nervous system).[18]

Statistical analysis

Statistical analyses were carried out using SPSS version 17.0 (IBM, Armonk, NY, USA). The Student's *t*-test was used for statistical analyses of two independent samples with a normal distribution. The rank sum test and Chi-squared test were used for analyses of discrete data. A value of $P < 0.05$ was considered statistically significant.

Results

Demographic data

One-hundred and four participants (age: 18–83 years [mean, 52 ± 15 years]) formed the study group. Among them, 47 (45.2%) were grouped as definite and 57 (54.8%) as probable according to the RegiSCAR criteria. There were 38 (36.5%) males and 66 (63.5%) females (1:1.74 ratio). Incubation period was 13 (interquartile range [IQR]: 10–17) days. Duration of hospital stay was 9 (IQR: 7–12) days. Eleven cases (10.6%) had a history of drug allergy, and the culprit drugs were penicillin, sulfonamides, cefdinir, paracetamol, levofloxacin, and erythromycin. One patient developed allergies twice to erythromycin. Sixty-five patients had underlying diseases, the most common being high blood pressure (22 cases); Type II diabetes mellitus (ten); hyperuricemia (seven); liver disorder (seven); coronary heart disease (six); peripheral nerve pain (six); tuberculosis (four); kidney disorder (four); hyperthyroidism (three); Sjögren's syndrome (three); epilepsy (three); peptic ulcer disease (three); cerebral infarction (two); depression (two). Less common diseases (only single patient) were rheumatic heart disease, sick sinus syndrome, systemic lupus erythematosus, hemifacial spasm, multiple sclerosis, bipolar disorder, leukopenia, anemia, adenomyosis, eczema, psoriasis, chronic urticaria, sigmoid-colon cancer, infiltrating ductal carcinoma, and acquired immune deficiency syndrome [Table 1].

Culprit drugs

Among the 104 patients, three had a history of drug use but could not name the specific drugs they had taken; seven had used multiple drugs and the culprit one could not be identified definitively.

Culprit drugs from the remaining 94 patients were analyzed, and the most common were antibiotics (n = 37, 35.6%), followed by 14 cases with antiepileptic drugs and 14 cases with traditional Chinese medicines (TCMs; n = 14, 13.5%). Specifically, the most common drugs were carbamazepine and the processed TCMs Xiaojinwan, with each accounting for seven cases (6.7%), followed by cefaclor and levofloxacin, with each accounting for six cases (5.8%) [Table 2].

Clinical features

All patients had a rash. Erythematous papules accounted for 88 cases (84.6%), followed by facial swelling (n = 28, 26.9%). Additional wheals, macules, patches, ulcers, pustules, purpuric rashes, and target-shaped occurred in some patients. Eighty-two cases (78.8%) had a rash area >50% body surface area (BSA). Eighty-one cases (77.9%) had a body temperature ≥38°C, and 62 cases (59.6%) ≥38.5°C.

Table 1: Demographic characteristics of patients (n = 104)

Variables	Value
Gender	
Male:female	38 (36.5):66 (63.5)
Mean age (years)	52 ± 15
Median hospital stay (days)	9 (7–12)
Median onset (days)	13 (10–17)
Case classification according to RegiSCAR score	
Definite (score >5)	47 (45.2)
Probable (score 4–5)	57 (54.8)
History of drug allergy	11 (10.6)
Underlying disease	65 (62.5)
HIV	1 (1.0)
Comorbidities	
Convulsion disorder	4 (3.8)
Tuberculosis	4 (3.8)
Hypertension	22 (21.2)
Diabetes mellitus	10 (9.6)
Collagen vascular disease	4 (3.8)
Hyperuricemia	7 (6.7)
Preexisting liver disorder	7 (6.7)
Preexisting kidney disorder	4 (3.8)
Recent cancer	2 (1.9)
Others	32 (30.8)
Concomitant medication	
Corticosteroid (weeks)	
≤8	2 (1.9)
>8	2 (1.9)
Immunosuppressive or immunomodulating agents (weeks)	
≤8	1 (1.0)
>8	3 (2.9)

Values are presented as median (IQR), mean ± SD or n (%). Recent cancer: Diagnosed during the last 2 years before index date or if diagnosed earlier, still being treated. IQR: Interquartile range; SD: Standard deviation; HIV: Human immunodeficiency virus; RegiSCAR: Registry of Severe Cutaneous Adverse Reaction.

Seventy-two cases (69.2%) had eosinophils ≥0.7×10^9/L, and 35 cases (33.7%) ≥1.5×10^9/L. Seventy-four cases (71.2%) had enlarged lymph nodes at two or more sites [Table 3].

Laboratory findings

Damage occurred most commonly to the liver (as evidenced by the 94 cases [90.4%] who had increased levels of liver enzymes), followed by damage to the kidneys (n = 9, 8.7%). Seven cases had lung damage, six had heart damage, two had increased levels of pancreatic enzymes, one patient suffered damage to the gastrointestinal tract, and one had damage to the nervous system.

Damage to multiple organs occurred in 19 patients, and most involved was the liver. Seventeen cases suffered damage to two organs: liver plus kidneys (six cases); liver plus heart (five); liver plus lungs (five); and kidneys plus lungs (one). One patient had damage to the liver, kidneys, and pancreas. One patient had damage to the liver, heart, lungs, and nervous system [Table 3].

Treatment and clinical course

Among the 104 cases, 58 (55.8%) received systemic treatment with a glucocorticoid, including one patient who had intravenous immunoglobulin (IVIG) and one patient who had cyclosporine A combined with a glucocorticoid. The initial dose of glucocorticoid, if converted to the dose of prednisone, was 60 ± 21 mg/d (range, 33–150 mg/d). In addition, one patient had IVIG and 45 (43.3%) had an anti-histamine (p.o.).

Patients were divided into two groups. Group A (n = 45) received anti-histamines only and Group B (n = 59) received glucocorticoids/immunosuppressants/IVIG. In Group A, 13 were definite patients and 32 were probable patients. In Group B, 31 were definite and 28 probable. These two groups showed no significant difference in terms of sex (χ^2 = 0.033, P = 0.856), age (t = 0.199, P = 0.478), incubation period (Z = −0.484, P = 0.629), or number of patients with a body temperature of ≥38.5°C (χ^2 = 0.543, P = 0.461). Between these two groups, duration of hospital stay was shorter in Group A (median: 9 [IQR: 7 − 12] days) compared with Group B (median: 10 [IQR: 7 − 13] days), but this difference was not significant (Z = −0.818, P = 0.413). However, the number of patients meeting the criteria of "definite" and "probable" (χ^2 = 5.852, P = 0.016), with an eosinophilic granulocyte count of ≥1.5×10^9/L (χ^2 = 7.129, P = 0.008), and with rash area of >50% BSA (χ^2 = 7.129 P = 0.029), was significantly different [Table 4]. One patient died after treatment, but the remaining patients recovered/improved from DRESS and were discharged from the hospital.

Discussion

Incubation period

DRESS is a rare, severe side effect of drug use. It is characterized by a rash, fever, and enlarged lymph nodes and accompanied by abnormal blood tests and organ involvement. It has a long incubation period and mortality is about 10%.[5]

The incubation period of the 104 patients in the study was 13 days (IQR: 10–17 days). The shortest incubation lasted for 1 day and the longest for 120 days (one patient each). The remaining patients all had an incubation period of 7–60 days. One-day incubation was noted in a male patient aged 60 years: he took erythromycin (p.o.) for a sore throat 20 days before DRESS occurred. Four days after drug initiation, he developed systemic mild itching and a few erythematous papules. An anti-histamine (p.o.) was administered and glucocorticoids (topical) applied, and the symptoms receded in 3 days. He developed skin eruptions again after a repeat trial of erythromycin (p.o.) for 1 day and further development of DRESS, suggesting that drug reuse shortened the incubation period and aggravated DRESS severely. Furthermore, the allergic reaction at this time was significantly more severe than that observed initially and developed ultimately into DRESS, which was combined with thrombocytopenia as well as functional lesions in the

Table 2: Culprit drugs of the drug reaction with eosinophilia and systemic symptoms syndrome in the study (n = 104)

Culprit drug(s)	Value, n (%)
Anticonvulsants	
Carbamazepine	7 (6.7)
Lamotrigine	5 (4.8)
Phenytoin	1 (1.0)
Gabapentin	1 (1.0)
Allopurinol	4 (3.8)
Antibiotics	
Cefaclor	6 (5.8)
Levofloxacin	6 (5.8)
Amoxicillin	4 (3.8)
Cefuroxime axetil	4 (3.8)
Amoxicillin-potassium clavulanate	3 (2.9)
Azithromycin	2 (1.9)
Clindamycin	2 (1.9)
Tinidazole	2 (1.9)
Ampicillin sodium	1 (1.0)
Aztreonam	1 (1.0)
Erythromycin	1 (1.0)
Piperacillin sodium, sulbactam sodium	1 (1.0)
Cefprozil	1 (1.0)
Cefdinir	1 (1.0)
Ceftriaxone	1 (1.0)
Vancomycin	1 (1.0)
Antipyretic analgesics	
Acetaminophen	1 (1.0)
Aspisol	1 (1.0)
Aceclofenac	1 (1.0)
Others	
Methimazole	3 (2.9)
Tetanus antitoxin	2 (1.9)
Tetanus immunoglobulin	1 (1.0)
Atorvastatin calcium	1 (1.0)
Pirarubicin	1 (1.0)
Propylthiouracil	1 (1.0)
Iohexol	1 (1.0)
Lercanidipine	1 (1.0)
Pantoprazole	1 (1.0)
Rosuvastatin	1 (1.0)
Compound medicine	
Compound diclofenac sodium and chlorphenamine maleate	1 (1.0)
Pseudoephedrine hydrochloride	1 (1.0)
Aminophenazone and barbital	1 (1.0)
Paracetamol and caffeine	1 (1.0)
Compound pseudoephedrine hydrochloride	1 (1.0)
Paracetamol and oxycodone	1 (1.0)
Traditional Chinese medicine	
Xiaojinwan (capsules)	7 (6.7)
Xueshuantong	2 (1.9)
Xinqingning	1 (1.0)
Baotaijixuegent	1 (1.0)
Herbal medicine	3 (2.9)
Combination formulations	
Isoniazid, rifampicin, and pyrazinamide	2 (1.9)
Isoniazid, rifampicin, and pyrazinamide	1 (1.0)
Amoxicillin-potassium clavulanate, hydrotalcid, esomeprazole	2 (1.9)
Amoxicillin-potassium clavulanate, hydrotalcid, omeprazole	1 (1.0)
Others	4 (3.8)
Unknown	3 (2.9)

liver, kidneys, and pancreas. These findings suggest that reuse of sensitized drugs might cause serious complications or even endanger life. Incubation of 120 days was noted in a female aged 38 years. Her condition was caused by lamotrigine (p.o.) (used to treat depression). In general, if a drug has been used continuously for >3 months, then it is not the causative agent.[17] However, this patient had not used other drugs before DRESS development, and she presented with the typical symptoms of DRESS. Therefore, lamotrigine was identified as the allergy-inducing drug. This observation suggests that clinicians should obtain a full history of medication administration, especially if the clinical manifestations point strongly to a drug response. A full history of medication-taking going back >3 months should be sought.

Culprit drugs

In the present study, we analyzed retrospectively cases of DRESS in a Chinese tertiary hospital over the past decade. Classes of allergy-inducing drugs were analyzed, and antibiotics were the most common type (accounting for 37 cases [35.6%]), followed by anticonvulsants (14, 13.5%). Unlike some of the conclusions reached from studies on Caucasian and Asian populations, antibiotic allergies were more common in our center, and allergy to sulfonamides was not observed. These differences might be explained by the medication profiles in specific countries and regions.[7,17,19-21] It is noteworthy that Chinese patent medicines and antiepileptic drugs were the second most prevalent category of sensitizing drug, with 14 cases (13.5%) each. The Xiaojinwan capsule of Chinese patent medicion and carbamazepine were the most common sensitizing drugs, with seven cases (6.7%) each. The observation showed that the allergic responses caused by TCMs were not different from those elicited by other drugs. The three herbal TCMs that caused an allergic reaction each contained multiple drug ingredients. Therefore, precise identification of the specific causative agent was difficult, and physicians could not provide clear recommendations to patients about this agent. TCMs are used widely in China.[22-25] The present study showed that TCMs were the second most prevalent class of sensitizing drugs. Hence, clinicians must be particularly cautious when prescribing TCMs.

When allergy-inducing drugs were analyzed, we noticed that drug combinations were used for the treatment of two diseases: tuberculosis and infection by *Helicobacter pylori*. When drugs are combined, determination of the causative

Table 3: Clinical characteristics of the study (n = 104)

Variables	Value, n (%)
Fever	90 (86.5)
≥38.5°C	62 (59.6)
Enlarged lymph nodes (≥2 sites)	74 (71.2)
Hematologic abnormalities	
Leukocytosis >1.0×10^9/L	54 (51.9)
Eosinophilia	72 (69.2)
0.7×10^9/L–1.499×10^9/L	37 (35.6)
≥1.5×10^9/L	35 (33.7)
Eosinophils, if leukocytes <4.0×10^9/L	
10–19.9%	5 (4.8)
≥20%	0
Atypical lymphocytes	26 (25.0)
Cutaneous symptoms	
Extent of rash >50%	82 (78.8)
Maculopapular rash	88 (84.6)
Wheal and flare	5 (4.8)
Vesicles or blisters	19 (18.3)
Plaque	2 (1.9)
Pustules	3 (2.9)
Patch	15 (14.4)
Purpura	6 (5.8)
Target lesion	9 (8.7)
Facial edema	28 (26.9)
Organ involvement	96 (92.3)
One organ involved	77 (74.0)
Two or more organs involved	19 (18.3)
Liver	94 (90.4)
Kidney	9 (8.7)
Lung	7 (6.7)
Heart	6 (5.8)
Pancreas	2 (1.9)
Gastrointestinal	1 (1.0)
Nervous disorders	1 (1.0)
Resolution ≥15 days	99 (95.2)
Evaluation of other potential causes	
Antinuclear antibody	4 (3.8)
Blood culture	0
Serology for HAV/HBV/HCV	18 (17.3)
Chlamydia/mycoplasma	3 (2.9)

HAV: Hepatitis A virus; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

drug is not possible. Tuberculosis was treated primarily using a combination formulation containing three drugs. Of the three patients who developed allergies when anti-tuberculosis drugs were administered, two had isoniazid plus rifampicin plus pyrazinamide and one had isoniazid plus rifampicin plus ethambutol. Three patients received a combination formulation against anti-*H. pylori* that contained amoxicillin-potassium clavulanate and magnesium carbonate plus esomeprazole or omeprazole. Of these 104 patients, one had combined treatment for tuberculosis: isoniazid, rifampicin, and pyrazinamide. The latter two agents were discontinued after a mild rash, and isoniazid was continued. The patient developed DRESS and received hospital treatment for 112 days. Upon discharge from hospital, the patient continued to take glucocorticoids for 5 months before being cured of tuberculosis. This observation suggests that failure to discontinue use of sensitizing drugs might lead to severe drug reactions. Conversely, it also shows that if sensitizing drugs are applied in combination with other drugs, determination of the sensitizing drug becomes difficult. If re-challenge with the drug is not appropriate, then a patch test is a feasible means of detection.[26,27]

Clinical features and laboratory findings

The clinical manifestations of DRESS varied, but the most common was widespread erythematous papules. A total of 78.8% of patients had a rash of area >50% BSA. The most typical visceral damage occurred to the liver and/or kidneys. Liver damage accounted for 90.4% of total cases, higher than those found in the literature (about 70%).[28] Kidney damage (or progression of original kidney damage) occurred in nine patients (8.7%). Lung damage (as manifested by dyspnea as well as patchy spots and ground-glass opacities on chest radiography) occurred in seven patients. The six patients with heart damage had increased levels of cTnT, CK-MB, lactate dehydrogenase, and α-hydroxybutyrate dehydrogenase, often accompanied with ST-T or T changes upon electrocardiography. More than 19 cases developed damage to two or more than two organs. One patient had damage to the nervous system (as manifested by language disorder and delirium) that might have resulted from liver damage and subsequent high levels of ammonia in blood. After treatment, blood levels of ammonia decreased and consciousness was recovered.

Treatment and clinical course

Systemic application of glucocorticoids and IVIG is effective for DRESS treatment.[29] Among 104 patients, 58 (55.8%) were subject to glucocorticoid treatment (including two patients having additional treatment with IVIG or cyclosporine A). Outcomes were satisfactory because DRESS symptoms were brought under control. Combination of IVIG or cyclosporine A was administered to patients who suffered relapses. IVIG was administered to the patient with tuberculosis who developed DRESS resulting from anti-tuberculosis treatment. The initial dose was insufficient due to concerns about the glucocorticoid effects on tuberculosis and because the symptoms were not brought under control completely. After relapse, the glucocorticoid dose was doubled and IVIG administered simultaneously, which resulted in complete control of DRESS. In a different patient, DRESS was brought under complete control initially with glucocorticoid, but the patient had a relapse with a rash when the glucocorticoid dose decreased. Possible explanations include rapid reduction of glucocorticoid use or additional development of drug-induced allergy. One-day application of IVIG aggravated the rash. Allergy to IVIG could not be ruled out, so cyclosporine A was administered instead, the symptoms were controlled, and the patient discharged from hospital. IVIG might be a suitable choice for patients in whom glucocorticoid therapy must be used with caution or is

Table 4: Diagnosis, body temperature, eosinophil counts, and rash area of patients who underwent systemic administration of glucocorticoids/immunosuppressants/IVIG or anti-histamines (n = 104)

Variables	Application of glucocorticoids/ immunosuppressants/IVIG, n	Anti-histamine, n	Total, n	χ^2	P
Diagnosis					
Definite	31	13	44	5.852	0.016
Probable	28	32	60		
Body temperature ≥38.5°C					
Positive	37	25	62	0.543	0.461
Negative	22	20	42		
Eosinophils ≥1.5×10^9/L					
Positive	25	8	33	7.129	0.008
Negative	34	37	71		
Rash area >50% BSA					
Positive	48	28	76	4.750	0.029
Negative	11	17	28		

IVIG: Intravenous immunoglobulin; BSA: Body surface area.

contraindicated. IVIG might be a relatively good choice if glucocorticoids are not ideal for controlling the disease, and a drug combination is needed.

Group A and Group B did not show significant differences between each other with respect to sex, age, incubation period, or the number of patients with pyrexia. However, Group B had a significantly larger percentage of definite patients (53%) than Group A (29%). Percentages of patients with eosinophils ≥1.5 × 10^9/L as well as rash area >50% BSA were also significantly higher in Group B. Patients with a score 4–5 were classified as probable and those with a score >5 as definite, following the RegiSCAR guidelines: the higher the score, the more severe was DRESS. Therefore, the two groups were significantly different in term of DRESS severity, but not in terms of duration of hospital stay. These results suggested that administration of glucocorticoids/immunosuppressants/IVIG could bring about disease control and shorten the duration of hospital stay more rapidly.

Cause of death of a patient

The mortality rate of DRESS has been reported to be about 10%.[20,30] Among the 104 patients enrolled in the study, 103 were discharged successfully after the disease had improved or been cured. Only one patient died, thereby yielding a much lower mortality rate (<1%) than that reported in the literature.[5] The patient who died had previous renal insufficiency and progressed rapidly to uremia after the current episode of DRESS. A large opacity developed in the inferior lobe of the right lung 4 days after hospital admission, and heart failure accompanied with dyspnea on day 7. Radiography of the chest showed a large shadow in bilateral superior lobes. Sputum culture revealed *Acinetobacter baumannii* and the patient died on day 7. *A. baumannii* is a common opportunistic pathogen distributed widely in the natural environment. Often, it is isolated from patients with poor immunity, on mechanical ventilation, or experiencing a long stay in hospital. It is a common pathogen in hospital-acquired infections, with resistance to a wide range of drugs, and makes anti-infection therapy extremely difficult.[31] Therefore, physicians need to prevent hospital-acquired infections among DRESS patients, strengthen monitoring of drug-resistant pathogen strains, and apply antibiotics appropriately.

As a retrospective study carried out in a tertiary-care setting in China, it was limited by the sample size and because the findings (e.g., proportions and types of allergy-inducing drugs) might have been biased. In addition, >90% of our patients suffered from liver damage, which was higher than those noted in the literature (70%),[20] which might be explained by the more severe cases present in a tertiary-care setting. In addition, the low mortality rate could also be a result of the small sample size.

In conclusion, antibiotics were associated with allergic reactions, but TCMs also had an important role in the present study. The incubation period for DRESSS was ≤120 days. Allergy resulting from repeat use of the same drug was more severe with a shorter incubation period. The most typical rash was widespread erythematous papules. Liver damage accounted for >90% of cases. Glucocorticoid application was the most effective treatment, and its combination with IVIG or cyclosporine A was effective in patients suffering relapses.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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