National Journal of Physiology, Pharmacy and Pharmacology

CASE REPORT

Drug reaction with eosinophilia and systemic symptoms for phenytoin

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Received: May 23, 2016; **Accepted:** Jun 09, 2016

ABSTRACT

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a hypersensitivity syndrome characterized by fever, skin eruptions, hematologic abnormalities, and systemic involvement frequently reported with anticonvulsants, allopurinol, nevirapine, and sulfasalazine. We report a case of DRESS syndrome in a patient with neurocysticercosis receiving phenytoin. A 60-year-old male patient was diagnosed with seizures due to neurocysticercosis and was prescribed phenytoin. 2 weeks after therapy, the patient had fever, burning micturition, decreased appetite, and generalized weakness for which he was treated symptomatically by a local practitioner. 2 days later, fever had recurred with generalized cutaneous hyperemia which was treated with antimicrobials in a local hospital, as it did not resolve patient was referred to our hospital. The findings on examination were icterus, periorbital edema, oral mucositis, facial puffiness, and generalized maculopapular rashes. Eosinophils, erythrocyte sedimentation rate, and liver enzymes were elevated, abdominal scan revealed hepatomegaly and cystitis. It was diagnosed as DRESS and phenytoin were discontinued. He was treated with corticosteroids. There was a clinical improvement, and liver function test was normal after a month. DRESS is a Type IV delayed hypersensitivity reaction which manifests after 2-4 weeks of treatment with an offending agent. This report indicates that the occurrence of DRESS has a higher preponderance in patients receiving phenytoin for seizures due to neurocysticercosis.

KEY WORDS: Phenytoin; Neurocysticercosis; Drug Reaction with Eosinophilia and Systemic Symptoms

INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a hypersensitivity syndrome characterized by fever, skin eruptions, hematologic abnormalities, and systemic/visceral involvement. 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.[1] Anticonvulsants are the most common offending agents manifesting with DRESS syndrome although they have been reported following intake of allopurinol, nevirapine, and sulfasalazine.[2] 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,[3] there still exists lack in awareness and delay in diagnosis, thus enhancing the risk of dermatological and systemic sequelae.

Access this article online	
Website: www.njppp.com	Quick Response code
DOI: 10.5455/njppp.2016.6.0614809062016	

CASE REPORT

A 60-year-old male patient with 1 month history of seizures was diagnosed with neurocysticercosis and was prescribed tablet

phenytoin 100 mg twice daily to control seizures and tablet albendazole 400 mg stat for neurocysticercosis. A week later, on seeking the second opinion at a tertiary care center, he was started on tablet levetiracetam 500 mg twice daily as an add-on therapy. After 2 weeks of therapy with the above drugs, the patient manifested with fever, burning micturition, decreased appetite, and generalized weakness for which he was treated symptomatically by a local practitioner. 2 days later, fever had recurred with generalized cutaneous hyperemia which was treated with antimicrobials in a local hospital, as it did not resolve patient was referred to our hospital. On admission, his pulse rate was 80 beats/min and blood pressure 130/90 mm of Hg. The findings observed on examination were pallor, icterus, conjunctival redness, periorbital edema, oral mucositis, palatal congestion, facial puffiness, and generalized erythematous maculopapular rashes (Figure 1). Eosinophils (differential count - 5%), erythrocyte sedimentation rate (32 mm/h), and liver function tests (LFTs) (total bilirubin - 2.65 mg/dl, aspartate transaminase - 454 U/l, alanine aminotransferase - 302 U/l, alkaline phosphatase - 1507 U/l, and γ-glutamyl transferase - 2800 U/l) were elevated; abdominal scan revealed hepatomegaly and cystitis. However, renal function test, creatinine phosphokinase, urine examination, chest X-ray, and electrocardiography were normal, and serologies for typhoid fever, brucellosis, leptospirosis, and hepatitis B were negative. Based on European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) study group, scoring of more than or equal to four (hospitalization, acute onset exanthema with fever, involvement of at least one internal organ), the patient was diagnosed to have DRESS syndrome.[4] Phenytoin was discontinued and he was treated with injection dexamethasone 8 mg and tablet levetiracetam was continued to control seizures. Following treatment, there was rapid remission of fever, but the rash eventually developed to exfoliative dermatitis. On discharge, the patient was advised to switch over to oral prednisolone 4 mg for 4 days in a step-down manner. Follow-up after 2 weeks, clinical remission was observed though LFTs failed to normalize. However, he defaulted on further reviews. A telephonic conversation confirmed that his LFTs had normalized after a month.

DISCUSSION

DRESS syndrome, also referred to as drug hypersensitivity syndrome, 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.[5] The HLA gene specific for DRESS due to allopurinol (HLA-B*5801) and nevirapine (HLA-DRB1*0101) are well established, but the same for phenytoin is yet to be determined. HLA-B*1502 is a gene which predisposes to most phenytoin-induced cutaneous hypersensitivity reactions.[6] 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.[7] 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 cysticercus granuloma and receiving phenytoin.[8]

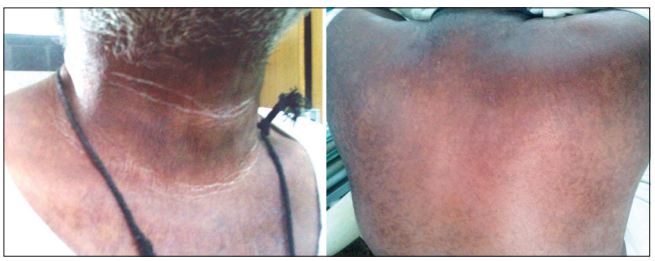

Figure 1: Erythematous maculopapular rashes over neck and back

The diagnosis of DRESS is challenging due to its plethora of clinical features and long latency between first dose and occurrence of symptoms. The RegiSCAR 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 (>38°C), lymphadenopathy, hematological 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.[2] 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.

CONCLUSION

In conclusion, phenytoin is a relatively safe medication; however, due to increased incidence of DRESS syndrome with anticonvulsants than any other group of drugs, close observation is required along with adequate instruction to the patient. In particular, if fever and rash are indicated as main symptoms, as seen in this patient, there may be a potential delay in the diagnosis as there are innumerable causes simulating this clinical presentation; thus, special cautions should be taken regarding the medication histories and symptoms of patients.

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How to cite this article: Chinnaiyan S, Krishnaswamy B, Narayana S, Srinivas RT. Drug reaction with eosinophilia and systemic symptoms for phenytoin. Natl J Physiol Pharm Pharmacol 2016;6(6):634-636.

Source of Support: Nil, **Conflict of Interest:** None declared.