PHENYTOIN INDUCED DRESS SYNDROME – A CASE REPORT

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ABSTRACT
Drug reaction with eosinophilia and systemic symptoms (DRESS) is a delayed hypersensitivity reaction. It is characterised by fever, skin rash, haematological abnormalities and systemic involvement such as hepatitis. This usually presents 2-6 weeks after drug initiation. Here we present a case of DRESS syndrome due to phenytoin exposure 4 weeks after drug initiation in a 63-year-old male patient. Laboratory investigations revealed atypical lymphocytosis, eosinophilia and elevated liver enzymes. Immediate cessation of phenytoin and initiation of corticosteroid therapy were the mainstay of management. Early recognition of drug reaction with eosinophilia and systemic symptoms syndrome and initiation of appropriate therapy are imperative in limiting morbidity.

KEYWORDS: DRESS syndrome, phenytoin, eosinophilia, maculopapular rashes.

INTRODUCTION
DRESS syndrome is also known as Drug Induced Hypersensitivity Syndrome (DIHS), this is one of the major Drug Induced Severe Cutaneous Adverse Reaction (SCAR). DRESS is a type IV delayed hypersensitivity reaction.1 DRESS is occurring in 1:1000 to 1:10,000 patients prescribed with anti-epileptic therapy and these type of cases are very rare.2 The major characteristic features of this life-threatening syndrome includes a severe skin eruption, fever, haematological abnormalities like eosinophilia or atypical lymphocytes and internal organ involvement. Discontinuation of phenytoin and supportive care is the major therapy for phenytoin hypersensitivity syndrome. A positive response to steroids is illustrated in most of the case reports.3,4,5,6
CASE REPORT
A 63-year-old male patient was admitted with the complaints of one episode of prolonged generalised seizure lasting for 20 minutes followed by disorientation in the early morning hours. There was no history of bowel or bladder incontinence, fever, trauma and he was not on any drugs. No past history of seizures. Blood investigation were within normal limit, EEG was normal, CSF Study was normal, MRI brain taken showed diffuse hyper intensity in bilateral medial and temporal region suggestive of hypoxic changes. The provisional diagnosis was viral encephalitis. In view of generalised seizures, intravenous phenytoin was started conservatively and there was no further episode of disorientation after admission. He got discharged with stable condition IV Phenytoin changed to oral phenytoin 100mg 1-0-2 for 6 weeks orally started during discharge.

After 4 weeks, patient got admitted with complaints of fever and non pruritic erythematous maculopapular rashes all over the body with no history of vomiting, altered sensorium, palpitation. Phenytoin toxicity probably DRESS syndrome was suspected and phenytoin was discontinued. Blood investigation showed elevated total count with eosinophilia, Liver function test showed elevated transaminases, suggestive of hepatitis, viral markers were negative. Absolute eosinophil count was high. Peripheral blood smear showed leukocytosis with eosinophilia and reactive lymphocytes. Detailed investigations of report are shown in the following table:

<table>
<thead>
<tr>
<th>TEST</th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
<th>D5</th>
<th>D6</th>
<th>D7</th>
<th>D9</th>
<th>D10</th>
<th>D12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total count (cells/cumm)</td>
<td>17,100</td>
<td>16,200</td>
<td>21,200</td>
<td>29,900</td>
<td>34,100</td>
<td>28,300</td>
<td>13,600</td>
<td>12,400</td>
<td>7,800</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>32</td>
<td>34</td>
<td>36</td>
<td>35</td>
<td>38</td>
<td>38</td>
<td>69</td>
<td>80</td>
<td>59</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>47</td>
<td>48</td>
<td>46</td>
<td>28</td>
<td>28</td>
<td>27</td>
<td>25</td>
<td>13</td>
<td>37</td>
</tr>
<tr>
<td>Eosonophils (%)</td>
<td>18</td>
<td>14</td>
<td>16</td>
<td>33</td>
<td>30</td>
<td>30</td>
<td>3</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>SGOT (U/L)</td>
<td>277</td>
<td>-</td>
<td>134</td>
<td>-</td>
<td>-</td>
<td>65</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SGPT (U/L)</td>
<td>399</td>
<td>-</td>
<td>346</td>
<td>-</td>
<td>-</td>
<td>75</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>455</td>
<td>-</td>
<td>393</td>
<td>-</td>
<td>-</td>
<td>150</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Absolute Eosonophil Count</td>
<td>2720</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Atypical Lymphocytes</td>
<td></td>
<td></td>
<td></td>
<td>Reactive Lymphocytes</td>
<td></td>
<td></td>
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</tbody>
</table>

He was started on intravenous steroids as well as antibiotics and showed remarkable clinical response to treatment. Leucocytosis and Eosonophilia responded well to steroid therapy and he was continued on conservative management. At the time of discharge, his condition was
better and tablet phenytoin discontinued and advised to take tablet prednisolone 20mg 2-0-0 for 1 week orally.

**DISCUSSION**

One of the first line therapies in patients with seizure disorder is phenytoin. During the initiation of new therapy, anti-epileptic drug can frequently cause cutaneous eruption like widespread maculopapular rash, hypersensitivity syndrome, psoriatic dermatitis and occasionally severe reactions such as Steven Johnson syndrome, toxic epidermal necrolysis and erythema multiforme.\(^7\) A one year survey was conducted by Chaterjee et-al in the year of 2007 and was found to be urticaria and fixed drug rashes were the most common reaction types, the commonly contributing drugs were carbazepine (16.23%), phenytoin (15.15%) and cotrimoxazole (13.53%).\(^8\) Haematological abnormalities like eosinophilia or atypical lymphocytes which are positive for DRESS syndrome, were present in our case too. A recently developed scoring system for the DRESS syndrome is RegiSCAR scoring system. A study was conducted by kardaun SH et-al was found for phenytoin was 3 possible and probable cases, there were no definite case for phenytoin according to RegiSCAR scoring system.\(^9\) The RegiSCAR score was 2 indicating possible DRESS in our case. The other method to find out the probability of an ADR can be determined by Naranjo scale.\(^10\) According to naranjo scale of causality assessment, the ADR found to be highly probable in our case.

The onset of reaction usually takes 2-6 weeks after the first exposure of culprit drug.\(^11\) In this case patient presented to hospital with maculopapular rashes after 4 weeks of therapy. The first case of DRESS caused by phenytoin was reported in 1950’s and coined the term Dilantin hypersensitivity.\(^12\) Phenytoin related SCARs are associated with CYP2C genes 16 single nucleotide polymorphism.\(^13\)

Human Herpes Virus (HHV)-6 was identified in patients with this hypersensitivity syndrome in 1997\(^14\), followed by two other reports from Japan in 1998\(^15\). But in this case all the viral markers were negative.

A French society of dermatology suggests using systematic corticosteroids in the presence of elevated serum transaminases level or involvement of any other organs.\(^16\) After discontinuation of phenytoin, corticosteroid started and the patient responded well to the treatment.
CONCLUSION
In conclusion, phenytoin is one of the most common anti-epileptic drugs causing DRESS syndrome. Even though the diagnosis of DRESS syndrome is challenging prompt withdrawal of causative drug after recognition of adverse drug reaction limits its progression. If Patients present skin rash and systemic abnormalities like fever, eosnophilia, liver involvement after a recent change in medications, clinicians must consider DRESS syndrome as a possible diagnosis.

REFERENCES


