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Case Study

Phenytoin-Induced Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome: A Case Report

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ABSTRACT

Background: Epilepsy is a common neurological disorder. The main goal of treatment is to achieve seizure control without adverse effects. Phenytoin is a commonly used sedative antiepileptic medication in many countries. It is used against tonic-clonic and complex partial seizures. Phenytoin is reported to cause a range of deleterious and erratic side effects at therapeutic and toxic doses. Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is an uncommon but serious hypersensitivity drug reaction most frequently associated with anti-epileptics. Clinical manifestations include rash, fever, eosinophilia and visceral organ involvement, most commonly hepatitis. The mortality rate associated with DRESS syndrome is approximately 10%, the majority due to fulminant liver failure.

Case report: We report a case of phenytoin induced DRESS syndrome in a 50 years old female patient who has presented with pruritic, erythematous and maculopapular rashes associated with periorbital swelling, fever, breathlessness (grade-III) and generalized swelling all over the body since 4 days. Vitals are increased. Temperature:103.60 F, BP:110/90 mmHg, respiratory rate 18 cpm, lab investigations shows WBC count is 7.9 thousand/mm3, with 60% neutrophils, 8.0% lymphocytes, and 4.0% eosinophil. Liver function tests revealed increased AST and ALT levels. Patient got admitted in inpatient ward for drug induced hypersensitivity reactions. Four days prior to presentation she noted pruritus and rash over her extremities, which over the next several days progressed to her chest, back, legs and face. She had past history of seizures that began 20 days prior to this admission treated with oral phenytoin 100mg BID daily. Based on the presenting signs and symptoms, her condition was diagnosed as phenytoin induced Dress syndrome. The symptoms improved significantly after the offending drug was withdrawn. Alternatively she was started on oral carbamazepine 200 mg BID. Naranjo's and WHO causality assessment was done, indicating a probable relationship between the patient's symptoms and her use of phenytoin. Patient was later managed with IV fluids, dexamethasone injection, and cetirizine tablet. After 5 days of therapy symptomatic relief was observed and patient was discharged. Conclusion: This case report highlights the adverse drug reactions of phenytoin and the need of regular monitoring in patients on long term therapy.

Keywords: Epilepsy, Phenytoin, Complex-Partial Seizures, Tonic-Clonic Seizures, DRESS Syndrome, eosinophilia.

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1. INTRODUCTION

Epilepsy is a common neurological disorder. The main goal of treatment is to achieve seizure control without adverse

effects[1]. Phenytoin sodium is the most frequently administered anticonvulsant, due to its high therapeutic efficacy and cost-effectiveness. Phenytoin (5,5-diphenylhydantoin) is one of the most effective[2] and widely prescribed[3]drug for the treatment of epilepsy due to its low cost and easy availability[4]. It was introduced as an antiepileptic drug in 1938. Phenytoin is commonly used to treat all types of tonic-clonic and complex partial seizures, except absence seizures[3]. Phenytoin metabolism is dose dependent. Elimination follows first-order kinetics at low drug concentrations, and zero-order kinetics at higher drug concentrations which carries a special risk of dose-related toxicity that is an important issue in emergency medicine. Its wide pharmacokinetic variability and narrow therapeutic range often leads to toxicity which may have varied manifestations[5].The wide pharmacokinetic variability and low toxicity threshold of phenytoin can often result in its intoxication[2, 6, 7]. The toxic effects of chronic use may present with wide variety of clinical symptoms and signs. Here we report a case of phenytoin toxicity in an adolescent female presenting with multiple adverse drug reactions (ADRs). Drug reaction with eosinophilia and systemic syndrome (DRESS) is a rare, potential drug induced hypersensitivity syndrome. It is initially manifested as hyperthermia and rashes. Also systemic involvement includes liver (80%), kidneys (40%), lungs (33%), heart (15%), or pancreas (5%). Synonyms for dress syndrome are-HSS (Hypersensitivity syndrome), AHS (Anti-convulsing hypersensitivity syndrome), DISH (Drug induced hypersensitivity syndrome), DIDMOHS (Drug induced delayed multi-organ hypersensitivity syndrome), and Drug induced pseudo lymphoma[2].The drugs commonly causing this syndrome are phenytoin, carbamazepine, phenobarbital, minocycline, sulfonamides, allopurinol, modafinil and dapsone.

The objective of this report is to describe a rare case of DRESS syndrome caused by phenytoin and is important for the clinicians to be aware of its presentation. It is important to identify the causative agent as early as possible and withdrawal of it is necessary for critical management.

We report a case of phenytoin induced DRESS (Drug rash with eosinophilia and systemic symptoms) syndrome in a 50 years old female patient who had past history of seizures that began 20 days prior to this admission treated with oral phenytoin 100mg BID daily. The following case report demonstrates the necessity of prompt recognition and initiation of appropriate therapy in preventing the potential sequelae of DRESS syndrome

2. CASE PRESENTATION:

A 50-year old female visited the outpatient department of general medicine unit of Mandya Institute of Medical Sciences and Teaching Hospital, Mandya, Karnataka, India. She presented with pruritic, erythematous and maculopapular rashes associated with periorbital swelling, fever, breathlessness (grade-III) and generalised swelling all over the body since four days (Figure 1). Four days prior to presentation she noted pruritus and rash over her extremities, which over the next several days progressed to her chest, back, legs and face. She had past history of seizures that began 20 days prior to this admission treated with oral phenytoin 100mg BID daily. The patient is a known case of adenocarcinoma of gastroesophageal junction and on chemotherapy. No other significant past medical history and drug allergies.

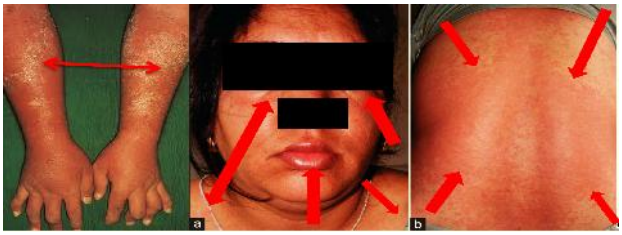

Fig 1: Phenytoin induced DRESS syndrome.

3. INVESTIGATIONS

General Physical examination of the patient on day-1 examination, the patient was febrile elevated temperature to 39.8°C (103.6°F) with a heart rate of 84 beats/minute, respiratory rate of 19 cpm and blood pressure of 100/70 mmHg.The patient was well built and nourished, 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 with involvement of the palms and soles. There was profound periorbital edema that prevented eye opening. Her abdomen was soft and non-distended with no tenderness, guarding, or hepatospleenomegaly. No focal deficits were appreciated on neurological examination.

The patient was admitted to hospital with a presumptive diagnosis of drug-induced hypersensitivity. At this point the differential diagnosis included druginduced hypersensitivity, erythema multiforme, toxic epidermal necrolysis, vasculitis, an exanthematous due to viral infection such as Epstein–Barr virus (EBV), cytomegalovirus (CMV) and auto-immune conditions such as systemic lupus erythematous. Laboratory results revealed a white blood cell count of 10.9 thousand/mm3 (normal from 4.0 to 10.0 thousand/mm^3), with 69% neutrophils, 15.0% lymphocytes, and 8.0% eosinophil's (absolute 0.32 thousand/mm^3). Her basic metabolic panel was within normal limits. Hepatic function panel revealed an AST (aspartate aminotransferase) of 175 U/L (normal from 0 to 37 U/L) and alanine aminotransferase (ALT) of 184U/L (normal from 0 to 41 U/L). 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 her chest and abdomen.

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 intravenous dexamethasone 4mg TID daily and methyl prednisolone 30mg/kg body weight and recovered slightly for 7days. Thus causality assessment was shown in Table: 01.

4. TREATMENT:

On day-1 the patient was treated with following medications- IV fluids, Intravenous Dexamethasone 8 mg TID, and Intravenous Chlorpheniramine 4 mg TID.Parenteral anti-biotic (ceftriaxone 1gm IV BD), Parenteral Proton-Pump Inhibitor (Pantoprazole 40 mg IV OD), Oral Eptoin 100 mg BID and Paracetamol 650 mg TID, furosemide 40 mg OD. The symptoms has not been reduced. So the patient has been referred to take dermatologist opinion. The dermatologist evaluated the patient and confirmed the case as phenytoin induced dress syndrome and advised to stop phenytoin and use alternative anti-epileptic drug and liquid paraffin. No fresh complaints on day-2 and patient were continued with the same medications. This dress syndrome was mainly due to the T. Phenytoin. The common ADR's of phenytoin is poor coordination, hirsutism, gingival hypertrophy, hypotension, itching and toxic epidermal necrolysis. On day-2, the physician dechallenged the drug after that patient was recovered from the presenting symptoms and an alternative anti-epileptic agent; Carbamazepine 200 mg twice daily was prescribed. The rashesand fever persisted for about 6 days.

5. OUTCOME AND RECOVERY:

The patient was discharged after 7 days of stay after she attained complete recovery. At discharge, only mild rashes were present. During the discharge, the following medications such as oral cetirizine, topical liquid paraffin were advised till suppression of full rashes and to for epilepsy carbamazepine 200 mg twice daily was advised.

6. ADVERSE DRUG REACTION ANALYSIS:

After collecting the past and current medication history from the patient it was suspected that the patient had developed druginduced DRESS syndrome. After analysing the ADR profiles of all the drugs that has administered to the patient, it was found that the most suspected drug for producing DRESS syndrome was Phenytoin. We have further analysed to establish the relationship between the drug and the observed ADRs, through causality assessment by using Naranjo's scale, WHO-UMC ADR assessing scale as well as Karch and Lasagne scale, results were shown in Table 01. The Naranjo's criteria and WHO probability scale were applied to determine the causality for suspected ADRs. The causality assessment with both scales revealed that adverse reaction due to phenytoin in this case was probable (Naranjo overall score: 7). The severity of ADRs were evaluated using Modifid Hartwig and Siegel, based on which it was categorized as moderate level 4(b) reaction

Table 1: causality assessment of suspected ADRs

Suspected drug	Consequence of suspected drug (ADR)	Naranjo's scale	WHO-probability scale	Karch and Lasagnas scale
Phenytoin	DRESS (Drug rash with eosinophilia and systemic symptoms) syndrome	Possible	Probable	Probable

Severity: Moderate level 4b
Predictability: Unpredictable
Preventability: Probably preventable

7. MANAGEMENT OF ADVERSE DRUG REACTION:

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

Fate of suspected drug: Drug withdrawn
Treatment Given: Specific
Outcome: Recovered

8. DISCUSSION:

Phenytoin has a narrow therapeutic range of 10-20 mcg/mL[1,4]. At plasma concentrations below 10 mcg/ mL, elimination follows fist order. However, at higher concentrations, including those in the therapeutic range (10-20 mcg/mL), the metabolic pathway becomes saturated and elimination shifts to zero order[4]. Half-life of phenytoin varies between six and twenty four hours at plasma concentrations less than 10 mcg/ml, but increases with higher concentrations[1,3]. As a result, the plasma concentration rises disproportionally even with small increments in dose[4,6]. Toxicity generally correlates with the increasing plasma levels. The increased half-life due to zero order pharmacokinetics can also result in prolonged duration of toxic symptoms[9].

The symptoms experienced by the patient in question are comprehensible in terms of complex pharmacokinetics, narrow therapeutic index and individual variability in metabolism and elimination of phenytoin[2,6,7]. These symptoms of toxicity experienced by the patient gradually developed over a period of five years at the usual dose of 200 mg/day. Toxic effects may develop at therapeutic concentrations in some patients. This may be attributed to the unpredictable relationship between serum levels of phenytoin and their side effects[6, 7]. Previous studies point out that phenytoin toxicity may develop over months to year after starting the drug. This may be due to gradual accumulation of phenytoin over the time period as a result of non-linear pharmacokinetics[6]. These effects can be reversed by withdrawing or reducing the dose of phenytoin[3, 7].

Drug reaction with eosinophilia and systemic syndrome (DRESS) was from 1936s as cited by Criado et al [8]. The incidence of it ranges from 1 in 1000 to 1 in 10,000 as

conversed by Dong-Hyun Kim et al [11].Drugs are the main perpetrators for the syndrome or systemic effects. Symptoms ascend at least after the 3 weeks-3 month of the initiation of the offending drug [12]. In our study, patient developed rashes after 20days of the drug treatment. This was in correlation with the study conducted by Lee et al where the latency period ranged from 3-105 days. The same study shows that higher frequency of DRESS was with anti-convulsive drugs (47.4%), followed by antibiotics (18.4%), non-steroidal anti-inflammatory drugs (NSAIDs) (13.2%), allopurinol (5.2%), and undetermined agents (15.8%) [13].

Diagnosis at least fulfils the following criteria: rashes, lymphocytosis, and involvement of the organ system as versioned by Lens et al[14]. In our study patient shown eosinophilia, and alteration in the liver function tests. Treatment includes according to the symptoms, usage of corticosteroids along with alteration or deletion of the causative drug. Present case patient showed complete improvement once the drug was stopped and with the help of certain other supportive measures.

9. CONCLUSION:

This case report of phenytoin toxicity helps to alert physicians about the toxic manifestations of phenytoin in patients on long term therapy. Long term therapy with phenytoin should be individualised based on the patient's clinical response, plasma drug levels and signs of toxicity. There is also need for regular follow up to assess compliance and response to therapy. Monitoring of serum phenytoin levels and ADRs should be done even when the seizure is under control and especially when there are doubts of early toxic effects.

This report also highlights the importance of educating patients and their caregivers about the clinical manifestations of phenytoin toxicity, so that it can be recognized early and treated appropriately. Hence, this case report serves to alert clinicians to remain clinically vigilant for such manifestation in patients with active cognitive lifestyles who are on long term phenytoin therapy. Caution needs to be exercised when making dosage changes as we saw that even a small change can precipitate or mitigate the side effects. There is a need to keep in mind the erratic association of serum levels and toxic effects especially in case of phenytoin so that the progression to such possibly hazardous behavioural changes and the dramatic consequences thereof can be prevented. Immediate withdrawal of the causative drug is mandatory to avoid a possible fatal outcome in DRESS syndrome.

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CONFLICTS OF INTEREST:

The authors declare that there is no conflicts of interestthat are directly relevant to the content of the case report.

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