Case study

Sulthiame-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome

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Abstract

Background: Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare and potentially life-threatening acute drug-induced hypersensitivity reaction. Antiepileptic drugs (AEDs) predominantly aromatic AEDs are commonly reported in DRESS. To date there are no reports of sulthiame AED causing DRESS syndrome.

Method: We report a 10-year-old girl of Indian descent with AED resistant epilepsy on maintenance sodium valproate and clonazepam. Sulthiame AED was initiated to try to improve her seizure control. Five weeks after commencing sulthiame, she developed fever with a diffuse erythematous morbilliform maculopapular rash, elevated transaminases and atypical lymphocytes. At day 3 of illness, she deteriorated with worsening elevation of liver transaminases, thrombocytopenia, progression of rash, hepatosplenomegaly, pneumonitis and markedly elevated inflammatory markers. Immunomodulatory treatment of pulse methylprednisolone was given from day 7 which was associated with improvement in inflammatory markers and complete resolution of rash from day 30 of illness.

Results: The diagnosis of sulthiame-induced DRESS syndrome was made based on clinical, laboratory and skin histology findings. She was HLA-B heterozygous for HLA-B*15:123 and 15:240 and HLA-A homozygous for HLA-A*11:01:09. Both these HLA-A and HLA-B typing has not been reported before in cutaneous drug reactions.

Conclusion: This is the first reported case of sulthiame-induced DRESS syndrome. Our case expands the list of possible susceptible HLA alleles associated with cutaneous drug reactions. It also raises the awareness of possible DRESS syndrome among patients commenced on sulthiame who will require immediate discontinuation of sulthiame and consideration of prompt treatment of corticosteroids.

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1. Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare and potentially life-threatening acute drug-induced hypersensitivity reaction occurring typically 2–6 weeks after drug administration. DRESS is characterized by cutaneous manifestation, fever, hematological abnormalities with internal organ involvement most frequently affecting the liver in both adults and children. The cutaneous involvement is typically a morbilliform eruption with facial oedema. Cutaneous involvement is typically a morbilliform eruption with facial oedema. Antiepileptic drugs (AEDs) predominantly the aromatic AEDs (especially carbamazepine, phenobarbitone and phenytoin) and carbonic anhydrase inhibitors (especially zonisamide) are commonly reported in DRESS. New generation AEDs like lamotrigine, levetiracetam and more recently perampanel have also been associated with DRESS. Apart from AEDs, sulfonamides such as dapsone and sulfasalazine are also responsible for DRESS. Sulthiame is a cyclic sulfonamide derivative [4-(1,1-dioxothiazinan-2-yl) benzenesulphonamide] without antimicrobial activity acting as a central carbonic anhydrase inhibitor. Sulthiame was introduced as an AED in the 1960s and was found to be effective in both focal and generalised epilepsy. From the 2000s, papers have also shown the usefulness of sulthiame in the benign childhood focal epilepsies and focal epilepsies associated with electrical status epilepticus during slow sleep.

Common adverse effects include dose-related hyponatraemia, paresthesia, anorexia and drowsiness. Otherwise sulthiame has a relatively good safety profile which does not require blood-monitoring with good patient tolerance. We report a sulthiame-induced DRESS syndrome with hepatitis and pneumonitis requiring corticosteroid and intravenous (IV) immunoglobulin treatment. To our knowledge, this is the first reported case of sulthiame-induced DRESS syndrome.

2. Case report

A 10-year-old girl of Indian descent presented to our tertiary hospital with fever and maculopapular rash. She is known to our unit for ongoing treatment of lesion negative AED-resistant left-sided focal tonic-clonic seizures from 7-years of age. Her AED history included carbamazepine, lamotrigine, levetiracetam, topiramate and phenytoin which were all discontinued because of lack of efficacy on seizure control. She was still experiencing multiple daily focal motor seizures on AED combination of sodium valproate and clonazepam for the last 1 year. Five weeks prior to presentation she was commenced on sulthiame AED; initiating at 50 mg once daily titrating up weekly to maintenance dose of 200 mg twice daily (8.5 mg/kg/day) by week 4.

On day 1 of illness, she had persistent high grade fever ranging 38.5–40 °C together with a diffuse erythematous morbilliform maculopapular rash covering over 70% of her body affecting her whole trunk and proximal limbs. There was no mucosal involvement and her Nikolsky sign was negative. She did not have lymphadenopathy. There was no prior history of exposure to other herbal or traditional remedies. Her laboratory investigation showed presence of atypical lymphocytes, thrombocytopenia and elevated transaminases (Table 1). Serial acute phase reactants of both C-reactive protein and ferritin were also elevated. She was treated initially with intravenous penicillin.

Her condition deteriorated further and at day 3 of illness, her maculopapular morbilliform rash spread to her face and extremities with facial swelling. She developed hepatosplenomegaly, worsening elevation of transaminases, bilateral pleural effusion and pneumonitis. She was then transferred to the Paediatric Intensive Care Unit as she became haemodynamically unstable requiring 2 weeks of inotropic support and marked respiratory distress requiring 3 weeks of mechanical ventilation (including high frequency oscillation). Her serial liver function tests showed progressive derangement associated with markedly elevated inflammatory markers.

Skin biopsy done at day 7 of illness showed perivascular lymphocytic inflammatory infiltrate at the superficial papillary dermis with occasional eosinophil (Fig. 2). Blood investigations were negative for autoimmune screen (antinuclear, antineutrophil cytoplasmic and antidual strand DNA antibodies), hepatitis serology (hepatitis B antigen, hepatitis C antibody and anti-hepatitis A IgG), viral PCR (including herpes simplex virus (HSV)-1, HSV-2, enterovirus, human herpes virus (HHV)-6, HHV-7, cytomegalovirus (CMV), EBV, parvovirus B19, and varicella-zoster virus) and viral serology (dengue virus Ig M/IgG/NS1, measles IgM, EBV IgM and CMV IgM). Her echocardiogram was normal.

She received 1 g/kg IV immunoglobulin at day 5 and 30 mg/kg/day IV pulse methylprednisolone at day 7–10 and day 13–18. She was then converted to 60 mg prednisolone orally and given a slow tapering regimen over 5 months. She responded clinically whereby she was afebrile from day 9 and showed marked improvement in her rash from day 21 with complete resolution of rash at day 30 (Fig. 1). At 6-months post-illness, she was healthy with normal surveillance blood laboratory values.

3. Discussion

DRESS syndrome was suspected in our patient because of: (i) the close temporal relationship with the onset of symptoms occurring within 2–6 weeks of initiation of sulthiame; (ii) typical clinical features of DRESS syndrome together with other investigation tests ruling out autoimmune disorders and connective tissue disease; iii) clinical improvement with corticosteroid treatment. Our patient had persistent fever >38 °C, classical rash, hepatitis, pneumonitis, haematological blood abnormality of leukocytosis and thrombocytopenia with atypical lymphocytes of 4%. Although she did not have an eosinophilia, studies have shown that this is only seen in up to 70% of the reported cases. In addition the histopathologic analysis of the skin biopsy also supported the diagnosis with the typical perivascular lymphocytic infiltrate together with the presence of eosinophil and dermal oedema. To assess the likelihood of this patient having an adverse drug...
**Table 1** – Serial laboratory values from day of admission (abnormal values highlighted bold; NA = not available).

<table>
<thead>
<tr>
<th>Laboratory test (reference range)</th>
<th>Day 1</th>
<th>Day 3</th>
<th>Day 6</th>
<th>Day 14</th>
<th>Day 24</th>
<th>Month 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>White cell count (5–13 × 10⁹/L)</td>
<td>14.3</td>
<td>13.2</td>
<td>8.9</td>
<td>7.8</td>
<td>10.3</td>
<td>6.7</td>
</tr>
<tr>
<td>Eosinophils (0.1–1 × 10⁹/L)</td>
<td>0</td>
<td>1</td>
<td>0.45</td>
<td>0</td>
<td>0</td>
<td>0.17</td>
</tr>
<tr>
<td>Atypical lymphocyte in %</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Haemoglobin (11.5–15.5 mg/L)</td>
<td>13.9</td>
<td>13.2</td>
<td>9.4</td>
<td>9.3</td>
<td>10.4</td>
<td>12.9</td>
</tr>
<tr>
<td>Platelet (180–400 × 10⁹/L)</td>
<td>119</td>
<td>113</td>
<td>61</td>
<td>205</td>
<td>346</td>
<td>224</td>
</tr>
<tr>
<td>Alanine aminotransferase (10–49 u/L)</td>
<td>156</td>
<td>238</td>
<td>97</td>
<td>53</td>
<td>56</td>
<td>18</td>
</tr>
<tr>
<td>Aspartate aminotransferase (&lt;34 u/L)</td>
<td>174</td>
<td>391</td>
<td>232</td>
<td>123</td>
<td>72</td>
<td>27</td>
</tr>
<tr>
<td>Ferritin (10–291 ug/L)</td>
<td>NA</td>
<td>NA</td>
<td>898.8</td>
<td>506</td>
<td>191.9</td>
<td>27.3</td>
</tr>
<tr>
<td>Lactate dehydrogenase (120–246 u/L)</td>
<td>NA</td>
<td>NA</td>
<td>1578</td>
<td>600</td>
<td>310</td>
<td>223</td>
</tr>
<tr>
<td>C-reactive protein (&lt;0.8 mg/dL)</td>
<td>7.8</td>
<td>11.9</td>
<td>NA</td>
<td>NA</td>
<td>0.5</td>
<td>NA</td>
</tr>
</tbody>
</table>

Fig. 1 – A: At day 3 with diffuse erythematous morbilliform maculopapular rash, B: At day 30 showing completely normal skin with no areas of desquamation or pigmentation.

Fig. 2 – Haematoxylin-eosin stain of histological section of skin. A (low power 4×) and B (medium power 10×): Small focus of basal vacuolar degeneration, spongiosis and infiltration of the epidermis by lymphocytes. Scattered apoptotic keratinocytes (Civatte bodies) are present. The underlying superficial papillary dermis is oedematous and infiltrated by lymphocytes predominantly around the superficial vascular plexus. C (medium power 10×) and D (high power 100×): Occasional eosinophil present within the dermis shown at arrowhead.
reaction (ADR) related to sulthiame, the Naranjo ADR probability scale was used. The Naranjo ADR probability scale is a 10 point scale (score 0: doubtful ADR, score 1–4: possible ADR, score 5–8: probable ADR and score 9–10: definite ADR).12 This patient had a Naranjo ADR probability scale score of 6 indicating a probable ADR relationship between sulthiame and the development of DRESS syndrome in our patient.12

To date there is no reliable gold standard to diagnose DRESS syndrome and diagnosis is made through clinical and laboratory abnormalities. There are currently 3 proposed sets of diagnostic criteria for DRESS syndrome: (i) Bocquet et al. proposed the original criteria; (ii) European Registry of Severe Cutaneous Adverse Reaction (RegiSCAR); and (iii) Japanese Research Committee of Severe Cutaneous Adverse Reaction (J-SCAR).1 Our patient fulfilled all 3 criteria of the Bocquet et al. criteria of DRESS syndrome as she had all the 3 criteria of cutaneous drug eruption, hematologic abnormalities with the presence of atypical lymphocytes, and systemic involvement of hepatitis with liver transaminases ≥2 times normal. On the RegiSCAR scoring system she had a score of 6 of the 7 criteria (criteria fulfilled: acute rash, reaction suspected to be drug-related, hospitalization, fever >38°C, involvement of ≥1 internal organ (she had liver and lung involvement), and blood count abnormalities of platelets under laboratory limits) classifying as a definite DRESS. On the J-SCAR criteria system; the presence of 5 criteria would be classified as atypical DRESS syndrome and presence of all 7 criteria would be classified as typical DRESS syndrome. She fulfilled 5 of the 7 J-SCAR criteria (criteria fulfilled: maculopapular rash developing >3 weeks after starting offending drug, prolonged clinical symptoms after discontinuation of the causative drug, fever >38°C, liver abnormalities of ALT > 100 U/L, and leukocyte abnormality of leukocytosis >11 × 10⁹/L) classifying her as atypical DRESS syndrome. Thus the diagnosis of DRESS syndrome in this patient was further supported by all these 3 proposed diagnostic criteria.

The exact pathophysiology of DRESS syndrome remains unknown. One hypothesis states the possible reactivation of viruses including HHV6 and other herpes virus (including CMV, EBV, HHV-7) that may act as an amplifier of an inadequate immune reaction.3,13 HHV6 in particular has been incriminated as a cofactor for the development of DRESS and is one of the diagnostic criteria in the J-SCAR scoring system.1 In our patient there was no viral PCR evidence of reactivation of HHV6 and the other tested human herpes viruses.

Another hypothesised risk factor of developing DRESS syndrome is the individual’s genetic predisposition which may result in accumulation of toxic metabolites triggering an immunological response.4 The genetic susceptibilities reported include slow acetylators in people of black ethnic origin; HLA B*5801 in Asians with allopurinol induced severe cutaneous adverse reactions; HLA-B*1502 in aromatic amine AEDs induced Steven-Johnson syndrome; and in DRESS syndrome reported HLAs include HLA-B*1508, HLA-B*1518, HLA-B*1511, HLA-A*3101.14,15 For our patient her HLA-B typing is heterozygous for HLA-B*15:123 and 15:240 and her HLA-A typing is homozygous for HLA-A*11:01:09. The HLA-B type found in this patient is rare with very limited data reported on it. However, the HLA-A type found in this patient is reported to be more common in the Asian population with frequency of 10–34% (particularly among the ethnic Indian population with frequency of 10–20%) when compared to the Caucasian population with frequency of 6–7%. Both these HLA-A and HLA-B typing in our patient has not been reported before in DRESS syndrome or other cutaneous drug reactions and expands the list of reported possible susceptible alleles particularly among people of Indian ethnicity for cutaneous drug reactions.

Although DRESS syndrome which often results in liver injury has been reported in sulfonamide drugs (sulfasalazine and dapsone) and antiepileptic drugs; to date there is no report of DRESS syndrome in association with sulthiame AED.4,15 The incidence of rash with sulthiame is not known due to the paucity of available data and the reported incidence of Steven Johnson syndrome is uncommon with rates of <1%.16 The most common AEDs to be associated with drug-induced hepatic injury are sodium valproate and carbamazepine. Sulthiame however has been listed among the AEDs to have been reported as suspected to cause drug-induced hepatic injury like in our patient.17 Our case of sulthiame-induced DRESS syndrome with hepatitis as the initial organ involvement adds to the current list of AEDs reported to be associated with DRESS syndrome.

The mainstay of management of DRESS syndrome is the withdrawal of the causative drug and the provision of supportive care.18 Systemic or pulse IV corticosteroid therapy is the current recommended treatment in all severe cases of DRESS syndrome with evidence of internal organ involvement.19 Despite withdrawal of sulthiame medication in our patient; she continued to deteriorate from day 1 to day 6 of admission necessitating treatment with pulse IV methylprednisolone at day 7 to day 10. Within 24 h of commencing of corticosteroids, there was a rapid treatment effect with cessation of fever associated with a reduction in serum inflammatory markers and normalisation of platelet levels.

4. Conclusion

We report the first case of sulthiame-induced DRESS syndrome with internal organ involvement of hepatitis and pneumonitis. Although sulthiame is well tolerated among the vast majority of patients, clinicians should be aware of the possibility of sulthiame causing DRESS syndrome. If DRESS syndrome is suspected immediate discontinuation of sulthiame should be considered and prompt treatment of corticosteroids.

Conflict of interest statement

All authors report none.

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