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# Case Report on Phenytoin induced Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome

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**ABSTRACT**

Phenytoin is aromatic amine which is a hydantoin derivative and used to be a first line anti-epileptic drug, but due to its frequent side effects is not used routinely now a days. Here in we reported Phenytoin induced Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome which is a serious Adverse Drug Reaction and concluded as possible category according to WHO-UMC causality assessment.

**Key words:** DRESS–Phenobarbitone–Phenytoin–Rash

## 1 INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare but potentially life-threatening syndrome characterized by skin rash, fever, lymph node enlargement, and involvement of internal organs [1] . Dermatologic manifestations of DRESS can be diverse, with morbilliform rash being the most common presentation. The condition not only involves the skin, but also certain organs, such as the lungs, kidneys, and heart so the character' R' in the acronym DRESS previously used to be' rash' was later revised to' reaction'.

Patients who recover from DRESS syndrome may have an increased risk of reaction to structurally unrelated drugs. This syndrome has a 10% mortality rate, most commonly from fulminant hepatitis with hepatic necrosis [2] . Due to an unfamiliarity with the condition and its guidelines, the DRESS syndrome is often ignored in clinical practice, particularly where the skin findings are limited and the diagnosis difficult.

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## 2 CASE DETAILS

A 13-year-old boy known case of epilepsy on treatment came to the hospital with the chief complaints of rashes all over the body for 15 days, fever for 10 days and cough and cold for 1 day. Fever was acute, progressive, high grade, continuous in nature and not relieved by medication and associated with cough and cold. The cough was acute in onset and with sputum production.

The patient was known case of epilepsy since past 2 years on medical treatment, and had associated intellectual disabilities. On taking his history, he was earlier on valproate therapy 300 mg OD, but since past one month therapy was changed to Tab. Phenytoin 100 mg + Phenobarbitone 50 mg BD due to poor control of seizure with sodium valproate.

On admission, his oral temperature was 104.6 F., Heart rate was 140 beats/min, blood pressure was 70/50 mm of Hg. Random Blood Sugar was 95mg%.

On examination there was diffuse blanchable erythema present over the entire body (more on the face), there was crusting presented on both the lips.

His investigational findings were:

HB:9.1, WBC: 11860 (N:41 L:40 M: 4 E:3 B:1) LFT (SGOT:489, SGPT:141 S.ALP:777 Total Bilirubin: 4.25) Urea: 40.7, Creatinine: 0.68 , CRP positive. Malarial Parasite, Dengue NS1, HIV, HBsAg, HCV, Widal all were negative.

He was diagnosed with DRUG RELATED EOSINOPHILIA WITH SYSTEMIC SYMPTOMS (DRESS) according to RegiSCAR score. Table 1 describes the diagnostic criteria RegiSCAR (Registry of Severe Cutaneous Adverse Reactions)**.**

Our **Patient** comes under **Probable case** according to RegiSCAR SCORE of **5** with lymphocytosis(1), skin rash >50%(1),biopsy(1), internal organ involvement(1), HAV, HBV, HCV negative(1).

| Score | −1 | 0 | 1 | 2 | Minimum | Maximum |
|---|---|---|---|---|---|---|
| Fever >38.58°C | No/U | Yes | | | −1 | 0 |
| Enlarged lymph nodes | | No/U | Yes | | 0 | 1 |
| Eosinophilia | | No/U | | | | |
| Eosinophils | | | 700-1499/µL | 1500/µL | 0 | 2 |
| Eosinophils, if leukocytes <4000 | | | 10-19.9% | 20% or more | | |
| Atypical lymphocytes | | No/U | Yes | | 0 | 1 |
| Skin involvement | | | | | | |
| Rash extent (>50% BSA) | | No/U | Yes | | −2 | 2 |
| Rash suggesting DRESS[a] | No | U | Yes | | | |
| Biopsy suggesting DRESS | No | Yes/U | | | | |
| Organ involvement[a] | | | | | | |
| Liver | | No/U | Yes | | 0 | 2 |
| Kidney | | No/U | Yes | | | |
| Lung | | No/U | Yes | | | |
| Muscle/heart | | No/U | Yes | | | |
| Pancreas | | No/U | Yes | | | |
| Other organ(s) | | No/U | Yes | | | |
| Resolution >15 days | No/U | Yes | | | −1 | 0 |
| Evaluation other potential causes | | | | | | |
| ANA | | | | | 0 | 1 |
| Blood culture | | | | | | |
| Serology for Hep A/ Hep B/ Hep C | | | | | | |
| *Chlamydia/Mycoplasma pneumoniae* | | | | | | |
| Other serology/PCR | | | | | | |
| If none positive and 3 or more of above negative | | | Yes | | | |
| Total score | | | | | −4 | 9 |

[a]After exclusion of other explanations: 1: 1 organ, 2: [1]2 organs. Final score <2: No case, Final score 2-3: Possible case, Final score 4-5: Probable case, Final score >5: Definite case, [a]Morphology is considered suggestive for DRESS: Scaling/desquamation, e.g., exfoliative dermatitis. Oedema, especially facial oedema (excluding lower leg oedema), purpura (excluding lower leg). Infiltration.[2][3] U: unknown/unclassifiable, DRESS: Drug reaction with eosinophilia and systemic symptom, BSA: Body surface area, ANA: Antinuclear antibody, PCR: Polymerase chain reaction, Hep A: Hepatitis A virus, Hep B: Hepatitis B virus, Hep C: Hepatitis C virus

**Figure 1.** RegiSCAR diagnostic Score

His physical appearance on admission is given as figures 2 and his laboratory findings were given in table 1.

His skin biopsy findings were Epidermis with irregular acanthosis with spongiosis in the epidermis and also showed prominent granular layer and focal vacuolar degeneration of basal keratinocytes. Interface dermatitis with infiltration of lymphocytes and histiocytes were also seen,Overall findings were consistent with the clinical diagnosis of **DRESS**".

On admission, tab. Phenytoin+Phenobarbitone was discontinued and changed to Tab. Clobazam 10 mg and Levetiracetam 500 mg and was treated with inj. Ceftriaxone, Pantoprazole, Ondansetron, Dexamethasone, Phenaremine malate, Paracetamol and Folic acid.

His condition was improved with of two antiepileptic drugs and was discharged after 11 days of hospitalization. Patient is better in respect to seizure control on regular follow up on Tab Clobazam 10 mg BD, Tab Leve-tiracetam 500 mg BD.

**Table 1.** Lab. Findings during the treatment period

| Lab tests (normal range) | On admission | After 3 days | After 7 days | At discharge |
|---|---|---|---|---|
| WBC (4000-11000) | 11800 | 11530 | 5230 | 8090 |
| S.Urea (15-45) | 40.7 | 36.5 | 30 | 17.1 |
| S.Creatinine (0.7-1.3) | 0.68 | 0.60 | 0.47 | 0.33 |
| SGOT(0-34) | 489 | 510 | 584 | 253 |
| SGPT(10-49) | 141 | 130 | 134 | 108 |
| S. ALP(45-129) | 777 | 692 | 674 | 447 |

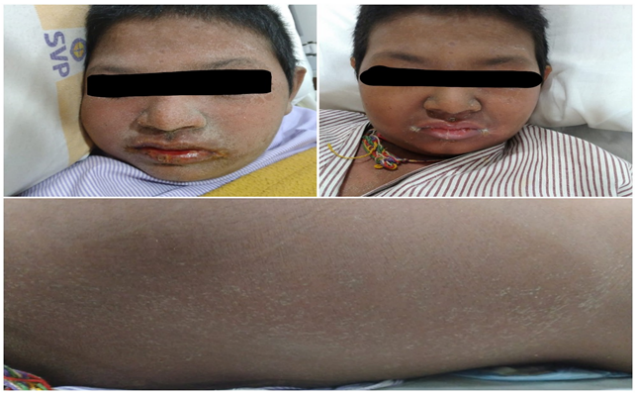

**Figure 2.** Rashes on admission and on 3rd day of discontinuation of drug. Below picture showing blanchable rashes on back.

## 3 DISCUSSION

The diagnosis of DRESS is complicated because there are no specific clinical manifestations. There is no evidence of a diagnostic symptom or pathological examination for DRESS. Diagnosis is clinical and determined by assessing the application of medications in the relevant clinical condition and time between the ingestion of medicines and the appearance of symptoms. DRESS syndrome is a severe drug-induced adverse reaction that arises most frequently following exposure to medications, such as anticonvulsants as in this case, sulfa derivatives, antidepressants, NSAIDS, and Antimicrobials [3] In the above case this adverse drug reaction is serious because it initiated hospitalization for 11 days.

In our case, both the antiepileptic drug phenytoin and phenobarbital are aromatic amines and they metabolized by CYP2C9, so there may increase the plasma concentration of phenytoin by competitive binding to same site [4].

The variation of the incidence of DRESS syndrome across families and ethnicities may suggest a significant role for genetics [5]. It has been found that DRESS syndrome is associated with certain human leukocyte antigens (HLAs), such as HLA-B*1502, HLA-B*1508, HLA-B*5701 and HLA-B*5801 [6] . Particularly **cytochrome P4502C9** marker has been reported to be associated with phenytoin induced severe cutaneous adverse reactions [7] .

Any abnormality in **epoxide hydroxylase** enzyme which detoxifies the metabolites of aromatic amine antiepileptics like Phenytoin, Phenobarbitone, and Carbamazepine, results in the activation of IL-5 upon the accumulation of toxic metabolites leading to activation of eosinophils and downstream inflammatory cascade [8] .

## 4 CONCLUSION

DRESS syndrome is a rare hypersensitivity reaction, which is serious and potentially fatal. It is classified among severe cutaneous adverse reactions (SCARs). Patients should be educated about the need for a strict avoidance of the offending as well as cross-reacting drugs. Although the mortality is low, early diagnosis can further decrease the mortality

due to this syndrome.

Prospective HLA screening can prevent certain patients from having serious idiosyncratic reactions such as drug-induced hypersensitivity syndrome (DIHS), Stevens-Johnson syndrome, toxic epidermal necrolysis, and DRESS. Prescribers should switch over patients to new alternative drugs which have unlikely to produce these drug-related problems. As early diagnosis and treatment dramatically strengthen outcomes, healthcare practitioners should be more cautious regarding the early diagnosis of this syndrome.

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