Phenytoin Induced Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Natt NK1, Tarsem S2, Anubha3, Simarjeet S4, Manu Sharma5, Harmanjit S6

Abstract
Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare and potentially fatal adverse effect characterized by a skin rash with visceral involvement and haematological abnormalities. This adverse drug effect is often misdiagnosed and under-reported especially in paediatric age group due to its rarity and high occurrence of skin rash in various other viral illnesses of children. We report a case of DRESS in a three months old male child. A high index of suspicion, rapid diagnosis and prompt withdrawal can be life-saving for the patient.

Key words: Adverse effect, Skin rash, Visceral involvement

Introduction
Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a severe, fatal drug reaction, characterized by the presence of fever, cutaneous rash and systemic involvement including hematologic abnormalities especially hyper-eosinophilia and lymphocytosis, enlarged lymph nodes, abnormal liver function, renal impairment, pulmonary or cardiac infiltrates1.

The clinical manifestations typically occur within 2–6 weeks after the initiation of drug. DRESS syndrome is rare, with a frequency of 1 in 10,000 to 1 in 1000 exposures to aromatic anticonvulsants. The overall mortality is 10%, but can be up to 40% in presence of organ failure2. DRESS has been reported mostly in adult age group with a mean age 40.7±20.9 years. In a literature review of DRESS syndrome, a total of 44 drugs were described to be associated with DRESS, the most frequently reported drugs causing DRESS being carbamazepine, allopurinol, sulfasalazine, phenobarbital, lamotrigine, and nevirapine3.

The Case
We present a case report of a three months old child who presented with DRESS syndrome two weeks after being put on phenytoin. A three months old male child presented with high grade fever since the last one week, vomiting and irritability since three days, refusal to feed and seizures since two days. On examination, temperature was 40°C, pulse 100 per minute and respiratory rate 40 per minute. On investigating haemoglobin, TLC, DLC were within normal limits. Reports of CSF cytology showed mild pleocytosis, biochemistry showed mildly elevated proteins. Chest X-Ray and USG head were normal. With above history, examination and lab reports child was diagnosed as case of viral meningoencephalitis. The child was put on antipyretics, ceftriaxone and intravenous fluid. Intravenous phenytoin was started to control the seizures.

1Dr. Natt Navreet K, Senior Resident, Department of Pharmacology, Government Medical College, Amritsar, 2Dr. Singh Tarsem, MBBS, MD, Assistant Professor, Department of Paediatrics, SGRD Institute of Medical Sciences and Research, Vallah, 3Dr. Anubha MBBS, MD Junior Resident, Department of Paediatrics, SGRD Vallah, Amritsar, 4Dr. Singh Simranjeet, MBBS, MD Junior Resident, Department of Paediatrics SGRD Vallah, Amritsar, 5Dr. Manu Sharma, MBBS, MD Junior Resident, SGRD Vallah, Amritsar, 6Dr. Singh Harmanjit, MBBS, MD Senior Resident, Department of Pharmacology, All India Institute of Medical Sciences , Delhi, India.
On the fifteenth day of treatment on above drugs, the child developed widespread rash (Figure 1). The macular rash started from face and then spread to trunk, upper extremities, abdomen and lower limbs. The widespread rash was accompanied by scaling. Physical examination showed icterus, lymphadenopathy and hepatomegaly. Laboratory results revealed a white blood cell count of 39 thousand/cumm (normal from 4.0 to 10.0 thousand/mm3), with 49% neutrophils, 38% lymphocytes, and 5.0% eosinophils (absolute 1900/mm3). Hepatic function panel revealed serum bilirubin 6g%, transaminis i.e. an aspartate aminotransferase of 1950U/L (normal from 0 to 37), alanine aminotransferase (ALT) of 1450 U/L (normal from 0 to 41) and PT INR of the patient was 4.2, all suggesting of acute liver failure. Evaluation for acute and chronic hepatitis with serology was negative for hepatitis A, B and C.

Since hepatic function was the main concern, phenytoin was stopped and he was put on corticosteroids, hepatoprotective agents, antibiotics, antihistamines. The child’s condition stabilized after five days of withdrawing phenytoin. His liver function tests started improving and rash started resolving slowly. He was discharged after 34 days in satisfactory condition.

Discussion

The patient is presented as a case of DRESS due to anti-epileptic drug phenytoin which is being widely used in developing countries due to its low cost and efficacy. DRESS syndrome is a cutaneous adverse drug reaction with systemic involvement, caused by anticonvulsants, especially those with an aromatic ring structure such as carbamazepine, phenobarbitone and phenytoin.

The diagnosis of DRESS syndrome involves three criterias:

1. Cutaneous eruption mostly maculopapular in nature, erythroderma and pustules may be present.
2. Hematologic abnormalities, mainly hyper-eosinophilia and lymphocytosis with large, activated, and sometimes atypical, circulating lymphocytes.
3. Systemic findings: at least one of these i.e. abnormal liver function, renal impairment, pulmonary or cardiac infiltrates or lymphadenopathy

In order to evaluate potential cases of DRESS, a scoring system with 8 diagnostic criterias was designed in 2007 as RegiSCAR (Severe Cutaneous Adverse Reactions) criteria: first, fever greater than 38.5°C; second, enlarged lymph nodes; third, eosinophilia; fourth, atypical lymphocytosis; fifth, skin involvement; sixth, organ involvement; seventh, resolution greater than 15 days; and eighth, evaluation and exclusion of other causes. The score indicates likelihood of DRESS:

- Score <2 indicates no DRESS
- Score 2 to 3 indicates possible case
- Score 4 to 5 indicates probable case
- Score >5 indicates definite case

The patient in this case report is a definite case of DRESS as per RegiSCAR criteria with fever, eosinophilia, typical skin rash, lymphadenopathy, liver involvement and resolution more than 15 days. There was no atypical lymphocytosis in this case. The clinical suspicion was high due to the typical rash, oesinophilia and hepatic involvement (highly deranged liver function tests) with normal serology for hepatitis A, B, C.

The adverse event should further be evaluated and a causal relationship between drug and adverse event be established using an acceptable causality scale. This adverse drug reaction was rated as probable using Naranjo ADR probability scale and the World Health Organization (WHO) Adverse Reaction Probability Scale.
Health Organization Utilization Management Criteria (WHO UMC) criteria. The causality of ADR could not be established as certain as the drug was not re-administered due to ethical reasons, nor were the blood concentrations of drug determined. Apart from this, there was no previous exposure to the drug in this three month old child.

Although not completely understood, the DRESS syndrome has been attributed to accumulation of toxic metabolites of aromatic anticonvulsants like arene oxides which are detoxified by epoxide hydroxylases. But in some individuals, absence or mutation of these detoxifying enzyme systems may cause DRESS.

DRESS syndrome must be recognized at the earliest and the causative drug withdrawn. DRESS, if recognized before significant visceral involvement along with prompt withdrawal of offending drug, is associated with better prognosis. As liver failure is the most common cause of fatalities associated with DRESS, liver function tests should be closely monitored in these patients. The first line treatment for DRESS is systemic corticosteroids. Intravenous immunoglobulin (IVIG) and/or plasmapheresis can be done in case of further progression of disease. Recovery is usually slow and may take weeks to months.

**Conclusion**

Due to significant mortality attributed to drug reaction with eosinophilia and systemic symptoms syndrome, paediatricians should be aware of this potentially fatal adverse drug reaction and should ensure close follow-up after putting the patient on anti-epileptic therapy or other drugs suspected of causing DRESS. In patients presenting with skin rash with systemic abnormalities after recent change in medicines, DRESS should be considered as differential diagnosis. Lives can be saved by early recognition of this drug reaction and prompt withdrawal of culprit drug.

**References**