

# The Variable Clinical Picture of Drug-Induced Hypersensitivity Syndrome/Drug Rash with Eosinophilia and Systemic Symptoms in Relation to the Eliciting Drug

Yoko Kano, MD, PhD\*, Tetsuo Shiohara, MD, PhD

## KEYWORDS

- Anticonvulsant hypersensitivity syndrome
- Drug-induced hypersensitivity syndrome
- Drug rash with eosinophilia and systemic symptoms
- Eosinophilia • Human herpesvirus 6
- Liver dysfunction • Skin rash

Drug-hypersensitivity syndrome is a life-threatening adverse reaction characterized by skin rashes, fever, leukocytosis with eosinophilia or atypical lymphocytosis, lymph node enlargement, and liver or renal dysfunctions.<sup>1</sup> The syndrome develops 2 to 6 weeks or longer after initiation of administration of a specific drug. It has been estimated to occur in between 1 in 1000 and 1 in 10,000 exposures with antiepileptic drugs.<sup>2</sup> Mortality is approximately 10% and is primarily associated with systemic organ involvement, such as liver dysfunction, renal impairment, and interstitial pneumonitis.<sup>3</sup> Previously, there had been no consistent term for this syndrome; various

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This work was supported in part by grants from the Ministry of Education, Sports, Science, and Culture of Japan (to Y.K. and T.S.) and Health and Labo Sciences Research grants from the Ministry of Health, Labor, and Welfare of Japan (to T.S.).

Department of Dermatology, Kyorin University School of Medicine, 6-20-2 Shinkawa Mitaka, Tokyo, 181-8611, Japan

\* Corresponding author.

*E-mail address:* [kano@ks.kyorin-u.ac.jp](mailto:kano@ks.kyorin-u.ac.jp) (Y. Kano).

Immunol Allergy Clin N Am 29 (2009) 481–501

doi:10.1016/j.iac.2009.04.007

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terms had been used to refer to this syndrome after generic names of the culprit drugs or the pathophysiologic consequence, such as *phenytoin syndrome*, *allopurinol hypersensitivity syndrome*, *dapsone syndrome*, *eosinophilic pneumonia*, and *exfoliative dermatitis*. All these entities may represent different clinicopathologic expressions of a single pathologic process. Bocquet and colleagues<sup>4</sup> proposed the term *drug rash with eosinophilia and systemic symptoms* (DRESS) to simplify the nomenclature of drug-hypersensitivity syndromes. Then, Descamps and colleagues,<sup>5</sup> the authors' group,<sup>6</sup> and Hashimoto's group<sup>7</sup> demonstrated a relation between this drug reaction and human herpesvirus (HHV)-6 reactivation. Subsequently, the authors' group and Hashimoto's group coined the term *drug-induced hypersensitivity syndrome* (DIHS) to reflect the association with HHV-6.<sup>8,9</sup> There have been no significant differences in the clinical findings of cases reported under the name of DRESS or DIHS, although it seems that patients fulfilling the criteria of DIHS may represent those with more severe DRESS. Although the reaction is caused by a limited number of drugs, there are some differences in the clinical and laboratory findings depending on the drug given, underlying physiologic state, and genetic background. It is useful to know these differences in clinical appearance depending on the causative drugs for the early diagnosis of this life-threatening adverse drug reaction. In this review, the authors have focused on the clinical picture of DIHS/DRESS in relation to different eliciting drugs.

#### **DIAGNOSIS OF DRUG-INDUCED HYPERSENSITIVITY SYNDROME/DRUG RASH WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS**

The criteria for the diagnosis of DRESS proposed by Bocquet and colleagues<sup>4</sup> are as follows: (1) cutaneous drug eruption; (2) hematologic abnormalities, including eosinophilia greater than  $1.5 \times 10^9$  eosinophils/L or the presence of atypical lymphocytes; and (3) systemic involvement, including adenopathies greater than 2 cm in diameter, hepatitis (liver transaminases values  $>2$  N), interstitial nephritis, interstitial pneumonia, or carditis. The criteria emphasize two important characteristics: multiple organ involvement and eosinophilia.<sup>10</sup>

The criteria for the diagnosis of DIHS established by the Japanese groups are as follows: (1) maculopapular rash developing longer than 3 weeks after starting a limited number of drugs; (2) prolonged clinical symptoms 2 weeks after discontinuation of the causative drug; (3) fever higher than 38°C; (4) liver abnormalities (alanine aminotransferase [ALT]  $>100$  U/L); (5) leukocyte abnormalities, including leukocytosis ( $>11 \times 10^9$  leukocytes/L), atypical lymphocytosis ( $>5\%$ ), or eosinophilia ( $>1.5 \times 10^9$  eosinophils/L); (6) lymphadenopathies; and (7) HHV-6 reactivation. Diagnosis of definite or typical DIHS requires the presence of the seven criteria. Probable or atypical DIHS is diagnosed in patients with typical clinical presentations (criteria 1–5) in whom HHV-6 reactivation cannot be detected, probably because of inappropriate timing of sampling. Renal dysfunction can serve as a substitute for liver abnormalities. Considering that HHV-6 reactivation is rarely detected in patients who develop a milder form of the disease, the detection of this viral reactivation is a useful marker for the diagnosis of DIHS.<sup>9</sup> The authors have recently demonstrated that various herpesvirus reactivations, in addition to HHV-6, contribute to internal organ involvement and the relapse of symptoms observed long after discontinuation of the causative drugs.<sup>11</sup> The criteria proposed by Bocquet and colleagues<sup>4</sup> are fundamentally similar to those of the authors with regard to the clinical and laboratory findings, except for HHV-6 reactivation. Using the authors' criteria, other types of drug reactions, such as the maculopapular-type drug eruption, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), can be differentiated from DIHS/DRESS. Differential diagnoses attributable to the

most likely infectious diseases, such as measles and infectious mononucleosis, need to be excluded, however. Other differential diagnoses include Kawasaki syndrome, serum sickness-like reaction, hypereosinophilic syndrome, and drug-induced pseudolymphoma (**Box 1**).<sup>4,12</sup> Pseudolymphomas have also been reported to develop in association with phenytoin and carbamazepine (CBZ).<sup>13,14</sup> A diagnosis of drug-induced pseudolymphoma can be based on the histologic findings or the clinical presentation, ranging from solitary nodules to multiple infiltrative papules or plaques, without evidence of extracutaneous lymphoma, or resolution of the eruption with cessation of the drug.<sup>15</sup> The delay between the start of the drug and the eruption was up to 110 days, which is longer than that in DIHS/DRESS. No fever or multiple organ involvement is observed. Thus, the drug-induced pseudolymphomas represent a distinct entity from DIHS/DRESS, with different clinical and histologic features and outcomes.

The clinical features of this syndrome include the stepwise development of multiorgan failure and frequent deterioration of clinical signs, such as fever, skin rashes, and liver or renal dysfunction, occurring even after discontinuation of the causative drug.<sup>12</sup> Internal organ involvement, which can be asymptomatic, may occur even several months after the onset. It includes hepatitis, renal insufficiency, pneumonitis, myocarditis, and thyroiditis.<sup>8–12</sup> Recently, encephalitis<sup>16</sup> and type 1 diabetes mellitus<sup>17</sup> have been reported to develop during the course of DIHS/DRESS (**Box 2**). The highly variable waxing and waning nature of the clinical manifestations occurring in different organs is the most prominent feature of DIHS/DRESS. There is great variability in the target organs involved and in severity. Such variability allows for a delay in diagnosis, which can lead to significant morbidity. A recent survey of cases from the French Pharmacovigilance database and the literature revealed particular clinical patterns in DIHS/DRESS caused by certain drugs (eg, renal dysfunction was associated with allopurinol-induced DRESS/DIHS, peripheral lymphadenopathy and eosinophilic pneumopathy in cases with minocycline, and, only rarely, eosinophilia with lamotrigine).<sup>18</sup>

In this article, the authors have included cases that were reported using various denominations, most of which fulfill their criteria for DIHS or the criteria of Bocquet and colleagues<sup>4</sup> for DRESS.

#### CHARACTERISTICS OF THE CAUSATIVE DRUGS

DIHS/DRESS is caused by a limited number of specific drugs, such as anticonvulsants, allopurinol, and sulfonamides. **Box 3** lists drugs that reportedly cause DIHS/DRESS. It remains unknown, however, why a limited number of drugs can cause

##### Box 1

##### Differential diagnosis in DIHS/DRESS

- Drug-induced lupus erythematosus
- Hypereosinophilic syndrome
- Infectious mononucleosis
- Kawasaki disease
- Measles
- Pseudolymphoma/immunoblastic lymphadenopathy
- Serum sickness-like reaction
- Staphylococcal toxic shock syndrome

**Box 2****Internal organ involvement in DIHS/DRESS**

Colitis/Intestinal bleeding  
 Diabetes mellitus  
 Encephalitis/aseptic meningitis  
 Hepatitis  
 Interstitial nephritis  
 Interstitial pneumonitis/respiratory distress syndrome  
 Myocarditis  
 Serositis  
 Syndrome of inappropriate secretion of antidiuretic hormone  
 Thyroiditis

the development of DIHS/DRESS because they do not have any pharmacologic actions or structural similarities in common.

Various factors may contribute to the development of DIHS/DRESS. The authors have demonstrated that there is a decrease in serum immunoglobulin levels, including IgG and IgA, and of circulating B cells at onset in patients who have anticonvulsant<sup>19</sup> and allopurinol<sup>20</sup> hypersensitivity syndromes. Several reports have also demonstrated a transient hypogammaglobulinemia at the onset of DIHS/DRESS.<sup>21</sup> More importantly, these drugs have been shown to inhibit B-cell differentiation to immunoglobulin-producing cells in vitro when purified B-cell populations were used.<sup>22,23</sup> Taken together, the causative drugs of DIHS/DRESS may have a pharmacologically mediated immunomodulatory effect on B cells and possibly other cells of the immune system, and thus contribute to the development of DIHS/DRESS. The long latency period before the onset of DIHS/DRESS after starting therapy with causative drugs would represent the time required for immunoglobulin levels to decrease to lower than a threshold level. During the course of DIHS/DRESS, a variety of antiviral T cells

**Box 3****Causative drugs of DIHS/DRESS**

Anticonvulsant  
 CBZ  
 Phenytoin  
 Phenobarbital  
 Zonisamide  
 Lamotrigine  
 Allopurinol  
 Minocycline  
 Dapsone  
 Sulfasalazine  
 Mexiletine

are generated that may cross-react with the culprit drug; human leukocyte antigen (HLA) molecules are thereby reactivated, and thus play a key role in mediating DIHS/DRESS, similar to graft-versus-host disease.<sup>24</sup> These immunologic alterations occur initially subclinically, induced by the protracted administration of the causative drug, and may then lead to the development of DIHS/DRESS by means of sequential reactivations of herpesviruses.

#### **CLINICAL PICTURE OF DRUG-INDUCED HYPERSENSITIVITY SYNDROME/DRUG RASH WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS INDUCED BY DIFFERENT ELICITING DRUGS**

##### ***Aromatic Anticonvulsants***

Anticonvulsant hypersensitivity syndrome is a life-threatening syndrome that occurs after exposure to aromatic anticonvulsants, including CBZ, phenytoin, and phenobarbital. The incidence of this syndrome induced by these anticonvulsants is thought to be in the range of 1 per 1000 to 10,000 exposures.<sup>2</sup> Cross-reactivity between CBZ, phenytoin, and phenobarbital may be as high as 70% to 80%;<sup>25</sup> this may explain why symptoms persist or recur after switching to another aromatic anticonvulsant. In addition, there is a familial tendency to hypersensitivity to anticonvulsants; this is not related to the dosage or serum concentration of these drugs. The frequency of this reaction is higher with CBZ and phenytoin than with phenobarbital, which may reflect a greater use of the two former agents.

Although SJS and TEN are often regarded in the literature as the most severe form of drug eruptions induced by these anticonvulsants, these two drug eruptions are not extensively reviewed in this article.

##### ***Carbamazepine***

CBZ is an iminostilbene derivative chemically related to the tricyclic antidepressants. CBZ is currently the primary drug used for the treatment of partial and tonic-clonic seizures.<sup>26</sup> The drug is also effective in treating pain of neurologic origin and psychiatric disorders, such as bipolar affective disorders and schizophrenia. These numerous uses of CBZ explain the widespread utilization of the drug. Cutaneous adverse effects, such as erythematous rashes, urticaria, pruritus, or alopecia, are not unusual with the use of CBZ.<sup>27</sup> More serious adverse reactions, such as SJS, TEN, and DIHS/DRESS, may occur. Of these three aromatic anticonvulsants, CBZ is the most commonly implicated drug for DIHS/DRESS because of the frequency of use. Therefore, the clinical and laboratory findings of CBZ-induced DIHS/DRESS (CBZ-DIHS/DRESS) are the major prototype of this syndrome.

CBZ-DIHS/DRESS is a severe reaction characterized by skin rash, fever, leukocytosis with eosinophilia or atypical lymphocytosis, lymph node enlargement, and liver or renal dysfunction, as described in the previous section. According to the authors' analyses, the mean interval between drug intake and onset is 36.8 days (**Table 1**). In some cases, the interval was longer than 6 months. It is likely that the time interval between drug intake and onset is longer for phenobarbital.<sup>25</sup> The initial symptoms of CBZ-DIHS/DRESS include general fatigue, low-grade fever, and sore throat, any of which can precede cutaneous manifestations by 1 to 4 days. This stage is usually interpreted as an upper respiratory infection by most patients. Maculopapular rashes, which are frequently accompanied by facial and neck edema, tend to appear first over the trunk and face and spread to the proximal upper extremities. Marked periorbital edema is frequently observed, which is a characteristic cutaneous manifestation of DIHS/DRESS (**Fig. 1**). Small crusts and scales along the nasolabial sulci are often observed at the initial stage. The maculopapular rashes coalesce to form larger plaques and often progress to diffuse erythema over the trunk with a high-grade fever

Table 1

## Clinical characteristics in relation to causative drugs

	Carbamazepine	Phenytoin	Phenobarbital	Allopurinol	Minocycline	Dapsone	Mexiletine
Duration <sup>a</sup>	36.8 (n = 8)	40.5 (n = 2)	31.7 (n = 4)	32.2 (n = 4)	(n = 0)	19.0 (n = 1)	32.6 (n = 3)
Skin eruption	++	++	++	++	++	+	++
Facial edema							
Others	Maculopapular EM-like Purpuric Exfoliative	Maculopapular EM-like Purpuric	Maculopapular EM-like Purpuric Pustular Exfoliative	Maculopapular EM-like Pustular Exfoliative	Maculopapular EM-like Pustular Exfoliative	Maculopapular Exfoliative	Maculopapular EM-like Pustular Exfoliative
Leukocytosis	++	++	++	++	++	++	++
Eosinophilia	++	++	++	++	+++	+	++
Atypical lymphocytosis	++	++	+++	++	++	+++	+
Lymphadenopathy	++	++	+++	+	+++	+++	+
Liver dysfunction	++	+++	++	+	+++	+++	+
Renal dysfunction	+	+	+	+++	+	+	+
Pulmonary insufficiency	+	+	+	+	+++	+	+

Frequencies were described using scales ranging from + to +++.

Abbreviation: EM, erythema multiforme.

<sup>a</sup> Duration between initial drug intake and onset in the authors' analyses.



Fig. 1. Marked facial edema (CBZ).

(Fig. 2). Purpuric lesions are noted on the lower extremities (Fig. 3). This process can take several days after withdrawal of CBZ. Marked edema in the upper dermis over the upper extremities often gives rise to blisters, which may mimic those of TEN (Fig. 4). Mucosal involvement in buccal and genital regions is not frequently observed. Most mucosal lesions are hyperemic with petechia but resolve rapidly on withdrawal of the drug; this finding is in sharp contrast to those of SJS or TEN.

Histopathologic findings of a skin biopsy specimen obtained from maculopapular rashes at an early stage include exocytosis of lymphocytes in the epidermis and focal hydropic degeneration of the basal cell layer. A lymphocytic infiltrate containing eosinophils is often observed in the edematous papillary dermis. The cellular infiltration in the dermis is generally denser in DIHS/DRESS than in other types of drug reaction. Blister may be formed beneath the epidermis because of the prominent edema in the upper dermis. Histochemical staining of the skin lesion reveals that CD8+ cells are more frequently observed than CD4+ cells.

Bilateral cervical, axillary, and inguinal lymphadenopathies with tenderness are commonly present. Because of the severe lymphadenopathy and



Fig. 2. Diffuse erythema on the back (CBZ).



**Fig. 3.** Erythema with purpuric lesions on the legs (CBZ).

hepatosplenomegaly associated with the skin eruption, immunoblastic lymphadenopathy or pseudolymphoma is often suspected. The clinical and laboratory findings, showing skin rashes with facial edema, atypical lymphocytosis with severe lymphadenopathies, and hepatosplenomegaly, may mimic those of infectious mononucleosis. A lymph node biopsy may show paracortical hyperplasia and eosinophilia suggestive of dermatopathic lymphadenopathy or lymphadenitis.

Hematologic abnormalities, especially eosinophilia and mononucleosis-like atypical lymphocytosis, are common. Marked leukocytosis with eosinophilia or atypical lymphocytosis is observed at the acute stage, a finding different from that observed



**Fig. 4.** Blisters on erythematous lesions on the upper arm (CBZ).



in SJS or TEN. Internal organ involvement is usually observed from 2 weeks to several months after discontinuation of CBZ and includes hepatitis, interstitial nephritis, interstitial lung disease, or myocardial involvement with or without any clinical symptoms.<sup>10,25</sup> The liver is the organ most frequently involved, ranging from mild elevation in transaminase levels to fulminant hepatic necrosis.<sup>28</sup> ALT levels are commonly increased more than three times the reference range. In most patients, aspartate aminotransferase (AST) and ALT levels increase more than those of  $\gamma$ -glutamyl transpeptidase ( $\gamma$ -GTP) and alkaline phosphatase (ALP); however, isolated elevation of  $\gamma$ -GTP may occur in the absence of actual liver disease. The renal failure in CBZ-DIHS/DRESS is considered to be attributable to acute interstitial nephritis. Acute interstitial nephritis is typically reversible after withdrawal of the causative agent.

Empiric treatment with antibiotics often exacerbates the clinical condition attributable to unexplained cross-reactivity to multiple drugs, which is a unique characteristic of this syndrome. CBZ-DIHS/DRESS requires immediate discontinuation of the drug. Valproic acid can usually be substituted with minimal concern for cross-reactivity but should be cautiously used for seizure control in the face of liver dysfunction. Recovery is usually slow, and it takes 3 to 8 weeks for skin rashes and all laboratory abnormalities to return to normal.

### **Phenytoin**

Phenytoin (diphenylhydantoin) belongs to the hydantoin family, which includes meph-  
enytoin, phenylethylhydantoin, and fosphenytoin. Phenytoin has been demonstrated to be a highly effective anticonvulsant in the treatment of generalized and focal epilepsy. A broad spectrum of cutaneous and immunologic reactions to phenytoin has been reported. These reactions include tissue proliferative syndromes, such as gingival hyperplasia and coarse facies, DIHS/DRESS, and a possible association with lymphoma. Although cutaneous eruptions occur in up to 19% of patients receiving phenytoin, only a small percentage of these patients experience phenytoin-induced DIHS/DRESS (phenytoin-DIHS/DRESS).<sup>29</sup>

Phenytoin-DIHS/DRESS usually occurs within 3 weeks to 3 months after initiation of therapy. The major manifestations of this syndrome include fever, dermatitis, hepatitis, and lymphadenopathy. Often, the initial symptoms are fever with malaise and pharyngitis, sometimes with strawberry tongue, followed by eruptions similar to those of CBZ-DIHS/DRESS.<sup>29</sup> The eruption usually begins as patchy erythema; it evolves into a typical pruritic maculopapular eruption (**Fig. 5**) and may later progress to become erythroderma. The eruption can manifest various types of skin rashes; they include infectious mononucleosis-like eruption, staphylococcal toxic shock syndrome-like exanthema, and a generalized pustular eruption. Prominent facial edema occurs periorbitally.<sup>30</sup> Anemia and diarrhea may also be present.<sup>31</sup>

Systemic involvement is common in phenytoin-DIHS/DRESS; the liver, kidney, lung, or central nervous system can be involved. According to Shear and Spielberg,<sup>28</sup> kidney involvement is more frequently observed in phenytoin-DIHS/DRESS compared with CBZ-DIHS/DRESS and phenobarbital-induced (PB) DIHS/DRESS. Although most patients who have phenytoin-DIHS/DRESS are initially anicteric, severe cholestatic hepatitis with jaundice and peripheral eosinophilia is sometimes observed (see **Table 1**). Severe hepatitis portends a prolonged course characterized by multiple exacerbations and remissions of the rash and liver disease. Most deaths occur from hepatic necrosis in the setting of coagulopathy, and sepsis and 30% to 40% mortality have been reported in such patients.<sup>32</sup> Other manifestations include hypothyroidism, which may occur within 2 months after onset of the syndrome.<sup>29</sup>



Fig. 5. Violaceous lesions on the trunk (phenytoin).

### ***Phenobarbital***

The clinical picture of PB-DIHS/DRESS is similar to CBZ-DHIS/DRESS or phenytoin-DIHS/DRESS. Skin eruptions vary, ranging from erythema multiforme-like (Fig. 6), pustular, and purpuric eruptions to exfoliative dermatitis. With pustular eruptions, pinhead-sized pustules are often superimposed on diffuse erythema of the face and trunk (Fig. 7). According to a report by Shear and Spielberg,<sup>28</sup> atypical lymphocytosis is detected more frequently in PB-DIHS/DRESS compared with CBZ-DHIS/DRESS or phenytoin-DIHS/DRESS (see Table 1). A case of PB-DIHS/DRESS was misdiagnosed as cutaneous T-cell lymphoma because prominent T-lymphocytosis (ie, lymphoid leukemoid reaction) was observed.<sup>33</sup>



Fig. 6. Erythema multiforme-like lesions on the trunk (phenobarbital).



Fig. 7. Pustular eruption on the face (phenobarbital).

In some cases, systemic organ involvement is present in PB-DIHS/DRESS. For example, Descamps and colleagues<sup>5</sup> described a patient who had severe PB-DIHS/DRESS in whom a fulminant hemophagocytic syndrome associated with HHV-6 reactivation was noted. The authors also reported a case of syndrome of inappropriate secretion of antidiuretic hormone and limbic encephalitis associated with PB-DIHS/DRESS.<sup>34</sup> They also experienced a case of PB-DIHS/DRESS with an erythema multiforme-like eruption and severe prolonged liver dysfunction, in which various herpesvirus reactivations, including HHV-6, were observed. It has also been demonstrated that PB-DIHS/DRESS can share many clinical and laboratory findings with drug-induced lupus erythematosus, such as systemic involvement and serum immunologic abnormalities.<sup>35</sup>

### **Zonisamide**

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Zonisamide is an anticonvulsant that contains a sulfa moiety with potential to trigger hypersensitivity reactions. It displays similarity to sulfamethoxazole. The drug is generally regarded as a safe antiepileptic with minimal side effects. In the English literature, zonisamide-induced DIHS/DRESS has rarely been reported. According to the manufacturer, skin rash occurs in 1% to 2% of Japanese patients. Maculopapular and purpuric eruptions have been noted in addition to mild oral mucosal involvement. Teraki and colleagues<sup>36</sup> have recently reported a patient with clinical features of TEN attributable to zonisamide. In this case, however, significant increases in HHV-6 IgG titers and detection of HHV-6 DNA in leukocytes were observed during the course of the illness, indicating that HHV-6 reactivation occurred.

### **Lamotrigine**

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Lamotrigine is an antiepileptic drug that is structurally unrelated to aromatic anticonvulsants. It acts on voltage-sensitive sodium channels, stabilizes neuronal membranes, and inhibits the release of excitatory neurotransmitter glutamate or aspartate. The drug is considered effective for multiple types of seizures.<sup>37</sup> Despite a structural difference from the aromatic anticonvulsants, lamotrigine has been recently reported to

cause a potentially life-threatening adverse drug reaction resembling DIHS/DRESS induced by these anticonvulsants.<sup>38</sup> It has been estimated that the incidence of potentially life-threatening skin reactions, such as DIHS/DRESS, occurs in 1 in 1000 adults treated with lamotrigine and in 1 in 50 to 100 children, which is higher than that associated with the aromatic anticonvulsants.<sup>37</sup> In addition to age, the risk for exanthema is strongly associated with high initial serum levels and with a rapid increase in doses of lamotrigine.<sup>39</sup> Conversely, slow introduction of the drug has been reported to reduce the incidence of rash. The risk for lamotrigine-induced DIHS/DRESS (lamotrigine-DIHS/DRESS) has also been attributed to valproic acid comedication.<sup>37</sup>

According to the analyses of 26 cases by Schlienger and colleagues,<sup>40</sup> eosinophilia was noted in 19%, lymphadenopathy was reported in only 12% of the cases, and multiorgan involvement was reported in 46%; these rates are markedly lower than in other anticonvulsant hypersensitivity syndromes. Clinically, in the severe form of lamotrigine-DIHS/DRESS, severe maculopapular exanthema, fever, lymphadenopathy, and internal organ involvement are observed; however, many of the reported cases represent an abortive form. Cutaneous eruption, usually severe, occurs typically within the first 4 weeks of treatment in approximately 10% of patients but has been reported to develop up to 6 months after lamotrigine initiation.<sup>40</sup>

Cutaneous findings include a polymorphous eruption consisting of blanchable, erythematous, urticarial papules predominantly on the trunk, which spread to the face but spare the palms. The face becomes severely edematous and erythematous. Mucous membranes are rarely involved. Tender, firm, enlarged lymph nodes are found in the cervical, axillary, and inguinal regions. Lymphadenopathy and hepatomegaly are commonly present. Early rechallenge with this drug may cause a quick reappearance of the symptoms in patients who have lamotrigine-DIHS/DRESS.<sup>37</sup> As far as the authors were able to determine, HHV-6 reactivation was not detected during the course of lamotrigine-DIHS/DRESS. It has been reported that an adult patient developed transient diffuse alopecia and transverse onychodystrophy of all nails after resolution of lamotrigine-DIHS/DRESS.<sup>39</sup>

### ***Allopurinol***

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Allopurinol is an inhibitor of xanthine oxidase in clinical use. It is an effective urate-lowering drug that has been the mainstay treatment for hyperuremia and gout. The most serious side effects, which occur in less than 1 in 1000 cases, are exfoliative dermatitis, fever, liver dysfunction, eosinophilia, and acute interstitial nephritis (see **Table 1**). Numerous cases of allopurinol hypersensitivity syndrome have been reported. Up to 20% of patients with this type of reaction become extremely ill. According to Elasy and colleagues,<sup>41</sup> mortality is approximately 20% to 25%. Death is more likely to occur in patients who have preexisting renal disease or in those receiving diuretic therapy.<sup>42</sup> In more than 80% of cases of allopurinol-induced DIHS/DRESS (allopurinol-DIHS/DRESS), patients had evidence of renal impairment before commencing allopurinol.<sup>43</sup> Because renal function declines steadily with age, the elderly are most vulnerable to developing the reaction.<sup>43</sup> Other risk factors for the development of allopurinol DIHS/DRESS include chronic alcoholism and severe liver disease. Hung and colleagues<sup>44</sup> have recently reported a strong association between HLA-B\*5801 allele and allopurinol-related severe cutaneous reactions, including DIHS/DRESS, SJS, and TEN. Although HLA-B\* 5801 has been linked to the allopurinol-DIHS/DRESS in a series of Japanese patients, a strong association between HLA-B\*5801 and Japanese patients who have allopurinol-DIHS/DRESS has not been detected in the authors' series.<sup>45</sup>

The average interval between onset of the syndrome and initiation of allopurinol treatment is 2 to 6 weeks, but it can be up to 728 days.<sup>41,43</sup> The rash may take the form of erythema multiforme, diffuse maculopapular rash (**Fig. 8**), or exfoliative dermatitis. A fine papular rash or erythema multiforme usually evolves to a diffuse maculopapular rash in association with facial edema and erythema (**Fig. 9**). Edema is often observed on the extremities. In severe cases, blisters on the hands and feet are observed with superficial ulceration, mimicking TEN; however, the lesions originate from the severe edema in the upper dermis and not from the epidermal necrosis. Erythematous skin lesions later desquamate. Occasionally, superficial oral ulcers are observed.

With respect to the hematologic findings, leukocytosis is often characterized by eosinophilia and by the presence of band forms without clear evidence of infection.<sup>41,43</sup>

Regarding visceral involvement, renal involvement is particularly observed in allopurinol-DIHS/DRESS. In many cases, laboratory studies demonstrate worsening renal insufficiency, ranging from mild elevation in serum creatinine levels to severe interstitial nephritis. Severe renal insufficiency increases the risk for mortality. In addition to renal involvement, there has been a reported case of HHV-6 encephalitis after reduction of systemic corticosteroids in a patient who had allopurinol-DIHS/DRESS.<sup>13</sup> Another case presented with a diffuse erythematous rash and erosive lesions, and the clinical course was complicated by cytomegalovirus and HHV-6 reactivation in addition to sepsis during the course of DIHS/DRESS.<sup>46</sup> Sommers and Schoene<sup>47</sup> reported that fulminant type 1 diabetes mellitus developed 1 month after the onset of allopurinol-DIHS/DRESS. The authors have experienced a case of allopurinol-DIHS/DRESS with intestinal bleeding accompanied by the appearance of urticarial eruptions and scratch dermatitis during cytomegalovirus reactivation in the course of DIHS/DRESS.

### ***Minocycline***

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Minocycline is a semisynthetic tetracycline derivative commonly used to treat acne vulgaris that has antibiotic and anti-inflammatory activities. Serious adverse reactions



**Fig. 8.** Maculopapular eruption and erythema multiforme-like lesions on the trunk (allopurinol).



Fig. 9. Prominent facial edema (allopurinol).

include a serum sickness-like reaction, drug-induced systemic lupus erythematosus, and DIHS/DRESS. Minocycline-induced DIHS/DRESS (minocycline-DIHS/DRESS) occurs most frequently in young patients. Minocycline-DIHS/DRESS presents with fever, skin eruption, lymphadenopathy, and internal organ involvement developing within 8 weeks after initiation of therapy. Minocycline-DIHS/DRESS commonly begins with a fever 2 to 4 weeks after initiation of therapy, followed by atypical lymphocytosis, eosinophilia, lymphadenopathy, skin rash, and visceral organ involvement. Eosinophilia often persists during the entire course of this reaction. Patients complain of symptoms of headache and a nonproductive cough at the onset. The skin rashes may take the form of a morbilliform eruption, erythema multiforme-like lesions, exfoliative dermatitis, or pustular eruptions.<sup>48,49</sup> Macular eruptions progress to become purpuric, spreading to involve most of the body. Prominent facial edema or swelling of the scrotum secondary to lymphadenopathy is also observed. Arthralgia or arthritis is infrequently observed, which differentiates minocycline-DIHS/DRESS from serum sickness-like reaction.<sup>49</sup>

Lymphadenopathy is frequently observed in minocycline-DIHS/DRESS (see **Table 1**). Cervical posterior occipital, axillary, and inguinal lymph nodes are enlarged, soft, mobile, and tender to palpitation. With the prominent lymphadenopathy and atypical lymphocytosis seen in the peripheral blood, lymphoma and pseudolymphoma are also considered in the differential diagnosis. These differential diagnoses are excluded by skin and lymph node biopsy results.<sup>49</sup>

Cases of minocycline-DIHS/DRESS have been reported in terms of the most prominent single organ involvement, such as hepatitis, pneumonitis, and nephritis. Closer inspection of these cases often reveals the presence of a rash and fever, however, suggesting a diagnosis of DIHS/DRESS. Internal organ involvement usually manifests as hepatic injury. Although pulmonary involvement is rarely reported in DIHS/DRESS, interstitial pneumonia with eosinophilia is often observed in patients who have minocycline-DIHS/DRESS. Most patients who have this pneumonia survive with no permanent sequelae, but it may be life-threatening in some patients and show characteristic findings of adult respiratory distress syndrome.<sup>50</sup> Other systemic involvement includes myocarditis, interstitial nephritis, and rhabdomyolysis.<sup>50,51</sup>



### Dapsone

Dapsone (4, 4'-diaminodiphenylsulfone), a potent antiparasitic and anti-inflammatory compound, is mainly used in the treatment of leprosy. It has also been the drug of choice for the management for bullous dermatoses and inflammatory skin diseases, such as leukocytoclastic vasculitis and erythema elevatum diutinum. Common side effects include headache, methemoglobinemia, agranulocytosis, and hemolytic anemia. Dapsone-induced DIHS/DRESS (dapsone-DIHS/DRESS) occurs in less than 1% of patients treated with dapsone, however.<sup>52,53</sup> Dapsone-induced agranulocytosis and dapsone-DIHS/DRESS are two different adverse reactions; therefore, these two adverse reactions are not simultaneously observed. Dapsone-DIHS/DRESS has been reported in cases other than those associated with leprosy, such as *Pneumocystis carinii* pneumonia in patients who have AIDS.

The constellation of symptoms in this reaction includes fever, malaise, exfoliative dermatitis, lymphadenopathy, atypical lymphocytosis, and hepatitis. Cyanosis on the lips, fingers, and toes, is observed, followed by hemolytic anemia and methemoglobinemia. Dapsone-DIHS/DRESS usually begins 4 weeks or more after starting the drug.<sup>52,54</sup> The rash, which is often a morbilliform eruption (**Fig. 10**), may develop into diffuse erythematous dermatitis, which disappears with desquamation. Icterus and lymphadenopathy are observed in 80.7% of patients who have leprosy with dapsone-DIHS/DRESS, and hepatomegaly is seen in 73.0% of patients who have leprosy with this reaction (see **Table 1**).<sup>55</sup>

Rather common in dapsone-DIHS/DRESS is the absence of eosinophilia. Liver involvement displays a mixed hepatocellular and cholestatic pattern. ALT, AST, and total bilirubin levels are elevated. Hyperbilirubinemia is present in 85% of patients who have leprosy with dapsone-DIHS/DRESS,<sup>55</sup> which may be partly attributable to hemolysis in addition to hepatotoxicity. A liver biopsy reveals hepatitis, cholestasis, or granuloma formation.<sup>54</sup> Hepatitis may progress to liver failure and death; a cholestatic pattern may have a less severe clinical course and is characterized by high ALP and moderate transaminase levels. Cholangitis has also been reported in a patient who had dapsone-DIHS/DRESS.<sup>54</sup> Hypoalbuminemia is also a feature of dapsone-DIHS/DRESS, which is probably attributable to binding of dapsone to the circulating



**Fig. 10.** Maculopapular eruption (dapsone).

serum albumin.<sup>54</sup> A case with visceral involvement, including myocarditis, thyroiditis, serositis, and hepatitis, has been reported.<sup>56</sup> DIHS/DRESS has been reported to develop during treatment with dapsone for pemphigus foliaceus. In this case, anti-desmoglein 1 IgG antibodies decreased during the course of the illness, and not only HHV-6 reactivation but cytomegalovirus and Epstein-Barr virus reactivations were detected.<sup>57</sup>

### **Sulfasalazine**

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Sulfasalazine is a drug used to treat inflammatory bowel diseases, rheumatoid arthritis, and some forms of spondyloarthritis. Serious side effects with systemic involvement are less frequent. Nevertheless, a severe adverse reaction to sulfasalazine has been identified as a type of hypersensitivity reaction. Sulfasalazine-induced DIHS/DRESS is referred to as the “3-week sulfasalazine syndrome” that occurs 3 weeks after first administration of the drug. According to an analysis of 23 patients who had sulfasalazine-induced DIHS/DRESS, the period between drug administration and onset ranges from 1 week to 4 months.<sup>58</sup> The clinical features of sulfasalazine-induced DIHS/DRESS are similar to those of infectious mononucleosis. A high-grade fever, skin eruptions, lymphadenopathy, and hepatomegaly are usually seen. Skin eruptions manifest as erythematous papules and macules that become confluent (**Fig. 11**); this rash progresses over the whole body with the appearance of purpuric lesions. There is notable facial edema, especially on the eyelids.

Visceral complications are characterized by fulminant hepatitis, interstitial nephropathy, eosinophilic interstitial pneumonitis pericarditis, myocarditis, or pancreatitis. Pleural effusion is also observed. Symptoms often persist for several weeks after discontinuation of the drug. Laboratory tests reveal increases in serum transaminases and total bilirubin levels, reflecting hepatic cytolysis and cholestasis.<sup>59</sup> Some of these cases present with life-threatening fulminant hepatitis with symptoms of jaundice and persistent high-grade fever.

### **Mexiletine Hydrochloride**

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Mexiletine hydrochloride is an antiarrhythmic drug. A variety of drug eruptions attributable to mexiletine hydrochloride have been reported, including maculopapular eruption (**Fig. 12**), erythema multiforme, erythroderma, urticaria, and pustular eruptions. Several cases of mexiletine-induced DIHS/DRESS (mexiletine-DIHS/DRESS) have been reported in Japan.<sup>60–62</sup> In affected patients, prominent edema is usually observed on the periorbital lesions. There is an erythematous periorbital edema at



**Fig. 11.** Confluent erythematous macules on the abdomen (sulfasalazine).





Fig. 12. Diffuse erythema on the trunk (mexiletine).

the onset, which changes to a violaceous color. Edema on the lower legs is also observed; however, this may be related to preexisting cardiovascular disease. Erythema multiforme-like eruptions are observed on the trunk and extremities. Less frequently, tiny pustules are disseminated on the surface of large confluent erythematous plaques on the face and chest. This finding may resemble acute generalized exanthematous pustulosis (AGEP),<sup>63</sup> however, the pustules are not localized on the skin folds, such as the neck, axilla, and groin. The pustules gradually regress soon after discontinuation of mexiletine hydrochloride. It takes several weeks for the erythematous eruptions to disappear.

In regard to laboratory findings, eosinophilia is more frequently detected than atypical lymphocytosis (see **Table 1**). The neutrophil count is not prominently elevated as observed in AGEP. Liver dysfunction is usually mild.

Regarding herpesvirus reactivations, it has been reported that DIHS/DRESS developed 33 months after the onset of herpes zoster,<sup>60</sup> in which mexiletine hydrochloride was administered for 1 month. Sekiguchi and colleagues<sup>61</sup> have reported a patient who had mexiletine-DIHS/DRESS with evidence of HHV-6 reactivation and cytomegalovirus reactivation. In a separate case, HHV-7 reactivation, in addition to HHV-6, was detected during the course of DIHS/DRESS using polymerase chain reaction analysis and a serologic assay.<sup>62</sup> A patient who had fulminant type 1 diabetes mellitus after mexiletine-DIHS/DRESS has been reported.<sup>64</sup>

### **Other Culprit Drugs**

Other causative drugs, such as cyanamide,<sup>65</sup> tribenoside,<sup>66</sup> methimazole,<sup>67</sup> and clompiramine,<sup>68</sup> have also been reported to induce DIHS/DRESS.

### **SUMMARY**

DIHS/DRESS exhibits a broad range of clinical manifestations and laboratory abnormalities that are a result of the interplay of host immune status, the extent of sensitization to the drug, immunologic and pharmacokinetic properties of the drug, and the sites and types of viral reactions associated with this syndrome. They could also induce reactions with a different time sequence. Despite a variable clinical

appearance, however, DIHS/DRESS is a distinct clinical entity with highly reproducible clinical and immunopathologic features. A better understanding of the interplay in the development of DIHS/DRESS has implications for safer and more efficient treatment of this syndrome.

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