Drug-induced hypersensitivity syndrome (DIHS), also known as drug rash with eosinophilia and systemic symptoms (DRESS), is a severe drug reaction presenting with generalized skin eruption, organ failure and haematological abnormality (1, 2). Typical cutaneous manifestations include maculopapular, lichenoid, purpuriform, target-like and possibly also other types of lesions. Erythroderma with or without exfoliation or desquamation may sometimes be observed. We report here a case of DIHS/DRESS presenting with multiple diffuse follicular pustules on the trunk and extremities.

CASE REPORT
A 15-year-old Japanese male student was admitted to our hospital with generalized pruritic rash and high fever after treatment with carbamazepine for epilepsy over 5 weeks. The patient exhibited marked oedema on the face (Fig. 1A), cervical lymphadenopathy, and small follicular pustules diffusely distributed on his trunk and extremities (Fig. 1B). Bacterial cultures of both blood and pustules were negative. A skin biopsy from the back revealed a spongiotic pustule in the follicular infundibulum with moderate upper-dermal perivascular infiltrations of lymphocytes, neutrophils and a few eosinophils (Fig. 1C). A blood test indicated leukocytosis (white blood cell count, 12,000/ml) containing up to 5% atypical lymphocytes, marked eosinophilia (2,280/ml), elevated levels of liver enzymes (aspartate aminotransferase (AST) 367 IU/l and alanine aminotransferase (ALT) 1,637 IU/l), and positivity for human herpes virus (HHV)-6 DNA. Treatment with 30 mg oral prednisone resulted in improvement in the patient’s general condition and skin eruptions.

DISCUSSION
This case fulfils the criteria for both DIHS (7/7 of the Japanese consensus group criteria) and DRESS (8/9 of the Kardaun et al. criteria (7)) (Table I). The mechanism of DIHS/DRESS has not been fully elucidated. Immune responses by drug-reactive T cells, plasmacytoid dendritic cells, and activation of herpes viruses have been proposed (2, 3).

Before the concept of DIHS/DRESS was established, anticonvulsant hypersensitivity syndrome was recognized as a severe adverse drug reaction induced by anticonvulsants such as carbamazepine, phenytoin,
and phenobarbital sodium (4). Several cases of acute
generalized exanthematous pustulosis (AGEp) induced
by anticonvulsants have been reported (5), but isolated
pustules in the follicular infundibulum, as seen in our
case, are a clear contrast to AGEp, which usually mani-
fests histopathologically as confluent, flaccid pustules
with non-follicular, subcorneal or upper-epidermal
pustules.

We diagnosed the patient as typical DIHS, since
we observed the reactivation of HHV-6 in addition to
the clinical manifestations seen in DRESS. The case
was diagnosed as DIHS/DRESS with reactivation of
HHV-6. We describe here an atypical case of DIHS
presenting with diffuse follicular pustules on the trunk
and extremities, which was reasonably well controlled
by conventional therapy with an oral steroid.

REFERENCES

1. Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudo-
lymphoma and drug hypersensitivity syndrome (drug rash
with eosinophilia and systemic symptoms: DRESS). Semin
2. Shiohara T, Kano Y. A complex interaction between drug
allergy and viral infection. Clin Rev Allergy Immunol 2007;
33: 124–133.
3. Sugita K, Tohyama M, Watanabe H, Otsuka A, Nakajima S,
Iijima M, et al. Fluctuation of blood and skin plasmacytoid
dendritic cells in drug-induced hypersensitivity syndrome.
4. Shear NH, Spielberg SP. Anticonvulsant hypersensitivity
82: 1826–1832.
5. Son CH, Lee CU, Roh MS, Lee SK, Kim KH, Yang DK.
Acute generalized exanthematous pustulosis as a manifesta-
tion of carbamazepine hypersensitivity syndrome. J Investig
6. Shiohara T, Iijima M, Ikezawa Z, Hashimoto K. The diagnos-
is of a DRESS syndrome has been sufficiently established
on the basis of typical features and viral reactivations. Br J
Davidovici BB, Mockenhaupt M, et al. Variability in the
clinical pattern of cutaneous side-effects of drugs with
systemic symptoms: does a DRESS syndrome really exist?

Table I. Criteria for drug-induced hypersensitivity syndrome (DIHS; top) and drug rash with eosinophilia and systemic symptoms (DRESS; bottom). The patient met the criteria for DIHS (7/7) and DRESS (8/9)

### Criteria for typical DIHS (presence of all 7 criteria) (ref. 6)

1. HHV-6 reactivation
2. Prolonged clinical symptoms 2 weeks after discontinuation of causative drug
3. Maculopapular rash developing >3 weeks after starting with limited number of drugs
4. Fever >38°C
5. Lymphadenopathy
6. Liver abnormalities (alanine aminotransferase >100 U/l) or other organ involvement, e.g. renal involvement
7. Leukocyte abnormalities (at least one present)
   - Leukocytosis (>11×10⁹/l)
   - Atypical lymphocytosis (>5%)
   - Eosinophilia (>1.5×10⁹/l)

### Scoring system for classifying DRESS cases as definite, probable, possible, or no case (applicable items in **bold**) (ref. 7)

<table>
<thead>
<tr>
<th>Score –1</th>
<th>Score 0</th>
<th>Score 1</th>
<th>Score 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever ≥38,5°C</td>
<td>Yes</td>
<td>No/U</td>
<td>No/U</td>
</tr>
<tr>
<td>Enlarged lymph node</td>
<td>No/U</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>No/U</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>No/U</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Eosinophils, if leucocytes &lt;4.0×10⁹/l</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Atypical lymphocytes</td>
<td>No/U</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Skin involvement</td>
<td>No/U</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Skin rash extent (% body surface area)</td>
<td>No/U</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Skin rash suggesting DRESS</td>
<td>No/U</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Biopsy suggesting DRESS</td>
<td>No/U</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Organ involvement</td>
<td>No/U</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Liver, kidney, lung, muscle/heart, pancreas, other organ</td>
<td>No/U</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Resolution ≥15 days</td>
<td>No/U</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Evaluation of other potential causes</td>
<td>No/U</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Antinuclear antibody</td>
<td>No/U</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Blood culture</td>
<td>No/U</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Serology for HAV/HBV/HCV</td>
<td>No/U</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Chlamydia/mycoplasma</td>
<td>No/U</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>If none positive and ≥3 of above negative</td>
<td>No/U</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Total score < 2: no case; 2–3: possible case; 4–5: probable case; > 5: definite case.