



**PHENYTOIN-INDUCED DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS) SYNDROME: A CASE REPORT FROM DERMATOLOGY DEPARTMENT**

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**ABSTRACT**

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is an uncommon but serious hypersensitivity drug reaction most frequently associated with antiepileptic's. Clinical manifestations include rash, fever and visceral organ involvement, most commonly hepatitis. The mortality rate associated with DRESS syndrome is approximately 10%, the majority due to fulminant liver failure. We report one case of phenytoin-induced DRESS syndrome in patient department, A 48-year old man presented with a five-day history of pruritic, maculopapular rash with associated periorbital swelling, fever, and transaminitis. Five days prior to presentation he noted pruritis and rash over his extremities, which over the next several days progressed to his chest, back and face He had past history of seizures that began 35 days prior to this admission treated with phenytoin 100mg daily and vitals are increased temperature 104<sup>0</sup>F, BP 110/90mmHg, respiratory rate 18cpm, lab investigations show WBC count is 7.9 thousand/mm<sup>3</sup>, with 60% neutrophils, 8.0% lymphocytes, and 4.0% eosinophils. His free phenytoin level on admission was 0.4mcg/ml, liver function tests revealed increased levels. patient got admitted in inpatient ward for drug induced hypersensitivity reactions.

**KEYWORDS:** phenytoin, anticonvulsants, drug eruption, eosinophilia, DRESS.

**INTRODUCTION**

Drug reaction with eosinophilia and systemic symptoms syndrome is a potentially life-threatening hypersensitivity reaction with rash, fever, and internal organ involvement, often hepatitis, occurring most commonly two to eight weeks after initiation of a medication. The clinical picture has a wide inter-individual variability, making diagnosis a challenging task. These manifestations most often mimic the symptom and signs of either viral infection, neoplastic disease, or an autoimmune disease.<sup>[1]</sup> Anticonvulsants are the most common offending agents manifesting with DRESS syndrome although they have been reported following intake of allopurinol, nevirapine and sulfasalazine.<sup>[2]</sup> Phenytoin sodium is the most frequently administered anticonvulsant, due to its high therapeutic efficacy and cost-effectiveness. Although the first case report of DRESS syndrome due to phenytoin dates back to 1950,<sup>[3]</sup> there still exists lack in awareness and delay in diagnosis, thus enhancing the risk of dermatological and systemic sequelae.

**CASEREPORT**

A 48-year old man presented with a five-day history of pruritic, maculopapular rash with associated periorbital swelling, fever and transaminitis. Five days prior to presentation he noted pruritis and rash over his extremities, which over the next several days progressed to his chest, back and face. He had past history of seizures that began 35 days prior to this admission treated with phenytoin 100mg daily. The patient had no other significant past medical history, drug allergies, or alcohol and non-smoker.

On examination, the patient was febrile elevated temperature to 40.2°C (104.4°F) with a heart rate of 88 beats/minute, respiratory rate of 18cpm and blood pressure of 110/55mmHg. The patient was well nourished, well developed, alert and well oriented and appeared uncomfortable but not in distress. A fine exanthematous rash was noted on the face, upper and lower extremities in sun-exposed areas without involvement of the oral mucosa, palms, or soles. There

was profound periorbital edema that prevented eye-opening. His abdomen was soft and non-distended with no tenderness, guarding, or hepatosplenomegaly. No focal deficits were appreciated on neurological exam. At this point the differential diagnosis included drug-induced hypersensitivity, erythema multiforme, toxic epidermal necrolysis, vasculitis, an exanthematous due to viral infection such as Epstein–Barr virus (EBV), cytomegalovirus (CMV) and human immunodeficiency virus (HIV) and auto-immune conditions such as systemic lupus erythematosus. Laboratory results revealed a white blood cell count of 7.9 thousand/mm<sup>3</sup> (normal from 4.0 to 10.0 thousand/mm<sup>3</sup>), with 60% neutrophils, 8.0% lymphocytes, and 4.0% eosinophils (absolute 0.32 thousand/mm<sup>3</sup>). His free phenytoin level on admission was 0.4mcg/mL (therapeutic from 1.0 to 2.0mcg/mL). His basic metabolic panel was within normal limits. Hepatic function panel revealed an aspartate aminotransferase of 778U/L (normal from 0 to 37) and alanine aminotransferase (ALT) of 1274U/L (normal from 0 to 41). Acetaminophen and salicylate levels were below detectable limits. Evaluation for acute and chronic hepatitis with serology's was negative for hepatitis A, B, and C. The patient was admitted to our hospital with a presumptive diagnosis of drug-induced hypersensitivity. All medications were discontinued and the patient was monitored for signs of clinical recovery.

On day of admission patient condition worsened with increased facial swelling and rash extending to his chest and abdomen. He began to show signs of liver synthetic dysfunction with an elevated prothrombin time and international normalized ratio as well as an increasing

#### ADR analysis

**Table 01: causality assessment of suspected ADRs**

Suspected drug And Reaction(ADR)	Naranjos Scale	WHO-Probability Scale	Karch& Lasagnas Scale
Phenytoin induced DRESS SYNDROME	Possible	Probable	Probable

**SEVERITY:** -Moderate level 4.

**PREDICTABILITY:** -unpredictable.

**PREVENTABILITY:** -Probably preventable.

#### DISCUSSION

DRESS syndrome, also referred to as drug hypersensitivity syndrome, it is a cell-mediated Type IV delayed hypersensitivity reaction. It is clinically characterized by fever, skin rash, lymphadenopathy, hematological abnormalities and single or multisystem involvement. The etiopathogenesis is not clear but has been postulated that it can occur when a patient with genetic predisposition is exposed to the offending drug. Human leukocyte antigen (HLA) related genes have been identified as a predictor of certain severe cutaneous adverse drug reactions.<sup>[5]</sup> The HLA gene specific for DRESS due to allopurinol (HLA-B\*5801) and nevirapine (HLA-DRB1\*0101) are well established, but

transaminitis. A repeat complete blood count showed an atypical lymphocytosis and eosinophilia at 8.0%. Because of his deteriorating condition and thus phenytoin induced DRESS syndrome is seen in **figure:01** the patient was administered with dexamethasone 4mg orally four times daily and methyl prednisolone 30mg/kg body weight and recovered slightly for 7days. Thus causality assessment was shown in **Table: 01**.



**Figure 1: phenytoin induced DRESS syndrome.**

#### ADR Management

Generally, management of ADR includes withdrawal/suspension, dose reduction of suspected drug and administration of supportive therapy. Here in this case report the suspected phenytoin was discontinued.

the same for phenytoin is yet to be determined. HLA-B\*1502 is a gene which predisposes to most phenytoin-induced cutaneous hypersensitivity reactions.<sup>[6]</sup> The offending drug acts as hapten and interacts with HLA alleles to activate the T-lymphocytes. These activated lymphocytes increase eosinophils, proinflammatory cytokines and other mediators, which can be aggravated further in disease conditions such as neurocysticercosis.<sup>[7]</sup> These pathological factors could have predisposed to the occurrence of phenytoin-induced DRESS in our patient which can be substantiated by a study that has revealed a higher incidence of cutaneous reactions in patients having solitary cyst cercus granuloma and receiving phenytoin.<sup>[8]</sup> The diagnosis of DRESS is challenging due to its plethora of clinical features and long latency between first dose and occurrence of symptoms. The Regi SCAR study group diagnostic criteria state that patients with a drug rash

must fulfill at least three out of four systemic features, which consist of fever (>40°C) elevated temperature, lymphadenopathy, haematological abnormalities (leukocytosis or eosinophilia), or internal organ involvement. This syndrome presents in approximately 2% of patients typically after 2-4 weeks of treatment. Fever was reported in 95.1% and skin rash and eosinophilia in 93.1% of patients.<sup>[2]</sup> Even though it has a favorable outcome, mortality may reach 25% with hepatic failure, renal failure, or severe sepsis as the cause of death, in the order of rate of their occurrence.

### MANAGEMENT

Antipyretics should be preferred to reduce the effect of fever. Skin care may include the use of topical steroids to alleviate symptoms.<sup>[9]</sup> In case of exfoliative dermatitis, the main principals of therapy are same as for major burns: warning of the environment, correction, of electrolyte disturbances, high calorie intake and prevention of sepsis.<sup>[10]</sup>

### SYSTEMIC CORTICOSTEROIDS

Systemic corticosteroids can reduce symptoms of delayed hypersensitivity reactions. They are also known to inhibit the effect of IL-5 on eosinophil accumulation *in vivo*<sup>[11]</sup>, which may at least partly explain their benefit in the treatment of the idiopathic hyper eosinophilic syndrome.<sup>[12]</sup> As eosinophil accumulation is also thought to account for the internal organ involvement seen in DRESS syndrome, they might have a role in its management. Dramatic improvement in clinical symptoms and laboratory findings has been observed soon after corticotherapy in many independent case reports.<sup>[13-16]</sup> Relapses have also been described after tapering or withdrawal of systemic steroids<sup>[16]</sup>, which further suggests their therapeutic role in patients with DRESS syndrome. Several authors suggest their use when internal organ involvement exists.<sup>[10,16,17]</sup> However, randomized controlled trials are lacking, and whether steroids should be administered remains controversial. This controversy may be partly related to the confusion between DRESS syndrome and other severe drug reactions, such as TEN or SJS, for which several studies showed no benefit or even increased morbidity and mortality after corticosteroid therapy.<sup>[18,19]</sup> However, these reactions are thought to be mediated by mechanisms other than those operating in DRESS syndrome and their reported increased morbidity after corticotherapy could be related to septic complications occurring in patients with large areas of epithelium detachment. Nevertheless, the use of systemic steroids might promote viral activation, a potential risk factor for increased lymphocyte sensitivity to reactive drug metabolites<sup>[20,21]</sup>, which could be responsible for secondary cutaneous and visceral lesions. Obviously, corticotherapy may be associated with long-lasting, corticoid-dependent cases of DRESS syndrome.<sup>[22]</sup> Whether chronic HHV-6 activation promoted by systemic steroids explains these findings remains to be determined. --Interferon, a second-line therapy for

idiopathic hyper eosinophilic syndrome, could be tested in these long-lasting cases of DRESS syndrome.<sup>[22]</sup>

### PREVENTION

In the absence of a well-established therapy, primary and secondary prevention may have a key role in the management of DRESS syndrome.

#### Primary Prevention

Several studies have related the occurrence of skin rashes to lamotrigine in relation to the speed of lamotrigine dose escalation and have shown that this risk could be reduced by a gradual dose escalation from a low starting dose.<sup>[23]</sup> first degree relatives should be alerted to their elevated risk of such reactions to the same compound(s). Family counselling is a key component of patient management. The development of *in vitro* testing, may be an additional tool in the management of these patients. The lymphocyte toxicity assay is a measure of lymphocyte phenotypic detoxification systems.<sup>[24]</sup> Patient's lymphocytes are exposed to a drug's metabolites, and markedly increased sensitivity to these metabolites is used as evidence of impaired detoxification. However, these tests are hindered by the cost and the complexity of the procedure. Further prospective studies are required to determine their value in the Identification of patients at risk of an idiosyncratic reaction to a specific drug.

#### Secondary Prevention

Published cases of recurrences were all attributed to the same generic drug or to compounds chemically closely related.<sup>[22,24]</sup> Hence, patients should be advised to avoid re-exposure to these compounds. Corollary, adequate treatment alternatives, when possible, have to be found. As for primary prevention, *in vitro* studies could improve the management options for such patients. Lymphocyte toxicity assays can help to increase the accuracy of the causality assessment of the likely agent and to screen for 'cross-reacting' agents.<sup>[24]</sup> Reports of successful desensitization to drugs involved in HIV-related drug hypersensitivity reactions<sup>[25]</sup>, whose pathogenic mechanisms may be similar to those of DRESS syndrome, have been reported. The role of such desensitization regimens has not been evaluated so far in DRESS syndrome. The spectrum of the life-threatening risk associated with DRESS syndrome may partly explain the absence of such data. However, the involvement of the dose escalation rate in the occurrence of anticonvulsant-induced DRESS syndrome and the observation that patients experiencing a rash to lamotrigine may be considered for rechallenge at a slower escalation rate<sup>[26]</sup> suggest the potential role of desensitization regimens in patients for whom no valuable drug alternative can be found.

### CONCLUSION

Given the significant mortality attributed to DRESS syndrome, clinicians should be aware of the potential for this severe hypersensitivity reaction particularly in starting any new anti-epileptic medication. In patients

presenting with skin rash and systemic abnormalities after a recent change in medications, physicians should consider DRESS syndrome as a possible diagnosis and switch to more aggressive therapy if removal of the offending agent does not result in clinical improvement. Further study of potential pharmacological therapies is warranted given the significant morbidity associated with DRESS syndrome.

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