**Letters to the Editors**

**Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): an atypical case during treatment with sulfasalazine**

Sirs,

Serious adverse events occur infrequently with sulfasalazine (SSZ), a drug commonly used in the treatment of rheumatoid arthritis and inflammatory bowel diseases (1). We report an atypical case of SSZ-associated Drug Reaction with Eosinophilia and Systemic Symptoms, i.e. DRESS.

A 45-year-old Caucasian man complained of fatigue, abdominal discomfort, a rash over his right thigh, and fever (38.2°C) six days after SSZ (500 mg twice daily) was initiated for a flare-up of seronegative spondyloarthitis. Dose had been stable, he denied alcohol consumption and was not taking over-the-counter and recreational medications or herbal remedies. There was no personal or family history of allergy or liver and skin disorders; he had type II diabetes, gastro-esophageal reflux, seronegative spondyloarthritis and bronchial asthma managed with metformin, omeprazole, regaplinide, and on-demand salbutamol and non-steroidal anti-inflammatory drugs.

Six months prior, an abdominal sonogram showed fatty liver infiltration; liver and kidney function tests were normal at that time. The patient was fully alert and oriented; physical examination showed atrophic ulcers in the mouth, several cervical, axillary and inguinal non-tender lymph nodes, a few vesicles and pustules over his right thigh, mild scleral jaundice and no flapping tremor or any other stigmata of chronic liver disease. The rest of the examination was unremarkable. Blood tests disclosed anaemia, low white blood cells (WBCs), the presence of enlarged lymphocytes with ensuing lymphadenopathy, hepatitis, interstitial nephritis, pneumonitis or carditis, that was first described with phenytoin in 1950 (3, 4). The most frequently involved internal organ is the liver, followed by the kidney and lung (3, 4).

DRESS syndrome has produced diagnostic criteria and a scoring system to provide a better definition and assist in the diagnosis of DRESS (5). RegiSCAR inclusion criteria require at least three of the followings: hospitalisation, reaction suspected to be drug-related, acute skin rash, fever at least 38°C, enlarged lymph nodes at two sites, involvement of at least one internal organ, blood count abnormalities such as low platelets, raised eosinophils, or abnormal lymphocyte count (5). The RegiSCAR scoring system grades DRESS cases as no, possible, probable, or definite with scores of 5 or more being classified as definite DRESS syndrome. Our case scored 6 points and was therefore classified as definite DRESS syndrome.

This rare idiosyncratic reaction is most often associated with aromatic anticonvulsants (i.e., phenobarbital, phenytoin, primidone and carbamazepine) and allopurinol, with an estimated incidence of 1:1000 to 1:10 000 exposures to these drugs (3, 4). About 50 drugs are potential triggers of DRESS, with few cases described among users of SSZ (reviewed in 6). The incidence of DRESS caused by SSZ or other sulfonamides is however unknown. DRESS has a delayed onset, i.e. 2 to 8 weeks, after initiation of the causative drug and a timely diagnosis remains critical because the disorder usually improves after the offending drug is discontinued (3, 4). Treatment is supportive in almost all cases, complete recovery may require a prolonged time, the risk of recurrences remains high for several weeks or months even after initial improvement, and symptoms may recur upon re-challenge as soon as within one day of exposure (3, 4).

**Table I. Time course of laboratory tests.**

<table>
<thead>
<tr>
<th>Battery</th>
<th>Range</th>
<th>Day - 180</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 5</th>
<th>Day 8</th>
<th>Day 10</th>
<th>Month 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT (U/L)</td>
<td>10–36</td>
<td>28</td>
<td>760</td>
<td>521</td>
<td>334</td>
<td>120</td>
<td>55</td>
<td>31</td>
<td>15</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>10–36</td>
<td>34</td>
<td>581</td>
<td>448</td>
<td>297</td>
<td>187</td>
<td>48</td>
<td>28</td>
<td>25</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>0.6–1</td>
<td>0.7</td>
<td>4.2</td>
<td>3.5</td>
<td>2.3</td>
<td>1.6</td>
<td>0.9</td>
<td>1.1</td>
<td>0.7</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>38 mg/L</td>
<td>NA</td>
<td>36</td>
<td>38</td>
<td>29</td>
<td>31</td>
<td>21</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Eosinophils (cells/mm³)</td>
<td>0.5-5</td>
<td>75</td>
<td>799</td>
<td>650</td>
<td>420</td>
<td>310</td>
<td>330</td>
<td>295</td>
<td>103</td>
</tr>
<tr>
<td>Hemoglobin (Hb) (mg/dL)</td>
<td>12–18</td>
<td>14</td>
<td>2.8</td>
<td>3.2</td>
<td>3.5</td>
<td>3.8</td>
<td>6.4</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>HBV (g/dL)</td>
<td>12.5–15</td>
<td>14.5</td>
<td>10.1</td>
<td>9.9</td>
<td>10.2</td>
<td>10.3</td>
<td>10.8</td>
<td>12.1</td>
<td>12.6</td>
</tr>
<tr>
<td>Liver enzymes</td>
<td>normal</td>
<td>65</td>
<td>6.5</td>
<td>2.8</td>
<td>2.9</td>
<td>3.2</td>
<td>3.5</td>
<td>3.8</td>
<td>6.4</td>
</tr>
<tr>
<td>Platelets (×10³/mm³)</td>
<td>150–450</td>
<td>100</td>
<td>65</td>
<td>75</td>
<td>75</td>
<td>85</td>
<td>90</td>
<td>95</td>
<td>100</td>
</tr>
<tr>
<td>Activated lymphocytes</td>
<td>36–56</td>
<td>NA</td>
<td>36</td>
<td>38</td>
<td>29</td>
<td>31</td>
<td>31</td>
<td>31</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**

- ALT: alanine aminotransferase; AST: aspartate aminotransferase; CRP: C-reactive protein; NA: not available.
- Activated lymphocytes are enlarged lymphocytes with blast-like features i.e. abundant cytoplasm, vacuoles and indentations of the cell membrane seen on blood smear.
- Results of iron, copper, ceruloplasmin metabolism and α1-antitripsin were normal.
- Serological screening for viral hepatitis was negative.
- No cutaneous involvement is required to clinically recognise DRESS which lends support to the paradox that patients could be diagnosed with a definite DRESS even if they do not have a skin rash. Of concern, our patient had aphthous ulcers in the mouth which did reflect in our opinion the systemic involvement of the mucocutaneous tissues.

The patient was fully alert and oriented; physical examination showed atrophic ulcers in the mouth, several cervical, axillary and inguinal non-tender lymph nodes, a few vesicles and pustules over his right thigh, mild scleral jaundice and no flapping tremor or any other stigmata of chronic liver disease. The rest of the examination was unremarkable. Blood tests disclosed anaemia, low white blood cells (WBCs), the presence of enlarged lymphocytes with ensuing lymphadenopathy, hepatitis, interstitial nephritis, pneumonitis or carditis, that was first described with phenytoin in 1950 (3, 4). The most frequently involved internal organ is the liver, followed by the kidney and lung (3, 4). DRESS should be listed among the great mimickers in clinical medicine as it can present with many different symptoms, with fever and skin eruptions being the most common. A diffuse maculopapular and erythematous rash often associated with facial oedema is present in more than 70% of patients (3, 4). Furthermore, a wide spectrum of other cutaneous manifestations that range from erythema multiforme-like exfoliative dermatitis, acute generalised exanthematous pustular dermatosis-like eruption, erythrodema, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been described (3, 4).

Our patient had a localised rash which is not the usual skin manifestation in the course of the syndrome, however this does not rule out by itself the diagnosis since our case fulfilled the diagnostic criteria of the syndrome despite the presence of atypical features for classic DRESS such as the presence of a localised rather than diffuse rash, slightly increased eosinophils, and the very short time to complete recovery. This is an important teaching point implicating that a severe and diffuse involvement of the skin is not strictly required to clinically recognise DRESS which lends support to the paradox that patients could be diagnosed with a definite DRESS even if they do not have a skin rash. Of concern, our patient had aphthous ulcers in the mouth which did reflect in our opinion the systemic involvement of the mucocutaneous tissues.
evidence for their efficacy is lacking and symptoms may worsen on tapering doses (3, 4). Autoimmunity could develop after recovery (3, 4). Predictive factors for a serious course of DRESS are unknown and whether the type of causative drug may influence the ultimate outcome is also unclear. Previous studies have shown the death rate could be higher among patients with allopurinol-associated DRESS compared to DRESS cases caused by other drugs (7). Independent of the triggers, DRESS can progress to multiorgan failure and death, which is usually caused by fulminant liver failure, in up to 10% of patients (3, 4). DRESS-associated hepatitis can recur in the transplanted liver (8).

The pathogenesis is not understood. Mechanisms may include detoxification defects and reactive metabolite formation, slow acetylation, hypersensitivity, and reactivation of human herpes viruses (HHV), including Epstein-Barr virus, cytomegalovirus and HHV-6 and -7, or paramyxoviruses (3, 4). The detection of HHV-6 reactivation has been proposed as a diagnostic marker for DRESS but this needs to be further investigated (9). In our patient, serological screening for Epstein-Barr virus, cytomegalovirus, and herpes simplex was negative; we did not check for HHV-6. Genetic factors are also important as the risk seems to be greatly increased among individuals with a first-degree relative who did experience the syndrome (3, 4).

We should be aware of the potential risk of this severe systemic reaction when patients are started on SSZ. A close follow-up for early signs of DRESS is required particularly during the first weeks of therapy.

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References