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Characteristics of patients hospitalized for Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) at a Level 1 trauma center

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Abstract

The purpose of this study is to further characterize the population that is hospitalized for a severe cutaneous drug reaction or that developed once during their hospitalization. We conducted a chart review of patients seen by a dermatologist at the University of California Davis Medical Center for the diagnosis of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). Between January 2000 and July 2018, 25 cases of DRESS were diagnosed using RegiSCAR criteria. Twenty-two patients recovered, two were deceased, and one was transferred to another hospital. The most commonly implicated drugs in the development of DRESS were nafcillin (N=3) and carbamazepine (N=3). Of the 25 patients in our care, 88% developed eosinophilia, 50% developed renal involvement, and 44% had liver involvement. There was a positive correlation between age and creatine (P=0.01) and age and eosinophils (P=0.02). There was a negative correlation between age and liver enzyme abnormalities (AST P=0.01; ALT P=0.0003). Carbamazepine and nafcillin were commonly implicated drugs in DRESS. There was no significant difference between treatment group and patient outcome. Those who develop DRESS at an older age were more likely to have elevated creatinine and more profound eosinophilia, but were less likely to develop liver involvement.

Keywords: drug reaction with eosinophilia and systemic symptoms (DRESS); drug reaction

Introduction

With the increasing number of drugs used per hospital stay, adverse drug reactions have become more common causes of extended hospitalizations [1]. Although most are benign, about a third are severe, requiring further hospitalization, and 2% are life threatening [1]. Severe cutaneous adverse drug reactions include, but are not limited to, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS). Drug reaction with eosinophilia and systemic symptoms is a hypersensitivity syndrome that typically develops 2-to-6 weeks after drug initiation and is often associated with anticonvulsant use. Other drugs implicated in the development of DRESS include allopurinol, antibiotics (vancomycin, minocycline, trimethoprim-sulfamethoxazole), sulfasalazine, and anti-tuberculous agents [2].

Drug reaction with eosinophilia and systemic symptoms can be associated with fever, variations of cutaneous eruptions, prominent eosinophilia, and multi-organ involvement [3]. Mortality is as high as 10% and is most commonly related to fulminant hepatitis with necrosis [2]. Given the high mortality rate of this adverse drug reaction it becomes important to better understand the disease patterns and treatment outcomes to aid in providing timely diagnosis and treatment.

The purpose of this study is to further characterize the population that is hospitalized for DRESS or that

developed it during their hospitalization. In addition, we assessed the most common manifestations of severe drug reactions, demographic susceptibility to developing a severe adverse drug reaction, the implicated drugs, and treatment outcomes. The results of this study will help to better understand disease pattern and treatment for DRESS at a level 1 trauma center.

Methods

The study was reviewed and determined to be exempt by the University of California, Davis (UCD) Institutional Review Board. We conducted a chart review of patients seen by a dermatologist at a level 1 trauma center for the diagnosis of DRESS, based on the RegiSCAR criteria (**Table 1**), [4]. Kruskal-Wallis test was performed to compare ordinal data between three treatment groups: topical corticosteroids only, oral corticosteroids, and IV corticosteroids. Fisher test was used for nominal data. Spearman's rank correlation was used to assess correlation between age and elevations in eosinophils, creatinine, aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

Results

Between January 2000 and July 2018, 25 cases of DRESS were diagnosed using RegiSCAR criteria (**Table 2**). A majority of our patients were Caucasian, and the mean age was 48 years. More than half of our patients were women (Table 3). Three patients were treated with IV corticosteroids, 17 received oral corticosteroids, and four were treated with topical corticosteroids. Twenty-two patients recovered and two were deceased, for an overall mortality rate of 9%. One patient was transferred to another hospital.

Carbamazepine (N=3) and nafcillin (N=3) were two of the most commonly implicated drugs in our cohort (Table 4). Almost half of patients were febrile (>38.5°C), 88% developed eosinophilia >0.7 K/mm^3 (71% >1.5 K/mm^3), 50% had renal involvement (creatinine >1.5 mg/dL,), and 46% had liver involvement (AST>86u/L or ALT>126u/L), (**Figure 1**). Seven patients were tested for the presence of

Table 1. *Various diagnostic criteria for DRESS/DIHS*[1].

Demographics	
Age	**n**
0-18	2
18 – 40	5
41-60	10
61-80	8
81-100	1
Sex	**n**
Male	12
Female	14
Ethnicity	**n**
Unknown	3
African American or African or Black or Caribbean	2
American Indian or Alaska native	0
Hispanic or Latino or Spanish	4
Chinese	0
Japanese	0
Korean	1
Southeast Asian	1
Asian - Other	4
Native Hawaiian or Pacific Islander	1

[1]*a = References for the table: Table was adapted from Ang et al. [4, 12, 13, 14, 15]*
b = Abbreviations: DIHS, drug-induced hypersensitivity syndrome; DRESS, drug rash with eosinophilia and systemic symptoms; HHV, human herpesvirus

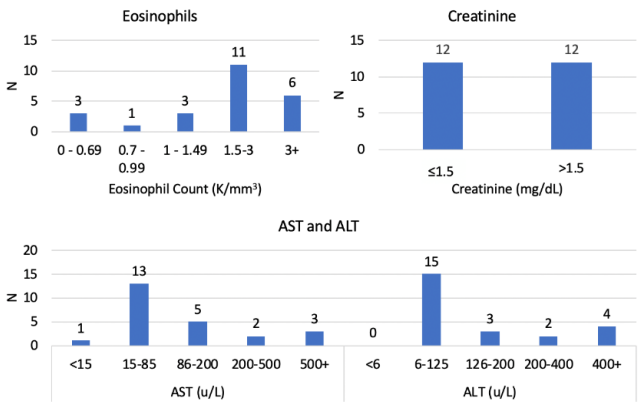

Figure 1. ***A)*** *eosinophil count,* ***B)*** *creatinine, and* ***C)*** *AST and ALT levels in patients hospitalized with Drug Reaction with Eosinophilia and Systemic Symptoms.*

Table 2. *Summary of study patients diagnosed with DRESS*[2].

Implicated Drugs (If multiple listed, then cause was not identified)	n
Metronidazole, Ceftazidime, Levetiracetam, or Vancomycin	1
Allopurinol	1
Azithromycin	1
Bactrim	1
Bactrim, Cephalexin	1
Carbamazepine	3
Carfilizomib	1
Ceftriaxone	1
Clindamycin, Lisinopril	1
Diltiazem, Promethazine	1
Imatinib	1
Levetiracetam	1
Levetiracetam, Bactrim, Piperacillin/Tazobactam	1
Nafcillin	3
Oxcarbazepine	1
Phenytoin	1
Quetiapine	1
RIPE - most likely isoniazid	1
Vancomycin	1

[2]*a = Abbreviations: DRESS, drug rash with eosinophilia and systemic symptoms; ACA, anterior cerebral artery; SAH, subarachnoid hemorrhage; T2DM, type 2 diabetes mellitus; HTN, hypertension; s/p, status post; TAH/BSO, total abdominal hysterectomy/bilateral salpingo-oophorectomy; c/b, complicated by; AKI, acute kidney injury; UGIB, upper gastrointestinal bleed; mo, month; GERD, gastroesophageal reflux disease; d/o, disorder, OSA, obstructive sleep apnea; CHF, congestive heart failure; CAD, coronary artery disease; afib, atrial fibrillation; MSSA, methicillin-sensitive staphylococcus aureus; VRE, vancomycin-resistant enterococcus; MRSA, methicillin-resistant staphylococcus aureus; TB, tuberculosis; ADHD, attention-deficit/hyperactivity disorder; MGUS, monoclonal gammopathy of undetermined significance; ARF, acute renal failure; CKD, chronic kidney disease; RIPE, rifampin, isoniazid, pyrazinamide, ethambutol; TSH, thyroid stimulating hormone; FT4, free T4.*

human herpes virus 6 (HHV6), and three were positive (IgG>1:10). Ten patients were assessed several months following the onset of DRESS for thyroid dysfunction, and two were found to have elevated TSH, with normal free T4. Anti-thyroglobulin, thyroid peroxidase, and TSH receptor antibodies were not obtained in these patients.

There was no significant difference between treatment option (topical, oral, or IV corticosteroids) and patient outcome. (P=0.11). The two deceased patients were treated with topical corticosteroids only (clobetasol 0.05% and desonide 0.05% ointment) and clobetasol 0.05% ointment with oral prednisone 60mg daily. In cases in which there was a causal drug identified, there was no relationship between drug and patient outcome (P=0.51). There was no significant difference between treatment option and liver involvement, as defined by AST>86u/L or ALT>126u/L (P=0.11) or renal involvement, as defined by creatinine >1.5mg/dL (P=0.46). We also did not find any relationship between implicated drug class with patient outcome (P=0.23).

Using Spearman's rank correlation, our data showed significance for a positive correlation between age and creatine (P=0.01) and age and eosinophilia (P=0.02). There was a negative correlation between age and liver enzyme abnormalities (AST P=0.01; ALT P=0.0003), (**Figure 2**).

Discussion

DRESS is an adverse drug reaction with a high mortality rate and increased risk of long-term sequalae such as organ failure and autoimmune disease. Although the pathogenesis of DRESS is unknown, it is proposed that a genetic polymorphism affecting metabolism of certain drugs predispose patients to drug sensitization and immune overactivation. Reactivation of HHV-6 is also found to play a role in development of DRESS and is

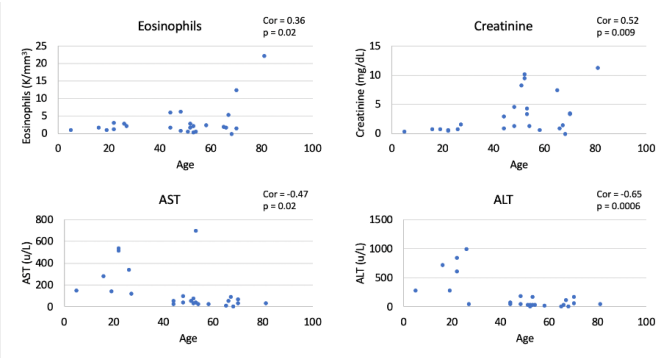

Figure 2. *Scatter plots showing the relationship between age and creatinine, eosinophils, AST, and ALT in our patients.*

one of the criteria proposed by a Japanese consensus group to diagnose DRESS [1, 4, 5].

Consistent with the literature, carbamazepine was commonly implicated in DRESS in our cohort [1, 2, 6]. However, in our study, nafcillin was a more common culprit than has been previously reported in the literature [6, 7]. Antibiotics as a class were most frequently implicated in DRESS at our institution, presumably because they are more commonly prescribed than anticonvulsants.

There are currently no established predictors of outcome for DRESS. Similarly, we did not find significance when comparing treatment modality, demographics, or laboratory values with patient outcome. The type of treatment also did not significantly affect the likelihood of developing multi-organ involvement during the hospitalization. Although carbamazepine and minocycline have been associated with a more severe presentation of DRESS, the two drugs implicated in the development of DRESS in our two deceased patients were quetiapine and nafcillin [8].

According to a previous retrospective cohort study, younger patients diagnosed with DRESS were more likely to develop autoimmune sequelae, whereas older patients were more likely to develop organ failure [9]. Consistent with these findings, we did find that those who develop DRESS at an older age were more likely to have renal involvement than younger patients. However, younger patients were more likely to have higher liver enzymes. Ten patients were assessed for post-disease autoimmune thyroid disorder and 20% develop subclinical hypothyroidism several months after their diagnosis of DRESS. In larger retrospective studies on patients with DRESS in Asia, the cumulative incidence of thyroid disease was 3.8 - 4.8% [9, 10]. A smaller study involving 11 DRESS patients in Mexico City found a cumulative incidence of 18% [11]. Our remarkably high incidence is similar to that of the smaller study and is likely related to our small cohort and the lack of follow-up care in our patient population.

Conclusion

In our retrospective study involving 25 patients diagnosed with DRESS at a level 1 trauma center, treatment with topical, oral, or systemic corticosteroids did not affect patient outcome, but age at diagnosis was correlated with differences in organ involvement. Larger multi-center studies will be necessary in the future to assess the relationship between age and patient outcome in DRESS.

Potential conflicts of interest

The authors declare no conflicts of interests.

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Table 3. *Demographics of patients hospitalized with DRESS between January 2000 and July 2018.*

RegiSCAR study group	At least 3 of the criteria marked with * are required for diagnosis
1. Hospitalization	
2. Reaction suspected to be drug related	
3. Acute rash*	
4. Fever above 38°C*	
5. Enlarged lymph nodes*	Must involve at least 2 sites
6. Organ Involvement*	Liver, kidney, lung, muscle, heart, pancreas, other
7. Hematologic abnormalities*:	Abnormal Lymphocytes, eosinophils, or platelets
Japanese consensus group	Typical DIHS (presence of all 7 criteria) Atypical DIHS (presence of all criteria except lymphadenopathy and HHV-6 reactivation)
1. HHV-6 reactivation	
2. Prolonged clinical symptoms 2 weeks after discontinuation of causative drug	
3. Maculopapular rash developing >3 weeks after starting with limited number of drugs	
4. Fever above 38°C	
5. Lymphadenopathy	
6. Organ involvement	Liver, renal, other
7. Hematologic abnormalities (at least one must be present)	Leukocytosis ($\geq 11\times10^9$/L); Atypical lymphocytosis (> 5%); Eosinophilia ($\geq 1.5\times10^9$/L)
Bocquet et al.	Diagnosis of DRESS is confirmed by presence of all 3 categories
1. Cutaneous drug eruption	
2. Adenopathy, hepatitis, interstitial nephritis, interstitial pneumonitis or carditis	
3. Hematologic abnormalities	Eosinophilia $\geq 1.5\times10^9$/L or atypical lymphocytes
Sontheimer and Houpt	Drug-induced delayed multiorgan hypersensitivity syndrome
1. Presenting within 3-6 weeks after initiation of drug therapy	
2. Cutaneous eruption	Generalized papulopustular or exanthematous rash
3. Facial edema	
4. Fever	
5. Lymphadenopathy	
6. Internal organ involvement	Liver, kidney, lungs, thyroid
7. Eosinophilia	

Table 4. *Drugs implicated in the development of DRESS in our patients.*

Age	Ethnicity	Sex	Medical Problems	Suspected Drug	Time from starting drug to DRESS onset	Treatment	Response to Treatment	Post-DRESS thyroid disease (time from rash onset)	Eosinophil Count	Creatinine	AST/ ALT
5	Hispanic or Latino	F	ADHD, neonatal narcotic withdrawal	Carbamazepine	4 weeks	Prednisone 20mg PO (0.5mg/kg, titrate to goal of 1-1.5mg/kg) daily	Resolving at discharge	N/A	1.04	0.32	153/280
16	White, not Hispanic or Latino	F	Elevated androgens	Sulfamethoxazole/ Trimethoprim	3 weeks	Prednisone 120mg PO daily, Clobetasol 0.05% ointment	Resolving at discharge	No - at 2 mo	1.8	0.74	279/721
19	White, not Hispanic or Latino	F	Benign brain tumor (suspect astrocytoma), unspecified seizure d/o	Oxcarbazepine	6 weeks	Prednisone 60mg PO daily, Triamcinolone 0.1% ointment	Resolving at discharge	No - at 3 mo	1	0.8	142/282
22	White, not Hispanic or Latino	F	Unspecified seizure disorder	Carbamazepine	4 weeks	Prednisone 60mg PO daily, Triamcinolone 0.1% ointment, Diphenhydramine, Hydroxyzine	Resolving at discharge	N/A	1.17	0.65	537/615
22	Hispanic or Latino	F	Anti-NMDA receptor encephalitis, right ovarian teratoma, left ovarian endometrioma, catatonia, psychosis, MSSA bacteremia	Levetiracetam	3 weeks	Solumedrol 80mg IV daily, Clobetasol 0.05% ointment, Hydrocortisone 2.5% ointment	Resolving at discharge	N/A	3.2	0.44	512/843
27	African American	F	Severe anoxic brain injury, asthma	Levetiracetam	8 weeks	Solumedrol 100mg IV daily, Lidex 0.05% ointment	Resolving at discharge	No - at 2 mo	2.2	1.59	123/49

44	White	F	HTN, back surgery with surgical site infection (1mo ago)	Vancomycin	7 weeks	Prednisone 60mg PO daily, Clobetasol 0.05% ointment, Desonide 0.05% ointment	Resolving at discharge	N/A	1.7	0.85	26/74
53	White, not Hispanic or Latino	F	GERD, depression, HTN	Quetiapine	2 weeks	Prednisone 60mg PO daily, Clobetasol 0.05% ointment	Deceased	N/A	0.4	4.36	700/166
54	White, not Hispanic or Latino	F	Chronic methamphetamine use, admitted for aneurysm of ACA, acute SAH, hydrocephalus	Levetiracetam, Sulfamethoxazole/ Trimethoprim, Piperacillin/ Tazobactam	Levetiracetam: 13 days; Bactrim: 3 weeks; Piperacillin/ Tazobactam: 12 days	Triamcinolone 0.1% ointment	Resolving at discharge	No - at 7 mo	0.6	1.31	25/40
58	Korean, Asian	F	GI stromal tumor s/p resection	Imatinib	7 weeks	Prednisone 60mg PO daily, Triamcinolone 0.1% ointment	Resolving at discharge	N/A	2.3	0.63	22/22
65	White, not Hispanic or Latino	F	Uterine carcinosarcoma s/p TAH/BSO with prolonged hospital course c/b peritonitis, sepsis, AKI, UGIB, delirium	Cefepime	4 days; 3 days	Solumedrol 48 mg IV daily, Diphenhydramine, Hydrocortisone 1% ointment, Lidex 0.05% ointment	Resolving at discharge	N/A	2	7.41	12/11
67	Asian - Pacific Islander	F	Diastolic heart failure, left tympano-mastoidectomy and posterior fossa craniotomy for abscess drainage for a large left-sided cholesteatoma and cerebellar abscess	Piperacillin/Tazobactam	4 weeks	Prednisone 60mg PO daily, Triamcinolone 0.1% ointment	Resolving at discharge	N/A	5.3	1.49	88/111

70	White, not Hispanic or Latino	F	Subacute bacterial endocarditis, diastolic cardiac dysfunction, MGUS, Meniere's disease, HTN	Nafcillin	3 weeks	Prednisone 60mg PO daily, Clobetasol 0.05% ointment	Resolving at discharge	TSH 3.74; FT4 1.09 - at 2 mo	1.6	3.45	69/165
26	Asian	M	None	Sulfamethoxazole/ Trimethoprim, Cephalexin	Both: 3-4 weeks	Prednisone 80mg PO daily, Triamcinolone 0.1% ointment	Resolving at discharge	N/A	2.8	0.75	338/996
44	N/A	M	ADHD, anxiety	Azithromycin	3 weeks	Prednisone 40mg PO daily, Triamcinolone ointment	Resolving at discharge	N/A	6.1	2.97	58/54
48	N/A	M	Epilepsy	Carbamazepine	4-6 weeks	Prednisone 40mg PO daily, Clobetasol 0.05% ointment	Resolving at discharge	N/A	0.7	1.36	96/181
48	Hispanic or Latino	M	Cerebral palsy, alcohol abuse, HTN, VRE/MRSA bacteremia, AKI	Vancomycin, Sulfamethoxazole/ Trimethoprim, Cephalexin	3 weeks	Prednisone 60mg PO daily, Clobetasol 0.05% ointment, Desonide 0.05% ointment	Resolving at discharge	N/A	6.3	4.64	40/54
51	Asian	M	T2DM, HTN, OSA, CHF, gout	Allopurinol	Started 3 weeks ago; dose increased from 300mg to 400mg daily 4 days prior to rash development	Prednisone 100mg PO daily, Clobetasol 0.05% ointment, Desonide 0.05% ointment	Resolving at discharge	No - at 5 mo	0.6	8.28	52/37
52	Asian	M	T2DM, HTN, OSA, CHF, gout	Ceftriaxone	First exposure 3 months prior, re-exposure 1 day prior	Clobetasol 0.05% ointment, Desonide 0.05% ointment	Resolving at discharge	No - at 8 mo	1.7	9.59	77/37
52	Asian	M	T2DM, HTN, OSA, CHF, gout	Nafcillin	1 day	Clobetasol 0.05% ointment,	Deceased	No - at 4 mo	2.8	10.21	30/7

						Desonide 0.05% ointment					
53	N/A	M	T2DM, HTN, admitted for right lower leg cellulitis	Clindamycin, Lisinopril	Clindamycin: 5 days; Lisinopril 4 days	Clobetasol 0.05% ointment, Desonide 0.05% ointment	Resolving at discharge	N/A	2.2	3.32	39/33
66	Southeast Asian - Laos	M	TB, T2DM, CAD	RIPE - most likely isoniazid	5-6 months	Prednisone 60mg PO daily, Clobetasol 0.05% ointment, Desonide 0.05% ointment	Resolving at discharge	No - at 5 mo	1.8	0.94	57/33
68	African American	M	Seizures, remote h/o TB (treatment status unknown), admitted for MRSA pneumonia, sepsis, ARF on CKD, respiratory failure s/p intubation and encephalopathy	Phenytoin	1-2 weeks	Bacitracin, Aquaphor	Transferred to another hospital	N/A	N/A	N/A	N/A
70	White, not Hispanic or Latino	M	Choroidal nevus, COPD, type II diabetes, HTN, Grave's disease, Myasthenia gravis, and obesity	Vancomycin	1-2 weeks	Prednisone 60mg PO daily, Triamcinolone ointment, Desonide ointment	Resolving at discharge	N/A	12.5	3.34	36/55
81	White, not Hispanic or Latino	M	CAD, paroxysmal afib, MSSA bacteremia, epidural abscess, and discitis	Nafcillin	4-6 weeks	Prednisone 80mg PO daily, Triamcinolone 0.1% ointment	Resolving at discharge	TSH 6.16; FT4 0.9 - at 3 mo	22.2	11.25	36/53