Tennessee Medicine E-Journal

Volume 2
Issue 3 *Issue 3*

Article 2

February 2017

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ABSTRACT

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare potentially life-threatening hypersensitivity reaction characterized by rash, fever, and internal organ involvement. RegiSCAR scoring system is most widely followed to better define the probability of having DRESS. While it has been associated with anticonvulsants such as phenytoin, no cases of phenytoin related definite DRESS based on RegiSCAR scoring system have been reported. We present a case of phenytoin related definite DRESS in a 33 yo African American male that was diagnosed within the emergency department and managed successfully.

INTRODUCTION

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a rare fatal Type IV hypersensitivity reaction, which classically presents 2-6 weeks (wks) post culprit drug exposure. A multitude of drugs have been reported with anti-epileptics, antiretrovirals, aromatic sulfonamides and allopurinol being the mostly commonly associated drugs (Table 1).[1] It classically presents with hematologic abnormalities (like eosinophilia, atypical lymphocytosis, thrombocytopenia) and clinical features of fever, leukocytosis, rash, lymphadenopathy and multi-organ dysfunction.[2,3] The overall mortality in DRESS can be as high as 10%, and the most common differential diagnoses for DRESS syndrome are Stevens-Johnson Syndrome/toxic epidermal necrolysis, hypereosinophilic syndrome and Kawasaki disease.[4-6] The prompt withdrawal of drug along with prolonged systemic corticosteroid therapy is used as treatment in many cases.[7] Noted for being a diagnosis of exclusion, DRESS can be classified by a scoring system developed by RegiSCAR study group based on a large multinational registry of severe cutaneous adverse reactions.[6] While DRESS has been implicated with phenytoin, to the best of our knowledge no definite phenytoin related DRESS cases have been reported. We report a definite case of phenytoin induced DRESS that was diagnosed during the

patient's Emergency department presentation and managed successfully over next 4 days.

CASE PRESENTATION

A 33-year old African American male with a history of seizure disorder was transported from prison to the Emergency Department after a 3-day history of fever, global erythroderma, skin desquamation, tender lymphadenopathy and facial swelling, 4 weeks after phenytoin start date (Figure 1). The patient's initial vitals included a blood pressure of 112/76 mm Hg, pulse of 106 beats/minute, temperature of 102.6°F, and respiratory rate of 18/minute. Initial labs showed WBC of 6000/mcL, eosinophilia (12.2%), CPK -1104 U/L, hemoglobin-11.2g/dl, platelet count- 94000/mcL, LDH-532 U/L and AST-51 U/L. CT imaging was negative except generalized lymphadenopathy involving bilateral inguinal and axillar aspects (Figure 2). All tests for possible infections including blood cultures, urine cultures, tuberculosis, hepatitis panel, EBV, HIV, CMV, parvovirus were negative except HHV-6, which was positive. The tests for autoantibody screening including ANA, anti-dsDNA, anti-scl70, anti-centromere were also negative. The skin biopsy showed intra-epidermal eosinophil infiltration and spongiosis (Figure 3). A probable association of this drug reaction with phenytoin was suspected based on Naranjo adverse drug reaction probability scale, which revealed a score of 5 for our case (Table 2). Most importantly, RegiSCAR score of 6 (Table 3) further suggested a definite diagnosis of DRESS. From Day 1, phenytoin was discontinued and levetiracetam was started along with 60 mg oral prednisone. Over the next three days, patients' clinical and laboratories abnormalities resolved. The patient was discharged on oral steroids for next 8 weeks with gradual taper, levetiracetam, education about phenytoin avoidance and follow up appointment in outpatient clinic.

CONCLUSION

The patient described in our study experienced a severe allergic reaction upon exposure to phenytoin, and his symptoms resolved shortly after its discontinuation.

DRESS syndrome is a disease of exclusion, and often goes unrecognized in patients in emergency setting.[3] The hallmark for DRESS syndrome is the presence of systemic manifestations such as inflammation of the liver, kidneys, heart or other organs along with the rash, swelling and eosinophilia often seen in most severe allergic reactions.[3,8,9] The incidence of this systemic reaction is 1/1000 to 10,000 exposures with a 10-20% mortality.[10] Notable clinical manifestations of the syndrome include fever, diffuse rash, lymphadenopathy and facial swelling while hematological manifestations include thrombocytopenia, atypical lymphocytosis, eosinophilia and leukocytosis. Typical onset of the hypersensitivity reaction is 2-6 weeks post-drug exposure. Common agents implicated in DRESS include anti-epileptics, allopurinol, sulfonamides, quinolones, minocycline, beta-lactams and anti-retrovirals.[1,3]

The overall mortality rate associated with this hypersensitivity reaction is about 10% with liver involvement associated with poor prognosis.[3,8] A differential diagnosis of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis, hypereosinophilic syndrome

and Kawasaki disease were considered but excluded based on the timeline of events, careful history and physical examination and laboratory results.

DRESS is often associated with HHV-6, HHV-7, EBV-primary infection or reactivation.[3] The only possible infectious mechanism that this patient encountered after continuing phenytoin was the reactivation of HHV-6. In other studies, reports of HHV-6 seroconversion occurring with DRESS syndrome and symptom flaring have led the RegiSCAR study group to consider inclusion of HHV-6 reactivation as part of the DRESS diagnostic criteria.[3,11-15] Some of the potential reactivators of HHV-6 in the setting of DRESS include immune dysregulation, genetic predisposition and the direct effect of certain medications.[11,15] While the reactivation of HHV-6 that occurs in the setting of DRESS has become a piece of the diagnostic criteria, no major biologic differences were found when comparing individuals with DRESS who were HHV-6 positive with individuals who were HHV-6 negative.[9]

Due to the impact of HHV-6 reactivation underlying DRESS, it is often treated with a slow steroid taper, which may prevent DRESS exacerbations.[11,12,15] In addition, a treatment of valganciclovir may be beneficial in terms of treatment for cases of reactivation of HHV-6 in DRESS, and may be helpful in symptom flaring.[11,15] We did not recognize this, but it would have been helpful to note the timing of the elevated liver enzymes and whether anti-HHV-6 IgM antibodies were present prior to the increased AST to determine the virus impact on the liver.

DRESS is a potentially fatal rare drug reaction and prognosis is dependent on early recognition of clinical features and diagnosis for favorable outcomes. The use of high dose oral steroid therapy along with prompt discontinuation of the culprit drug is essential in preventing exacerbation and treating acute process. We believe that early recognition of DRESS and appropriate treatment strategy played a key role in successful management of our patient.

COMPETING INTERESTS
The author(s) declare that they have no competing interests

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TABLES

Table 1. Medications Commonly Associated with DRESS

Common Medications associated with DRESS	
Anticonvulsants	Allopurinol
Sulfonamids	Quinolones
Minocycline	Antiretrovirals
Beta-lactams	

Table 2. Naranjo Adverse Drug Reaction Probability Scale

Question	Yes	No	DNW	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	1
2.Did the adverse event appear after the suspected drug was administered?	+2	-1	0	2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	1
4. Did the adverse event reappear when the drug was re - administered?	+2	-1	0	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	0
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	1
0 = doubtful ADR; 1-4 = possible ADR; 5-8 = probable ADR; ≥ 9 = definite ADR				5

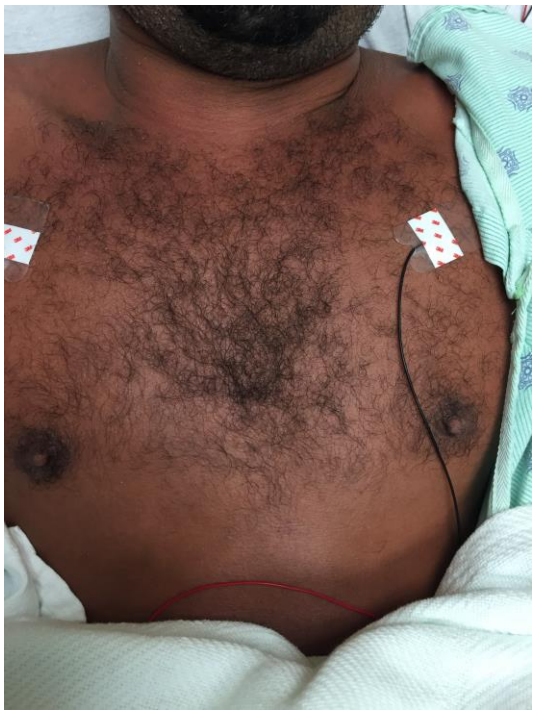
ADR = Adverse Drug Reaction; DNW = do not know

Table 3. RegiSCAR Scoring System

FEATURES	NO	YES	UNKNOWN	
Fever(≥38.5° C)	-1	0	-1	0
Enlarged Lymph Nodes(≥2 sites, ≥ 1 cm)	0	1	0	1
Atypical Lymphocytes	0	1	0	0
Eosinophilia 700-1499 or 10-19.9% ≥ 1500 or ≥ 20%	0	 1 2	0	 1
Skin Rash Extent >50% ≥ 2; Edema, infiltration, purpura, scaling Biopsy suggesting DRESS	0 0 -1 -1	 1 1 0	0 0 0 0	 1 1 0
Internal Organ Involvement One Two or more	0	 1 2	0	 1
Resolution in more than 15 days At least 3 biological investigation done and negative to exclude alternative diagnosis	-1 0	0 1	-1 0	0 1
Final score:- < 2 - No case ; 2–3 Possible case; 4–5 Probable case; >5- Definite				6

FIGURES

Figure 1. Erythroderma involving chest and lower extremity



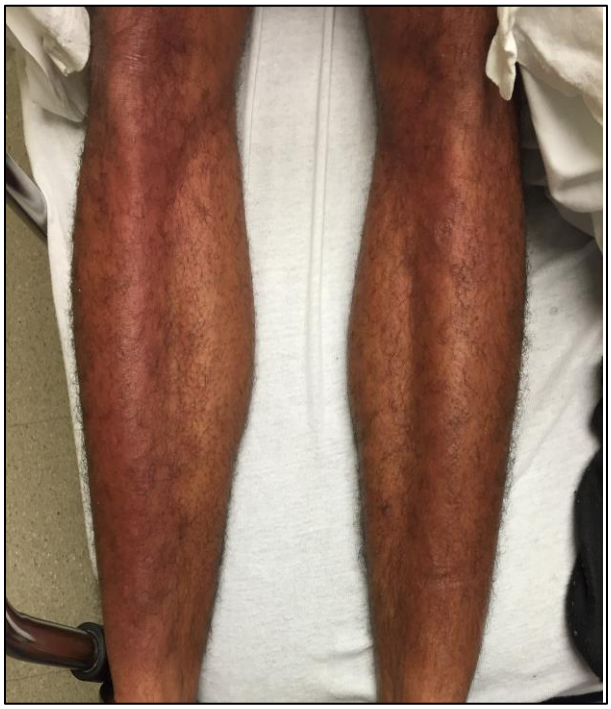
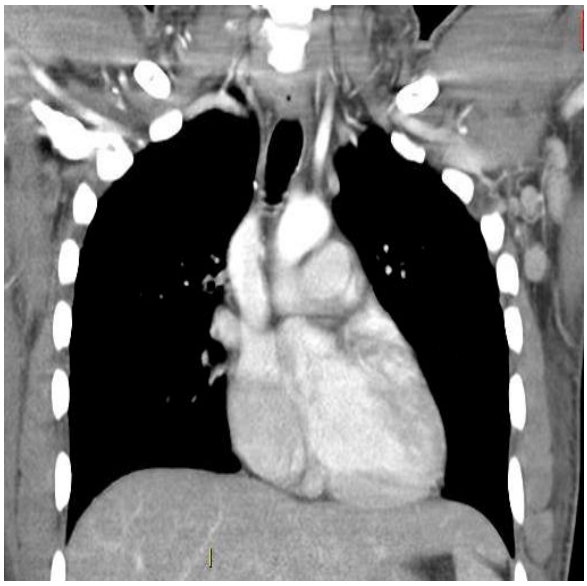


Figure 2. Helical CT scan showing lymphadenopathy in axillary and inguinal area



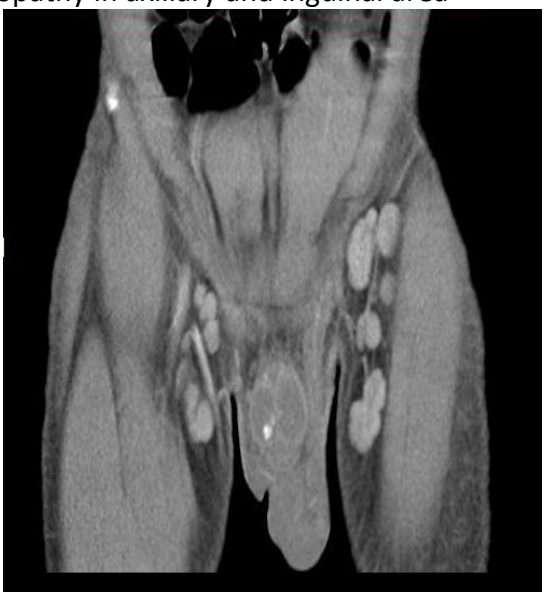


Figure 3. 100x H&E stain view- interface dermatitis with scattered eosinophils