taking herbal preparations in capsules, an imaginable common denominator of TEN development. A single or multiplier effect by idiosyncratic, dose-related or drug-interactive reactions of phytochemicals or contaminants might be involved in the development of TEN in these patients. The objective evaluation by the Naranjo adverse drug reaction (ADR) probability scale calculated a possible ADR by the herbal remedy in cases 1 and 3 and a probable cause in case 2. In all cases, the TEN-specific algorithm for epidermal necrolysis (ALDEN) confirmed a possible cause of herbal remedies in TEN development.10

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The serum level of HMGB1 (high mobility group box 1 protein) is preferentially high in drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms

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Dear Editor, Drug-induced hypersensitivity syndrome (DIHS), also known as drug reaction with eosinophilia and systemic symptoms (DRESS), is characterized by high fever, multiple
organ involvement and haematological disorders, essentially without severe erythema or epidermal apoptosis. Sequential reactivation of human herpes virus (HHV)-6 is deeply involved in the pathophysiology and persistence of DIHS/DRESS. A preceding increase in proinflammatory cytokines such as interleukin (IL)-6 and tumour necrosis factor (TNF)-α seems to be relevant to the viral reactivation in DIHS/DRESS, while the exact mechanism is still unclear.2

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), other severe cutaneous adverse drug reactions (cADRs), are characterized by high fever, severe erythema and widespread epidermal damage due to keratinocyte apoptosis. Activated cytotoxic T cells and natural killer cells are involved in SJS/TEN.3 The molecular cytotoxicity of Fas and cytotoxic proteins, including perforin/granzyme B and granulysin, are thought to contribute to induction of keratinocyte apoptosis.4

Activated cytotoxic T cells and natural killer cells are involved in SJS/TEN.3 The molecular cytotoxicity of Fas and cytotoxic proteins, including perforin/granzyme B and granulysin, are thought to contribute to induction of keratinocyte apoptosis.4 High mobility group box 1 protein (HMGB1) is a nonhistone nuclear protein that is released from severely damaged cells.5 HMGB1 plays a role in transcriptional regulation in the nucleus, while outside of the cell it serves as an activator of the inflammatory cascade.4 It was recently reported that HMGB1 levels are increased during the acute stage of SJS/TEN and can serve as an early diagnostic marker for SJS/TEN.5 However, the level of HMGB1 at the onset of other severe cADRs such as DIHS/DRESS has not been investigated. In addition, although there are limited reports on serum cytokine levels in cADRs,6 these cytokines have not been analysed with regards to HMGB1, which may induce aberrant cytokine production. To clarify the relationship between aberrant HMGB1 and cytokine production at disease onset, and the clinical manifestations elicited, we investigated serum HMGB1 and cytokine profiles in various cADRs.

Peripheral blood was taken from healthy controls and patients with various types of cADR including maculopapular (MP) type, erythema multiforme (EM), SJS, TEN and DIHS/DRESS at the time of onset and recovery. Onset is an acute exacerbation phase (<7 days) and recovery is a remission phase of cADRs. Serum was stored at −80 °C and cytokine levels were measured by luminometric bead array using the Bio-Plex Suspension Array System (BioRad, Hemel Hempstead, U.K.). HMGB1 was measured by enzyme-linked immunosorbent assay. The groups consisted of the following subjects (full details in Table 1): healthy controls, 14 cases; MP/EM, 11 cases; SJS/TEN, 17 cases and DIHS/DRESS, 17 cases. For comparison of cytokine levels between healthy controls and each cADR group at onset, and between onset and recovery in each cADR group, the Mann–Whitney test and Wilcoxon matched-pairs tests were used, respectively. Statistical significance was established at P < 0·05 and P < 0·01.

HMGB1 was high in both SJS/TEN and DIHS/DRESS compared with healthy controls and other cADRs, but the level was significantly higher in DIHS/DRESS than in SJS/TEN. Comparison of cytokine levels between SJS/TEN and DIHS/DRESS revealed a prominent increase in T helper (Th)2 cytokines/chemokines such as IL-5, IL-9 and IL-13 in DIHS/DRESS. Additionally, IL-10 (an anti-inflammatory cytokine) and IL-12 were elevated in DIHS/DRESS (Fig. 1a). Concerning the serum cytokine levels at the time of onset in each group, the following were significantly increased compared with healthy controls: IL-5, IL-6, chemokine (C-X-C motif) ligand 8 (CXCL)-8, IL-9, IL-12, eotaxin, granulocyte macrophage colony-stimulating factor (GM-CSF), CXCL-10 and vascular endothelial growth factor (VEGF) in MP/EM; IL-6, IL-12 and CXCL-10 in SJS/TEN; and IL-5, IL-6, IL-9, IL-10, IL-12, IL-13, IL-15, eotaxin, GM-CSF, interferon (IFN)-γ, CXCL-10 and VEGF in DIHS/DRESS. Proinflammatory cytokines such as TNF-α and IFN-γ were not necessarily high in severe cADRs. Most, but not all, cytokines returned to normal levels with treatment at the time of recovery (Fig. 1).

Although the levels of various types of serum cytokines were elevated at cADR onset, the levels of proinflammatory cytokines did not correlate with the types of cADR or disease severity. These results suggest that the overproduction of these cytokines contributes to promoting inflammation, but that mechanisms other than an increase of proinflammatory cytokines are essential for inducing the massive keratinocyte apoptosis observed in SJS/TEN.

In DIHS/DRESS, Th2 cytokines, HMGB1 and IL-10, were increased. Recent studies have reported that not only Th2 cytokines, but also Th2 chemokines such as thymus and activation-regulated chemokine, were elevated in serum in DIHS/DRESS.6,7 In addition, HMGB1 was more highly elevated than in SJS/TEN. HMGB1 has been shown to induce the differentiation of dendritic cells (DCs) to CD11clowCD45RBhigh DCs followed by shifting of Th1 to Th2 in vitro.8 Furthermore, high expression of HMGB1 in DIHS/DRESS skin has been reported.9 The area of expression of HMGB1 was larger in DIHS/DRESS lesions than in SJS lesions regardless of keratinocyte damage. Translocation of HMGB1 occurred in DIHS epidermal cells, and this HMGB1 attracted mononuclear precursors harbouring HHV-6, resulting in HHV-6 transmission to skin-infiltrating CD4+ T cells, which is essential for HHV-6 replication in DIHS/DRESS. On the other hand, IL-10, which is an anti-inflammatory cytokine, was also highly elevated in DIHS/DRESS. It has been reported that expansion of Foxp3+CD25+ T regulatory cells (Tregs) was observed

### Table 1 Profile of each group

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Sex (n)</th>
<th>Age (years), mean ± SD</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy controls</td>
<td>14</td>
<td>8/6</td>
<td>53±1 ± 15·3</td>
<td>–</td>
</tr>
<tr>
<td>MP/EM</td>
<td>11</td>
<td>6/5</td>
<td>65±3 ± 8·9</td>
<td>MP 6/EM 5</td>
</tr>
<tr>
<td>SJS/TEN</td>
<td>17</td>
<td>7/10</td>
<td>56±5 ± 19·1</td>
<td>SJS 13/TEN 4</td>
</tr>
<tr>
<td>DIHS/DRESS</td>
<td>17</td>
<td>10/7</td>
<td>53±5 ± 14·0</td>
<td>Typical 13/</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>atypical 4*</td>
</tr>
</tbody>
</table>

MP, maculopapular; EM, erythema multiforme; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; DIHS, drug-induced hypersensitivity syndrome; DRESS, drug reaction with eosinophilia and systemic symptoms. *Typical, with reactivation of human herpes virus (HHV)-6; atypical, without reactivation of HHV-6.
Fig 1. Serum high mobility group box 1 protein (HMGB1) and cytokine levels were analysed by enzyme-linked immunosorbent assay and luminometric bead array. To compare cytokine levels between healthy controls (HC) and each cutaneous adverse drug reaction (cADR) group at onset and between onset and recovery in each cADR group, the Mann–Whitney test and Wilcoxon matched-pairs tests were used, respectively. Significantly higher levels of (a) cytokines and (b) other proinflammatory cytokines in drug-induced hypersensitivity syndrome (DIHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) than in Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN). CXCL, chemokine (C-X-C) motif ligand; EM, erythema multiforme; GM-CSF, granulocyte macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; MP, maculopapular; O, onset of disease; R, recovery from disease; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor. *P < 0.05, **P < 0.01.
Correspondence

investigation. involvement of HMGB1 in cADRs therefore requires further development of DIHS/DRESS through Th2 cell activation, which onsets of severe cADR. HMGB1 may contribute to the pathophysiology of DIHS/DRESS in the early stage.

In conclusion, cytokine storm occurs in various types of cADRs, but factors other than cytokines are required for the onset of severe cADR. HMGB1 may contribute to the development of DIHS/DRESS through Th2 cell activation, which plays a key role together with Tregs in the disease. The involvement of HMGB1 in cADRs therefore requires further investigation.

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Conflicts of interest: none declared.

A case of pemphigus herpetiformis-like atypical pemphigus with IgG anti-desmocollin 3 antibodies

DEAR EDITOR, Pemphigus is an autoimmune blistering skin disease characterized by autoantibodies to keratinocyte cell surface antigens. Major autoantigens for pemphigus are desmogleins (Dsgs), transmembrane cell–cell adhesion proteins belonging to the cadherin family. Dsg1 and Dsg3 are antigens for pemphigus foliaceus and pemphigus vulgaris, respectively. In addition to the four Dsg isoforms (Dsg1–4), there is another group of desmosomal cadherins, the desmocollins (Dsc), which is composed of three isoforms (Dsc1–3).

Pemphigus herpetiformis (PH) is a distinct variant of pemphigus; clinically it shows dermatitis herpetiformis-like features characterized by pruritic annular erythemas with vesicles on the periphery, histopathologically, eosinophilic spongiosis and immunologically, IgG antibodies to keratinocyte cell surface antigens. Ishii et al. reported that the targets of IgG autoantibodies in PH were Dsgs. Anti-Dsg1 antibodies were detected in the majority of patients, while anti-Dsg3 antibodies were detected in some cases. In this study, we report a case of PH-like atypical pemphigus with IgG antibodies to Dsc3, but without antibodies to Dsgs.

A 57-year-old Japanese man visited us complaining of a 1-year history of erosive skin lesions. He was otherwise healthy with no particular medical history. Physical examination revealed pruritic, urticarial, annular erythemas on the trunk and extremities, with some showing small vesicles at the periphery (Fig. 1a). No mucosal involvement of the oral cavity was present. Blood tests and computed tomography showed no abnormalities.

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