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.[1] 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.[2] Mortality is approximately 10% and is primarily associated with systemic organ involvement, such as liver dysfunction, renal impairment, and interstitial pneumonitis.[3] Previously, there had been no consistent term for this syndrome; various

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 (Y. Kano).

Immunol Allergy Clin N Am 29 (2009) 481–501
doi:10.1016/j.iac.2009.04.007 **immunology.theclinics.com**
0889-8561/09/$ – see front matter

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[4] proposed the term *drug rash with eosinophilia and systemic symptoms* (DRESS) to simplify the nomenclature of drug-hypersensitivity syndromes. Then, Descamps and colleagues,[5] the authors' group,[6] and Hashimoto's group[7] 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.[8,9] 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[4] are as follows: (1) cutaneous drug eruption; (2) hematologic abnormalities, including eosinophilia greater than 1.5×10^9 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.[10]

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 (>11×10^9 leukocytes/L), atypical lymphocytosis (>5%), or eosinophilia (>1.5×10^9 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.[9] 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.[11] The criteria proposed by Bocquet and colleagues[4] 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