Clinical and laboratory improvement after intravenous immunoglobulin in drug reaction with eosinophilia and systemic symptoms

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Clinical Implications

- Drug reaction with eosinophilia and systemic symptoms is frequently associated with viral reactivation.
- This patient manifested corticosteroid-resistant drug reaction with eosinophilia and systemic symptoms with transient clearance of EBV viremia and clinical improvement after intravenous immunoglobulin administration.

TO THE EDITOR:

Drug reaction with eosinophilia and systemic symptoms (DRESS), also called drug-induced hypersensitivity syndrome, is a severe adverse drug reaction associated with immunologic abnormalities and viral reactivation. DRESS is difficult to diagnose because the symptoms mimic several other diseases and can appear long after initial drug exposure. RegiSCAR, a diagnostic tool developed to diagnose DRESS, is based on evaluating 7 criteria, including fever >38.5°C, acute skin rash, lymphadenopathy, internal organ involvement, and blood cell count abnormalities. Diagnosis is confirmed in individuals who exhibit 3 or more of the 7 criteria. Affected patients are treated with corticosteroids, and full recovery is achieved in up to 90% of cases; however, the mortality rate can be as high as 10%-20%, which correlates with the degree of hepatic or renal involvement.

DRESS can have a variable effect on the immune system. Although leukocytosis with atypical lymphocytes and eosinophilia of varying degrees are prominent features, leukopenia and lymphopenia can precede the development of leukocytosis in some cases. With regard to humoral immunity, reduced B cell numbers and dramatically decreased serum IgG, IgA, and IgM levels have been described. Recently, a significantly decreased number of circulating natural killer cells at disease onset was reported, which might be associated with subsequent reactivation of viruses, mainly within the herpesvirus family.

Although human herpesvirus (HHV) 6 is the most common virus reactivated during this severe reaction, other reactivated viruses have also been observed, such as EBV, cytomegalovirus, and HHV-7. Although the role of viruses in the pathogenesis of DRESS syndrome is unknown, analysis of the data shows that HHV-6 reactivation is associated with poor prognosis and a prolonged course of disease.

The current treatment for severe DRESS cases is limited to systemic corticosteroids and supportive care. The use of intravenous immunoglobulin (IVIG) to treat DRESS is currently anecdotal and controversial, and its mechanism of action is unknown. In this case report, we describe that viral clearance and clinical recovery occurred after IVIG administration to a 45-year-old female patient who presented with severe corticosteroid-refractory DRESS. The patient initially appeared in the emergency department with a maculopapular rash, and it was determined that she had been using phenytoin for 1 month for seizure prophylaxis after a subarachnoid hemorrhage (Figure 1). The patient was hospitalized, and systemic corticosteroid (prednisolone, 0.75 mg/kg/d) was administered. Results of initial laboratory tests showed normal liver enzyme levels and mild eosinophilia (Table I).

After the patient’s improvement, prednisolone was tapered on day 4 of hospitalization. However, symptoms worsened 2 days after lowering the corticosteroid dose, and the patient developed purpuric skin lesions, oral lesions, lymphadenopathy, and fever (Figure 1). Blood analysis indicated the presence of eosinophilia, atypical lymphocytosis, thrombocytopenia, increased liver enzyme levels, and hypergammaglobulinemia (Table I); moreover, a skin biopsy revealed lymphocytic and eosinophilic infiltration with spongiosis. Prednisolone thus was adjusted up to 1 mg/kg/d on day 8 of hospitalization.

While investigating an episode of gastrointestinal bleeding on day 7 of hospitalization, a macroscopic pattern typical of eosinophilic esophagitis was observed. An esophageal biopsy specimen revealed an eosinophilic infiltrate of >20 eosinophils per high power field, which supported the diagnosis (Figure 1). Serologic tests showed the presence of specific IgG antibodies to EBV, cytomegalovirus, and hepatitis A but not to HHV-6. The patient’s serum was also positive for EBV DNA by PCR analysis. The DRESS diagnosis was confirmed from these test results, with a RegiSCAR score of 8 (>5 is considered a definite case).

After 6 days without significant improvement despite the increased systemic corticosteroid dose, on day 14 of hospitalization, she received IVIG (1 g/kg/d) for 3 days and subsequently presented clinical and laboratory improvement. Her purpuric rash and lymphadenopathy improved, quantitative EBV DNA became undetectable, liver enzyme levels progressively returned to baseline, and eosinophil counts (already decreasing, probably due to the corticosteroid) continued to drop (Figure 2).

The patient was discharged 3 weeks after hospitalization with a prescription for oral prednisone (0.75 mg/kg/d). Before discharge, detectable quantitative EBV DNA had returned. Although the clearance of viremia was transient, it might have occurred at a crucial time for patient recovery. In terms of outpatient treatment, corticosteroids were tapered slowly over 6 months until discontinuation, with only 1 episode of mild recrudescence of the rash at present. The patient has had no additional DRESS signs or symptoms, and results of her laboratory tests continue to be normal while off corticosteroids (Table I).

Few reports exist about IVIG use in DRESS. The presented case here is the first report to our knowledge that shows that IVIG is...
associated with viremia clearance in DRESS. Although the effects of immunoglobulin on treating severe adverse drug reactions are not fully elucidated, immunomodulatory and anti-inflammatory activity may be involved. Regarding DRESS, IVIG antibodies may function to neutralize the virus; however, this is only speculation because no other studies have shown this effect until now. Moreover, although most researchers report hypogammaglobulinemia as a prominent immunologic feature of patients with DRESS, our patient presented with hypergammaglobulinemia; thus, although antibodies were present in high titers, they were unable to eliminate EBV. After IVIG infusion, however, her viral DNA levels became undetectable, which suggests that this extra dose of antibodies might have been beneficial.

Although an association among DRESS, low natural killer cell count, and viral reactivation has been recently described, a causal link has not yet been established. Thus, the low natural killer cell count observed in our patient could have contributed to viral reactivation or was otherwise a consequence of viral reactivation. In addition, another important finding in our patient’s case is the development of eosinophilic esophagitis, which has not been previously described in DRESS.

In conclusion, IVIG may be a beneficial therapy for patients with DRESS, particularly those with viral reactivation, independent of total immunoglobulin levels. Randomized controlled trials must be performed to confirm the present findings and to evaluate the therapeutic effect of IVIG in DRESS. A better understanding
of this puzzling disease will improve the way it is managed and provide further insights into immune system function.

**TABLE I. Laboratory test results (IVIG administered at day 14)**

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 11</th>
<th>Day 15</th>
<th>Day 18</th>
<th>Day 23</th>
<th>10 Months after hospital discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytes (3,500-10,500 cells/mm³)</td>
<td>6,580</td>
<td>27,330</td>
<td>12,250</td>
<td>6,220</td>
<td>11,830</td>
<td>5,200</td>
</tr>
<tr>
<td>Lymphocytes (900-2,900 cells/mm³)</td>
<td>600</td>
<td>12,800</td>
<td>8,430</td>
<td>2,140</td>
<td>2,860</td>
<td>1,390</td>
</tr>
<tr>
<td>T lymphocytes (CD³⁺) (1,035-2,333 cells/mm³); (59%-81%)†</td>
<td>-</td>
<td>10,450 (82%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>962 (69.1%)</td>
</tr>
<tr>
<td>CD⁴⁺ lymphocytes (507-1,496 cells/mm³); (31%-56%)†</td>
<td>-</td>
<td>6,528 (51%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>CD⁸⁺ lymphocytes (303-1,008 cells/mm³); (17%-41%)†</td>
<td>-</td>
<td>3,840 (30%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>B lymphocytes (CD₁⁹⁺) (140-950 cells/mm³); (8%-18%)†</td>
<td>-</td>
<td>1,857 (15%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Natural killer cell (90-600 cells/mm³); (7%-31%)†</td>
<td>-</td>
<td>128 (1.0%)</td>
<td>-</td>
<td>86 (4.0%)</td>
<td>-</td>
<td>164 (11.8%)</td>
</tr>
<tr>
<td>Neutrophils (1,700-8,000 cells/mm³)*</td>
<td>4,860</td>
<td>6,540</td>
<td>3,430</td>
<td>3,470</td>
<td>7,750</td>
<td></td>
</tr>
<tr>
<td>Eosinophils (50-500 cells/mm³)*</td>
<td>530</td>
<td>3,540</td>
<td>20</td>
<td>0</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Platelets (150,000-450,000 cells/mm³)*</td>
<td>202,000</td>
<td>97,000</td>
<td>33,000</td>
<td>94,000</td>
<td>297,000</td>
<td></td>
</tr>
<tr>
<td>AST (up to 31 U/L)*</td>
<td>42</td>
<td>134</td>
<td>1,911</td>
<td>186</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>ALT (up to 31 U/L)*</td>
<td>44</td>
<td>274</td>
<td>1,662</td>
<td>748</td>
<td>189</td>
<td>13</td>
</tr>
<tr>
<td>Quantitative EBV DNA (cutoff, 150 copies/mL)*</td>
<td>-</td>
<td>-</td>
<td>Positive, 298</td>
<td>Negative</td>
<td>Positive, 163</td>
<td></td>
</tr>
</tbody>
</table>

*Reference range.
†Percentage of total lymphocytes.

**FIGURE 2.** Eosinophil counts and ALT and AST levels evaluated over time. **(ALT,** Alanine aminotransferase; **AST,** aspartate aminotransferase.)

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ALT, Alanine aminotransferase; AST, aspartate aminotransferase.

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