REVIEW

THE AMERICAN JOURNAL of MEDICINE®

The DRESS Syndrome: A Literature Review

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ABSTRACT

The Drug Reaction with Eosinophilia and Systemic Symptom (DRESS) is a severe adverse drug-induced reaction. Diagnosing DRESS is challenging due to the diversity of cutaneous eruption and organs involved. We used the RegiSCAR scoring system that grades DRESS cases as "no," "possible," "probable," or "definite" to classify cases reported in the literature. We also analyzed the clinical course and treatments of the cases. A total of 44 drugs were associated with the 172 cases reported between January 1997 and May 2009 in PubMed and MEDLINE. The most frequently reported drug was carbamazepine, and the vast majority of cases were classified as "probable/definite" DRESS cases. Hypereosinophilia, liver involvement, fever, and lymphadenopathy were significantly associated with "probable/definite" DRESS cases, whereas skin rash was described in almost all of the cases, including "possible cases." Culprit drug withdrawal and corticosteroids constituted the mainstay of DRESS treatment. The outcome was death in 9 cases. However, no predictive factors for serious cases were found. This better knowledge of DRESS may contribute to improve the diagnosis and management of this syndrome in clinical practice.
 • *The American Journal of Medicine (2011) 124, 588-597*

KEYWORDS: Drug hypersensitivity; Drug rash; Eosinophilia; HHV-6; Systemic symptoms

The Drug Reaction with Eosinophilia and Systemic Symptom (DRESS) is a severe adverse drug-induced reaction. The estimated incidence of this syndrome ranges from 1 in 1000 to 1 in 10,000 drug exposures.[1] The acronym designated by Bocquet et al[2] describes a potentially life-threatening syndrome including a severe skin eruption, fever, hematologic abnormalities (eosinophilia or atypical lymphocytes), and internal organ involvement. The other noteworthy features are a delayed onset, usually 2-6 weeks after the initiation of drug therapy, and the possible persistence or aggravation of symptoms despite the discontinuation of the culprit drug.[2,3]

The pathogenesis of DRESS syndrome is partially understood. Different mechanisms have been implicated in its development, including detoxification defects leading to reactive metabolite formation and subsequent immunological reactions,[4] slow acetylation, and reactivation of human herpes, including Epstein-Barr virus and human herpesvirus (HHV)-6 and -7.[5-7] The detection of HHV-6 reactivation has even been recently proposed as a diagnostic marker for DRESS.[8]

The diagnosis of DRESS is challenging because the pattern of cutaneous eruption and the types of organs in-

Funding: This work was funded by Institut de Recherche Internationale Servier.

Conflict of Interest: Pr. Jean Claude Roujeau has provided punctual advice on cases of adverse reactions to drugs from more than 15 different pharmaceutical companies in the past 20 years. He has served as an expert on 3 trials related to severe drug reactions in US Courts. He is a member of advisory boards on Severe Cutaneous Adverse Reactions for Pfizer (2002-2007), Vertex (2008-ongoing), Servier (2008-ongoing), Boehringer Ingelheim (2010-ongoing), Roche (2010-ongoing). He has participated in the RegiSCAR research group, funded in part by several pharmaceutical companies (detailed list provided in publications by the RegiSCAR group, eg, Sassolas B et al. *Clin Pharmacol Ther*. 2010;88[1]:60-8). No other authors have any conflicts of interest to report.

Authorship: All authors had access to the data and played a role in writing this manuscript.

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0002-9343/$ -see front matter
doi:10.1016/j.amjmed.2011.01.017

volved are various. In addition, the multitude of denominations for this syndrome, such as drug hypersensitivity, drug-induced delayed multiorgan hypersensitivity syndrome,[9] and recently, drug-induced hypersensitivity syndrome (DIHS),[10] is confusing. However, recognizing this syndrome is of particular importance, as the mortality rate is up to 10%.

In an effort to define more accurately the DRESS syndrome, a scoring system has been recently developed: the RegiSCAR scoring system.[11] RegiSCAR constitutes a European registry of severe cutaneous adverse reaction (SCAR), including Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and DRESS. One of the aims of this registry is to delineate each of these SCARs as distinct entities. In this line, the RegiSCAR's scoring system has been designed to grade DRESS cases as "no," "possible," "probable," or "definite" case. The aim of this review was to classify cases reported as DRESS or drug hypersensitivity syndrome in the literature by using the RegiSCAR scoring system.[11] We also analyzed the clinical course and treatments of the reported cases. A better knowledge of DRESS may contribute to improving the diagnosis and management of this syndrome in clinical practice.

With this scoring system, cases could be classified as definite DRESS without fulfilling all 7 criteria, while diagnosis of DIHS requires that all 7 criteria be present.

CLINICAL SIGNIFICANCE

- Drug Reaction with Eosinophilia and Systemic Symptom (DRESS) is a potentially life-threatening syndrome including severe eruption, fever, hypereosinophilia, and internal organ involvement.
- The main culprit drugs are carbamazepine and allopurinol, even though 50 drugs can induce DRESS.
- DRESS can be associated with human herpesvirus 4, 6, and 7 infections; thus, serology of these viruses should be checked.
- The main treatments of DRESS are withdrawal of culprit drug and corticosteroid treatment.

MATERIALS AND METHODS

A systematic review of DRESS cases reported in the literature was carried out by searching PubMed-MEDLINE between January 1997 and May 2009. Search terms were "DRESS syndrome," "drug reaction with eosinophilia and systemic symptoms," "drug rash with eosinophilia and systemic symptoms," "drug hypersensitivity and eosinophilia," and "drug-induced hypersensitivity syndrome." Publications were limited to the English and French languages.

We used the RegiSCAR's scoring system recently published to classify the cases reported in the literature.[11] The scoring system is shown in Table 1 and includes the following items: fever, eosinophilia, enlarged lymph nodes, atypical lymphocytes, skin involvement, organ involvement, time of resolution, and the evaluation of other potential causes. Skin rash suggestive of DRESS encompasses maculopapular rash and erythematous skin eruption, often progressing to exfoliative dermatitis associated with facial edema.

The times of both onset and resolution of symptoms were recorded, as well as the detection of HHV-6 infection.

Data were extracted and recorded in a Microsoft Excel spreadsheet (Microsoft Corporation, Redmond, Wash). For each case report, a final score was calculated allowing the cases to be classified as "no case," "possible case," "probable case," and "definite case" of DRESS. Then, 2 groups were defined as the "no/possible cases" group and the "probable/definite" cases group. The characteristics of the 2 groups of patients were compared using the chi-squared or Wilcoxon test. Multivariate logistic regression was performed to define factors associated with "probable/definite cases."

The impacts of using DRESS in the title of the publication and of the year of the publication on the classification of DRESS also were assessed. Statistical analysis was performed using SAS version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

From a total of 131 independent published reports, 172 cases of DRESS were analyzed. Publications were excluded from analysis when they displayed data group summaries in which data could not be fully analyzed because the results were not assigned to a specific patient (Figure).

The drugs associated with DRESS and the distribution of the cases after RegiSCAR's score assignment are displayed in Table 2.[12-140] A total of 44 drugs were described to be associated with DRESS. Of these, the most frequently reported drugs were carbamazepine, allopurinol, sulfasalazine, phenobarbital, lamotrigine, and nevirapine. However, more than half of the drugs were associated with only one case of DRESS.

The vast majority of cases obtained through literature search were classified as either definite or probable cases of DRESS, whereas $<10\%$ of reported cases were not scored as DRESS according to the RegiSCAR system (Table 2).

The main demographic, clinical, and treatment characteristics associated with DRESS are shown in Table 3. Skin rash was reported in almost all cases. The cutaneous eruption was mostly described as a maculopapular rash or a generalized erythematous rash.

Internal organ involvement was mentioned in the vast majority of patients. The liver was the most frequently involved internal organ. Liver involvement was described by either the elevation of liver function tests or the presence of hepatomegaly. The levels of aspartate aminotransferase and alanine aminotransferase increased by approximately 9

Table 1 Scoring System for Classifying DRESS Cases as Definite, Probable, Possible, or No Case, from Kardaun et al[11]

Score	−1	0	1	2
Fever ≥38.5°C	No/U	Yes		
Enlarged lymph nodes		No/U	Yes	
Eosinophilia		No/U		
Eosinophils			0.7-1.499 × 10^9 L^{-1}	≥1.5 × 10^9 L^{-1}
Eosinophils, if leukocytes <4.0 × 10^9 L^{-1}			10%-19.9%	≥20%
Atypical lymphocytes		No/U	Yes	
Skin involvement				
Skin rash extent (% body surface area)		No/U	>50%	
Skin rash suggesting DRESS	No	U	Yes	
Biopsy suggesting DRESS	No	Yes/U		
Organ involvement*				
Liver		No/U	Yes	
Kidney		No/U	Yes	
Muscle/heart		No/U	Yes	
Pancreas		No/U	Yes	
Other organ		No/U	Yes	
Resolution ≥15 days	No/U	Yes		
Evaluation of other potential causes				
Antinuclear antibody				
Blood culture				
Serology for HAV/HBV/HCV				
Chlamydia/mycoplasma				
If none positive and ≥3 of above negative			Yes	

DRESS = Drug Reaction with Eosinophilia and Systemic Symptom; U = unknown/unclassifiable; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus.

*After exclusion of other explanations: 1, one organ; 2, two or more organs. Final score < 2, no case; final score 2-3; possible case; final score 4-5, probable case; final score > 5, definite case.

fold (range 1.5-160) and 10 fold (range 1.5-54) above the normal limits, respectively. Affection of other organs was rarely reported. In addition, no relevant link could be established between internal organ impairment and the type of causative drug. Following skin rash and systemic symptoms, hypereosinophilia was the third most frequently reported sign in patients having a DRESS. Fever and peripheral lymphadenopathy occurred in approximately more than half of the patients.

The mechanisms underlying DRESS development were not investigated in the vast majority of cases: detection of HHV-6 infection was performed in less than half of cases (Table 3). However, when HHV-6 infection was investigated, the results of the test (serology or polymerase chain reaction) were positive in 80% of cases. Of these cases, the positive diagnosis of HHV-6 infection was mostly based on an increase in the anti-HHV-6 immunoglobulin G titer, implicating an HHV-6 reactivation. Other potential causes of symptoms besides drugs were ruled out in 52 cases (30%) based on the following criteria: absence of antinuclear antibody, negative blood culture, and negative serology for hepatitis A, hepatitis B, and hepatitis C virus.

In all cases, patients were hospitalized and the culprit drug was withheld within the first days of hospitalization. The main treatment was corticosteroids (Table 3). The doses and route of administration were, however, rarely mentioned. Corticosteroids were combined with intravenous immunoglobulin in 10 cases. Overall, the mean time for recovery was 6.4 ± 9.4 weeks (range 0.5-90 weeks). However, DRESS syndrome resulted in death in 9 cases (5%). Characteristics of DRESS cases resulting in death are displayed in Table 4. The patients with severe DRESS cases tended to be older than those recovering from DRESS. Almost all of these cases were associated with liver involvement, and treatment with corticosteroids did not prevent a fatal outcome. The cause of death was cardiac or hepatic. In addition, no significant differences were found for demographic, clinical, and outcome parameters between cases resulting in death and those that resolved (data not shown).

When cases were classified into 2 groups based on the RegiSCAR's scoring system, that is, "no/possible cases" and "probable/definite cases," the 2 groups differed significantly regarding the vast majority of clinical and outcome parameters (Table 5). The following were significantly most reported in the "probable/definite" cases group: the presence of skin rash, liver involvement, high grade fever, hypereosinophilia, lymphadenopathy, and atypical lymphocyte. Consistently, the multivariate logistic regression identified fever, hypereosinophilia, liver involvement, and lymphadenopathy as factors significantly associated with "probable/definite" cases of DRESS.

When DRESS appeared in the title of a publication, cases were more often classified as "probable/definite" (Table 5). In addition, because the RegiSCAR's scoring system was

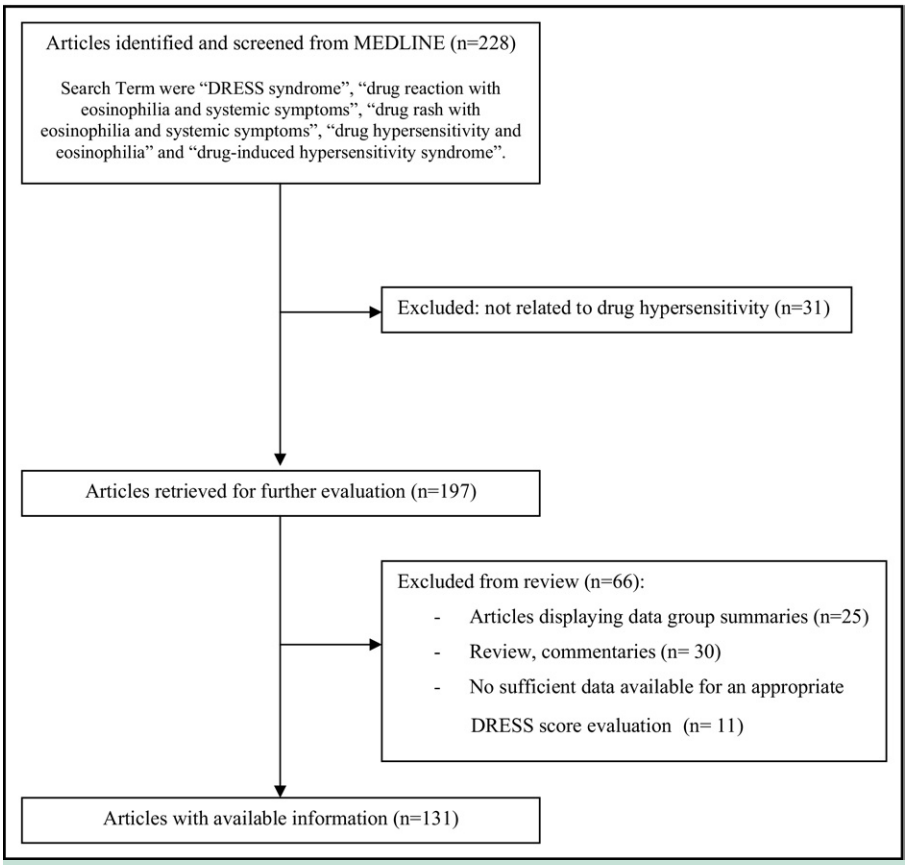

Figure Flow diagram of literature selection process. DRESS = Drug Reaction with Eosinophilia and Systemic Symptom.

published in 2007, we assessed the impact of the year of the publication on cases classification. The proportion of cases defined as "probable/definite" was not statistically different when cases were published before 2008 (Table 5).

DISCUSSION

In this review, we have done an extended analysis of 172 cases reported as DRESS or drug hypersensitivity syndrome in the literature by using the RegiSCAR scoring system.[11]

This review shows that DRESS is challenging to diagnose. Patients defined by the scoring system as "no/possible" cases of DRESS accounted for approximately one quarter of all the DRESS cases reported in the literature. However, cases classified as "probable/definite" by the RegiSCAR scoring system represented the vast majority (88%) of cases published under the denomination of DRESS. Consistently, fewer cases (63%) published under another denomination were classified as "probable/definite" cases. This indicates that the denomination DRESS is accurately used in the literature.

The presenting symptoms in almost all patients were skin rash, liver involvement, hypereosinophilia, and lymphadenopathy. Consistent with the fact that we have used a scoring system, the distribution of these clinical characteristics significantly differed between patients with "no/possible" DRESS cases and those with "probable/definite" DRESS cases. However, skin rash was the most frequently reported symptom in both groups, in accordance with the original signification of the DRESS acronym.[2] Here, only 5 of 172 cases were described with no skin involvement. Of these 5 cases, 3 were defined as "no DRESS." Nevertheless, skin rash also has been described in almost all of the "possible cases" and was not significantly associated with "probable/definite" cases. No pathognomonic pattern of skin rash emerged from the literature. The presence of facial edema was reported in only one third of cases.

In contrast to skin rash, hypereosinophilia, liver involvement, fever, and lymphadenopathy were significantly associated with "probable/definite" DRESS cases. Liver involvement was described either as raised aminotransferase or hepatomegaly. Other organs such as the kidney or the central nervous system were rarely involved. Altogether, these results indicate that DRESS should be suspected, not on the sole presence of skin eruption, but also on the presence of hypereosinophilia, liver involvement, fever, and lymphadenopathy. However, these symptoms also are common to other diseases such as connective tissue diseases, idiopathic hypereosinophilia, and viral hepatitis. These differential diagnoses of DRESS have been ruled out in only 30% of reported cases, on the basis of the absence of

Table 2 Classification of Published DRESS Cases According to the RegiSCAR's Score[11]

Drugs	Classification of DRESS cases n = 172				Nb of Cases n (%)
	No case n = 13 (8%)	Possible n = 35 (20%)	Probable n = 77 (45%)	Definite n = 47 (27%)	
Abacavir[12-16]	4	1			5 (3)
Allopurinol[17-29]	1	6	8	4	19 (11)
Amoxicillin plus clavulanic acid[30]			1		1 (0.6)
Amitriptyline[31,32]			2		2 (1)
Atovarstatin[33]			1		1 (0.6)
Aspirin[34]				1	1 (0.6)
Captopril[6]			1		1 (0.6)
Carbamazepine[5,18,24,35-63]	3	10	20	14	47 (27)
Cefadroxil[64]			1		1 (0.6)
Celecoxib[65]			1		1 (0.6)
Chlorambucil[66]			1		1 (0.6)
Clomipramine[67]			1		1 (0.6)
Clopidogrel[68]	1				1 (0.6)
Codeine phosphate[69]			1		1 (0.6)
Cotrimoxazole/cefixime[70]			1		1 (0.6)
Cyanamide[71]			1		1 (0.6)
Dapsone[72-75]			4		4 (2)
Diaphenylsulfone[76]		1			1 (0.6)
Efalizumab[77]			1		1 (0.6)
Esomeprazole[78]			1		1 (0.6)
Hydroxychloroquine[79,80]				2	2 (1)
Ibruprofen[5,81]			2		2 (1)
Imatinib[82]			1		1 (0.6)
Lamotrigine[52,83-91]	3	3	2	2	10 (6)
Mexilletine[24,92-95]		2	3		5 (3)
Minocycline[96-98]			2	1	3 (2)
Nevirapine[99-104]		3	3	2	8 (5)
Olanzapine[105]				1	1 (0.6)
Oxcarbazepine[106-108]			1	2	3 (2)
Phenobarbital[18,37,47,109-115]		3	4	3	10 (6)
Phenylbutazone[116]				1	1 (0.6)
Phenytoin[24,47,58,117-120]	1	3	3		7 (4)
Quinine and thiamine[121]			1		1 (0.6)
Salazosulfapyridine[5,122]			1	1	2 (1)
Sodium meglumine ioxitalamate[123]			1		1 (0.6)
Sodium valproate/ethosuximide[124]				1	1 (0.6)
Spironolactone[125]				1	1 (0.6)
Streptomycin[126]				1	1 (0.6)
Strontium ranelate[127]			1	1	2 (1)
Sulfalazine[62,93,128-135]		3	2	5	10 (6)
Sulfamethoxazole[14,136]			2		2 (1)
Tribenoside[13]				1	1 (0.6)
Vancomycin[137-140]		1	2	1	4 (2)
Zonisamide[18]				1	1 (0.6)

DRESS = Drug Reaction with Eosinophilia and Systemic Symptom.

antinuclear antibody, negative blood culture, and negative serology for hepatitis A, hepatitis B, and hepatitis C virus.

A delayed onset of symptoms 2-6 weeks after the initiation of causative drug is a feature of DRESS. Consistently, the onset of symptoms appeared to be more delayed in patients with "probable/definite" cases. The resolution occurred after a longer time period in the "probable/definite" cases compared with the "no/possible" cases. This resolution also was characterized by several flare-ups of clinical symptoms despite the management of DRESS. The type of DRESS management recorded in this review included the discontinuation of the causative drug in all the DRESS cases and treatment with corticosteroids. The rates of patients treated with corticosteroids were similar in both groups.

Table 3 Demographic, Clinical, and Treatment Characteristics Associated with DRESS

	n	%
Age (years)		
Mean ± SD (range)	40.7 ± 20.9 (0.1-84)	–
Sex		
Male	87/165	53
Female	78/165	47
Onset (weeks)*		
Mean ± SD (range)	3.9 ± 2.3 (0.5-16)	–
Skin rash	167/172	97
Maculopapular rash	101/167	60
Generalized erythematous rash	90/167	54
Facial edema	65/167	39
Internal organ involvement	151/172	88
Liver	142/151	94
Elevation of liver function tests	84/142	59
Hepatomegaly	17/142	12
Kidney	12/151	8
Lung	7/151	5
Central nervous system	3/151	2
Heart	3/151	2
Hypereosinophilia ($>0.7 \times 10^9$ L^{-1})	114/172	66
Eosinophils (10^9 L^{-1})		
Mean ± SD (range)	3.5 ± 4.1 (0.4-30)	–
Fever >38.5°C	111/172	64
Lymphadenopathy	96/172	56
Atypical lymphocytes	47/172	27
HHV-6 infection		
Detection	70/172	41
Positive	56/70	80
Treatment		
Corticosteroids	134/172	78
Intravenous immunoglobulin	16/172	9

DRESS = Drug Reaction with Eosinophilia and Systemic Symptom; HHV-6 = human herpesvirus 6.
*Time between the initiation of drug therapy and the occurrence of symptoms.

Unfortunately, the route of administration and dose of corticosteroid treatment were not reported in many case reports considered in this review, rendering it difficult to analyze these therapies. This highlights the lack of consensus guidelines on DRESS syndrome treatment and consequently the need for improving the management of DRESS.

Improving the management of DRESS is closely linked to better knowledge of its pathogenesis, including identification of the culprit drugs and viral reactivation. DRESS has been initially described as the anticonvulsant hypersensitivity syndrome.[4] Here, anticonvulsants including carbamazepine, lamotrigine, and phenobarbital accounted for one third of the drugs causing DRESS. In contrast, the vast majority of the other drugs were only associated with one case of DRESS. Some of these drugs even appeared not to be the causative drug of the DRESS syndrome. Indeed, of the 5 cases of drug hypersensitivity syndrome associated with the antiretroviral agent abacavir, 4 were scored as "no case." Genetic susceptibility has been shown to influence abacavir hypersensitivity,[141] suggesting that abacavir hypersensitivity could be a distinct clinical entity of DRESS. This variety of drugs, together with the clinical course characterized by slow resolution and relapse, suggests that drugs cannot be the sole etiology of DRESS. In accordance with this hypothesis, HHV-6 reactivation has been defined in previous studies as a potential contributor to DRESS development.[5,6] In this review, the detection of HHV-6 was performed in 41% of cases. This relatively low rate of detection may reflect the fact that the involvement of HHV-6 infection in DRESS development is a recent hypothesis. The majority of the cases reporting HHV-6 detection have been recently published. In the majority of these publications (52/70), HHV-6 infection was found to be reactivated. Consistently, the diagnosis of DIHS that represents the most recent proposal for DRESS denomination requires HHV-6 reactivation together with the presence of maculopapular rash, prolonged clinical symptom, fever, liver abnormalities, leukocyte abnormalities, and lymphadenopathy.[10] Because cases could be classified as definite DRESS without fulfilling all these criteria, DIHS has been regarded as a more severe form of DRESS.[10]

For some of the remaining cases without HHV-6 reactivation, other types of viral infection were reported, such as cytomegalovirus reactivation[142] and paramyxovirus infection.[143] The high prevalence of viral infection, mostly HHV-6 infection, supports an emerging role of HHV-6 and other types of virus in the pathogenesis of DRESS. Recently, in a prospective study including 40 DRESS patients, Epstein-Barr virus, HHV-6, and HHV-7 reactivations were found in 76% of the cases. Interestingly, the culprit drugs were able to trigger viral reactivations that induce a pathogenic antiviral CD8+ immune response.[7]

Because DRESS is a life-threatening syndrome, predictive factors for serious cases need to be defined. However, no differences for demographic and clinical variables were found between cases resulting in death and those that resolved, suggesting that recognizing serious DRESS cases remains an issue. The type of causative drug may influence the outcome of DRESS such as allopurinol. In this review,

Table 4 Characteristics of DRESS Cases Resulting in Death

	n = 9
Age (years)	
Mean ± SD (range)	49.0 ± 23.5 (13-80)
Sex	
Male	5
Female	4
Onset (weeks)*	
Mean ± SD (range)	3.6 ± 2.3 (0.5-8)
Skin rash	9
Liver involvement	8
Time between onset of symptoms and death	6.2 ± 5.2 (1-16)

DRESS = Drug Reaction with Eosinophilia and Systemic Symptom.
*Time between the initiation of drug therapy and the occurrence of symptoms.

Table 5 Comparison of Clinical and Outcome Parameters between "No/Possible" Cases and "Probable/Definite" Cases of DRESS: Analysis of Factors Associated with "Probable/Definite" Cases of DRESS

	Univariate Analysis			Logistic Regression		
	No/Possible Cases n = 48	Probable/Definite Cases n = 124	*P* Value	Odds Ratio	95% Confidence Interval	*P* Value
Age, mean ± SD	42.2 ± 21.3	40.1 ± 20.8	.535			
Sex			.107			
Male	30/48 (63)	57/117 (49)				
Female	18/48 (38)	60/117 (51)				
Skin rash	44 (92)	123 (99)	.022			
Internal organ involvement						
Liver	30 (63)	112 (90)	<.001	11	3-41	<.001
Kidney	1 (2)	11 (9)	.183			
Lung	1 (2)	6 (5)	.675			
Hypereosinophilia (>0.7 × 10^9 L^{-1})	12 (25)	102 (82)	<.001	29	9-88	<.001
Fever >38.5°C	23 (48)	88 (71)	.005	6	2-16	.001
Lymphadenopathy	16 (33)	80 (65)	<.001	10	3-28	<.001
Atypical lymphocytes	4 (8)	43 (35)	<.001			
HHV-6 infection	9/14 (64)	47 (84)	.135			
Treatment (corticosteroids)	38 (79)	96 (77)	.804			
Onset (weeks), mean ± SD	3.6 ± 2.0	4.1 ± 2.4	.042			
Resolution (weeks), mean ± SD	3.8 ± 2.8	7.3 ± 10.6	.007			
"DRESS" in the title of the publication	7 (15)	53 (48)	<.001			
Year of publication ≥2008	12 (25)	25 (20)	.488			

DRESS = Drug Reaction with Eosinophilia and Systemic Symptom; HHV-6 = human herpesvirus 6.

allopurinol was involved in 3 of 9 patients with serious DRESS. This finding is in accordance with previous studies showing that the death rate in patients with allopurinol-associated DRESS was higher than that described in DRESS cases due to other drugs.[144,145]

Our study has several limitations. The retrospective review is subject to publication bias. The conclusions we were able to draw are limited by data gaps in many reports. Details on clinical and outcome parameters or on therapy were often not described.

In conclusion, the diagnosis of DRESS should be highly suspected with the presence of skin rash, liver involvement, fever, hypereosinophilia, and lymphadenopathy. The high rate of HHV-6 and other herpes viruses reactivation associated with DRESS implies that HHV-6 and other herpes viruses should be detected in routine clinical practice. Besides the prompt withdrawal of causative drug as standard of care, further studies are needed to recommend specific treatment guidelines.

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