ORIGINAL ARTICLE

Clinical Features of Drug-Induced Hypersensitivity Syndrome in 38 Patients

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Abstract

Background: The clinical features of drug-induced hypersensitivity syndrome (DIHS) or drug rash with eosinophilia and systemic symptoms (DRESS) syndrome are complicated, and the incidence of this condition is very low.
Objective: To evaluate the clinical course of DIHS/DRESS and identify effective treatment options.
Methods: This study was a retrospective analysis of prospectively collected clinical data in 38 consecutive patients with DIHS/DRESS diagnosed between March 2004 and January 2009. We investigated the clinical features, response to treatment, and outcome of 38 patients.
Results: The study patients consisted of 18 men (47.4%) and 20 women (52.6%). The most common causative drugs were anticonvulsants (47.4%) and antibiotics (18.4%), followed by nonsteroidal anti-inflammatory drugs (NSAIDs) (13.2%), allopurinol (5.3%), and undetermined agents (15.8%). The latency period ranged from 3 to 105 days, with a mean (SD) of 25.2 (21.5) days. Systemic corticosteroids were administered to 16 patients (42.1%). Twenty-two (57.9%) patients were treated with topical corticosteroids and antihistamines (no systemic corticosteroids). Complete recovery was noted in 36 patients (94.8%). Two of the patients treated with systemic corticosteroids had a poor outcome: one died due to an opportunistic infection secondary to long-term systemic corticosteroid treatment; the other showed progressive deterioration of liver damage, although the final outcome is not known.
Conclusion: The drugs associated with DIHS/DRESS were variable and most frequently included anticonvulsants, ß-lactam antibiotics, and NSAIDs. The syndrome was more common than generally recognized. Additional studies are needed to evaluate the clinical indications for systemic corticosteroids in patients with DIHS/DRESS.

Key words: Drug hypersensitivity. Anticonvulsant. Corticosteroid.

Resumen

Antecedentes: Las características clínicas del síndrome de hipersensibilidad a fármacos (DIHS) o síndrome de exantema medicamentoso con eosinofilia y síntomas sistémicos (DRESS) son complejas. La incidencia de esta enfermedad es muy reducida.
Objetivo: Evaluar la evolución clínica del síndrome DIHS/DRESS e identificar opciones terapéuticas eficaces.
Métodos: Este estudio es un análisis retrospectivo de datos clínicos recopilados de forma prospectiva en 38 pacientes consecutivos con diagnóstico de DIHS/DRESS entre marzo de 2004 y enero de 2009. Se investigaron las características clínicas, la respuesta al tratamiento y el desenlace de 38 pacientes.
Resultados: En el estudio participaron 18 varones (47,4%) y 20 mujeres (52,6%). Los fármacos causantes más frecuentes fueron anticonvulsivos (47,4%) y antibióticos (18,4%), seguidos de antiinflamatorios no esteroideos (AINE) (13,2%), alopurinol (5,3%) y otros fármacos no determinados (15,8%). El periodo de latencia osciló entre 3 y 105 días, con un promedio (DE) de 25,2 (21,5) días. Se administraron corticoesteroides sistémicos a 16 pacientes (42,1%). Veintidós (57,9%) pacientes recibieron tratamiento con corticoesteroides tópicos y antihistamínicos (sin corticoesteroides sistémicos). Se notificó una recuperación completa en 36 pacientes (94,8%). Dos pacientes tratados con corticoesteroides sistémicos presentaron un desenlace desfavorable: uno murió debido a una infección oportunista secundaria a un tratamiento prolongado con corticoesteroides sistémicos; el segundo experimentó un empeoramiento progresivo de los daños hepáticos, aunque se desconoce el desenlace final.
Conclusión: Los fármacos asociados con DIHS/DRESS fueron diferentes. Los más frecuentes fueron los anticonvulsivos, antibióticos betalactámicos y AINE. El síndrome fue más frecuente de lo que se reconoce generalmente. Se requieren más estudios para evaluar las indicaciones clínicas de los corticoesteroides sistémicos en pacientes con DIHS/DRESS.

Palabras clave: Hipersensibilidad a fármacos. Anticonvulsivo. Corticoesteroide.

Introduction

Drug-induced hypersensitivity syndrome (DIHS), or drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, is a serious acute drug reaction that is characterized by fever, cutaneous eruption, and involvement of several internal organs in the form of enlarged lymph nodes, renal impairment, pneumonitis, carditis, and hematologic abnormalities (mainly hypereosinophilia and atypical lymphocytosis) [1]. Bocquet et al [2] recently proposed the term DRESS to define more specifically the hypersensitivity reaction caused by anticonvulsants. However, use of the term DRESS has been inconsistent, because eosinophilia is not a constant clinical finding and the cutaneous and systemic signs are variable [3,4]. According to a Japanese group [4], DRESS generally includes only the more severe cases. Therefore, a more precise term is required for this drug-induced reaction with multiple organ involvement. Here, we use DIHS/DRESS to include both the DIHS and DRESS syndrome.

DIHS/DRESS was first described by Chaiken et al in 1950 [5]. It is an unpredictable and potentially severe reaction to drugs, with an incidence ranging from 1 in 1000 to 1 in 10 000 in patients taking anticonvulsants or sulfonamides [6,7]. The hallmark of this syndrome is the long interval between the start of drug treatment and the onset of clinical symptoms. DIHS/DRESS is not related to the dose or serum concentration of the offending drug [7]. Aromatic antiepileptic drugs such as phenytoin, carbamazepine, phenobarbital, and primidone are the most common causative agents [8,9]. The most common clinical presentations of DIHS/DRESS are cutaneous eruption, fever, and enlarged lymph nodes [10]. Systemic corticosteroids have been regarded as the main treatment [9]; however, they may put patients at additional risk for severe infectious complications. The aim of this study was to evaluate the clinical course of DIHS/DRESS and identify effective treatment options.

Materials and Methods

The present study was a retrospective analysis of prospectively collected clinical data (February 2004 to January 2009) in 38 patients with DIHS/DRESS at Dong-A University Hospital in Busan, South Korea. We evaluated demographic characteristics, offending drugs, latency period, laboratory results, response to treatment, and outcome.

The diagnostic criteria used in this study were modified from previous reports [4,9,11] and included acute cutaneous eruption, fever (>38°C in a patient with a history of taking a specific drug), and at least 1 of the following internal organ abnormalities: lymphadenopathy at a minimum of 2 sites, hepatitis, nephritis, pneumonitis, carditis, thyroiditis, and hematological abnormalities (eosinophilia [defined as more than 10% of total white blood cells or >500/μL], presence of atypical lymphocytes, thrombocytopenia, and leukopenia). Liver and kidney involvement was defined as a 2-fold increase in liver enzymes over the normal value and the presence of abnormal urinalysis findings with hematuria and/or proteinuria, or increased serum creatinine.

The culprit drugs were identified by reviewing the medication history and clinical course (improvement of the cutaneous eruption and systemic symptoms after discontinuation of the suspected drugs).

Complete peripheral blood counts, liver function tests, determination of serum creatinine levels, and urinalyses were performed to identify internal organ abnormalities. Serological tests were performed for antinuclear antibodies (ANA), anti-DNA antibodies, and viral antibodies (eg, herpes simplex [HSV], cytomegalovirus [CMV], and Epstein-Barr virus [EBV]) to rule out other autoimmune or viral diseases. All patients consulted a dermatologist to rule out other possible skin diseases.

After the medication history was taken, all suspected causative drugs were discontinued. For the initial 5 to 7 days, all patients were treated conservatively with topical corticosteroid ointment and oral antihistamines. Prednisolone was administered at 1.0 mg/kg if there was evidence of internal organ involvement and persistent or aggravating clinical findings during the initial 5 to 7 days of conservative treatment. Patients with underlying infections or other contraindications to systemic corticosteroids were treated conservatively.

This study was approved by the institutional review board of Dong-A University Hospital. Verbal informed consent was obtained from patients or their representative.

Statistical analyses were performed using SPSS version 15 (SPSS Inc, Chicago, Illinois, USA). The laboratory values used were the highest values recorded during the clinical course. All values were expressed as the mean (SD). Laboratory results were compared using the Mann-Whitney and Kruskal-Wallis tests. Correlations between various clinical parameters were evaluated using the Pearson correlation coefficient. Statistical significance was set at $P<.05$.

Results

Demographic Data

According to the diagnostic criteria, 38 patients with DIHS/DRESS were included in this study. There were 18 men (47.4%) and 20 women (52.6%). The mean age of the patients was 56.6 years (15.7; range, 24-80 years) (Table 1).

Causative Drugs

The most common causative drugs were anticonvulsants (18 patients, 47.4%), followed by antibiotics (7 patients, 18.4%), nonsteroidal anti-inflammatory drugs (NSAIDs) (5 patients, 13.2%), allopurinol (2 patients, 5.2%), and undetermined agents (6 patients, 15.8%) (Tables 1 and 2).

Latency Period

The time from the introduction of the causative agent to the onset of clinical manifestations ranged from 3 to 105 days, with a mean of 25.2 (21.5) days. Anticonvulsants had the longest latency period (33.2 [24.6] d). The differences between anticonvulsants and antibiotics and between anticonvulsants

Table 1. Clinical Characteristics of Study Subjects

No.	Sex/Age	Underlying Disease	Culprit Drugs	Latency, d	Eosinophils/L	AST/ALT, IU/L	TB/DB, mg/dL	Systemic Corticosteroids	Days of Admission	Outcome
1	F/69	ICH	Phenobarbital	18	4852	109/313	0.3/0.2	Yes	35	Alive
2	M/51	Sprain	Ibuprofen	3	675	85/72	0.3/0.2	Yes	13	Alive
3	M/41	Epilepsy	Carbamazepine		3421	28/165	0.3/0.2	Yes	35	Alive
4	F/39	ICH	Phenytoin	15	817	205/274	0.4/0.2	Yes	27	Alive
5	F/76	Headache	Carbamazepine	60	1323	175/134	0.4/0.3	Yes	38	Alive
6	F/72	CI	Carbamazepine	22	1115	225/226	0.6/0.3	Yes	12	Alive
7	M/54	CI	Lamotrigine	32	696	152/135	0.7/0.2	Yes	12	Alive
8	F/67	Headache	Carbamazepine	30	3278	142/228	0.7/0.4	Yes	20	Alive
9	M/57	CI	Lamotrigine	26	770	95/68	0.9/0.4	Yes	17	Alive
10	M/66	Headache	Carbamazepine	63	940	114/26	1.6/0.7	Yes	17	Alive
11	M/41	Headache	Carbamazepine	105	2090	502/269	1.7/1.1	Yes	33	Alive
12	F/43	Depression	Carbamazepine	20	9996	107/181	1.9/1.1	Yes	19	Alive
13	F/32	Schizophrenia	Undetermined	55	11 256	3633/2150	16.0/13.5	Yes	152	Dead
14	M/41	ICH	Phenobarbital	20	7704	283/266	2.1/1.6	Yes	21	Alive
15	F/24	Encephalitis	Phenytoin	15	1515	1011/661	2.9/1.6	Yes	32	Alive
16	M/64	Sprain	Ibuprofen	5	15 060	1595/2360	8.8/5.1	Yes	15	Unknown
17	M/31	Gout	Allopurinol	5	792	214/226	0.3/0.2	No	3	Alive
18	F/43	URTI	Ibuprofen		1217	94/63	0.3/0.2	No	8	Alive
19	M/67	Pneumonia	Ceftriaxone	12	919	106/131	0.3/0.2	No	6	Alive
20	F/66	URTI	Undetermined	6	592	85/64	0.4/0.1	No	12	Alive
21	F/75	Epilepsy	Phenytoin		590	164/145	0.4/0.2	No	35	Alive
22	F/52	Pneumonia	Moxifloxacin	3	0	88/64	0.4/0.2	No	7	Alive
23	M/61	Pneumonia	Ceftriaxone	15	1471	58/84	0.5/0.2	No	15	Alive
24	F/32	PI	Ceftizoxime	12	0	915/1061	0.5/0.3	No	7	Alive
25	F/59	Abscess	Nafcillin	15	642	230/190	0.6/0.2	No	12	Alive
26	M/77	Gout	Allopurinol	46	531	203/205	0.6/0.3	No	7	Alive
27	M/63	URTI	Diclofenac	12	657	89/75	0.7/0.3	No	12	Alive
28	M/80	Headache	Carbamazepine	47	1241	68/103	0.9/0.3	No	22	Alive
29	M/70	Bronchitis	Lamotrigine	12	1425	88/20	1.1/0.4	No	7	Alive
30	F/42	Pneumonia	Undetermined	7	814	118/182	1.3/0.9	No	17	Alive
31	F/59	Epilepsy	Zonisamide	29	1580	131/117	1.5/1.0	No	18	Alive
32	M/58	PI	Ceftriaxone	13	114	84/119	1.6/1.2	No	16	Alive
33	M/37	Pulmonary tuberculosis	Undetermined	43	4220	1269/1296	13.5/12.8	No	15	Alive
34	F/79	ICH	Phenytoin	17	1019	92/62	2.0/1.0	No	16	Alive
35	F/49	LN tuberculosis	Undetermined	33	1890	838/816	4.3/3.1	No	33	Alive
36	M/73	Tonsillitis	Undetermined	15	1778	418/1195	5.0/2.5	No	17	Alive
37	F/80	Arthritis	Diclofenac		2331	520/485	5.0/3.4	No	16	Alive
38	F/62	Cholangitis	Cefotaxime	27	850	211/262	6.8/5.6	No	17	Alive

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, cerebral infarction; DB, direct bilirubin; ICH, intracerebral hemorrhage; LN, lymph node; P, period; PI, postoperative infection; TB, total bilirubin; URTI, upper respiratory tract infection.

Table 2. Clinical Characteristics of 6 Patients With Multiple/Undetermined Culprit Drugs

No.	Sex/Age	Underlying Disease	Culprit Drugs
13	Female/32	Schizophrenia	Risperidone, lithium
20	Female/66	URTI	Cefaclor, diclofenac
30	Female/42	Pneumonia	Tazobactam, moxifloxacin
33	Male/37	Pulmonary tuberculosis	Isoniazid, rifampin, pyrazinamide
35	Female/49	Tuberculous lymphadenitis	Isoniazid, rifampin, ethambutol, pyrazinamide, ofloxacin
36	Male/73	Tonsillitis	Cefotaxime, diclofenac

Abbreviations: URTI, upper respiratory tract infection.

and NSAIDs were statistically significant ($P<.05$, respectively) (Tables 1 and 3).

Laboratory Results

Eosinophilia was observed in the peripheral blood examination in 35 patients (92.1%). Atypical lymphocytosis was observed in 18 patients (47.4%) and thrombocytopenia in 9 patients (23.7%). Other rare findings included pancytopenia (1 patient, 2.6%) and leukopenia (1 patient, 2.6%). At least 1 internal organ was involved in all patients. The liver was the most commonly involved internal organ (100%). Other involved organs included lymph nodes (20 patients, 52.6%), kidneys (6 patients, 15.7%), lungs (1 patient, 2.6%), and muscles (1 patient, 2.6%). There was a statistically significant correlation between liver function test results (liver enzymes and bilirubin) and the number of eosinophils in peripheral blood (data not shown). None of the patients had positive findings for immunoglobulin M antibodies to CMV, EBV, or HSV.

Response to Treatment and Outcomes

Systemic corticosteroids were administered to 16 patients (42.1%); the remaining 22 patients (57.9%) were treated conservatively with topical corticosteroids and antihistamines. In patients treated with systemic corticosteroids, the mean number of days of treatment was 75.4 days (53.3; range, 25-208 d). Patients treated with systemic corticosteroids had significantly higher numbers of eosinophils and atypical lymphocytes than patients treated conservatively ($P<.05$, Table 3) However, there were no significant differences in liver enzyme and bilirubin levels or admission days between the 2 groups ($P>.05$, Table 3). Thirty-six patients (94.8%) recovered completely. One patient died due to liver failure and an opportunistic infection secondary to long-term high-dose systemic corticosteroids. Another patient had progressive deterioration of liver damage; however, in this case, the final outcome was not known, because the patient was referred to another tertiary hospital in a remote region.

Table 3. Statistical Analysis: Results of Laboratory Findings and Admission Days of Various Groups[a]

Parameters	Systemic Corticosteroids	Conservative	*P* Value
Eosinophils/μL	4094.3 (4496.6)	1121.5 (919.3)	<.05
Atypical lymphocytes/μL	1150.4 (2274.0)	259.0 (448.8)	<.05
AST, IU/L	528.8 (925.3)	276.5 (325.8)	>.05
ALT, IU/L	470.5 (712.4)	316.6 (394.4)	>.05
Total bilirubin, mg/dL	2.5 (4.2)	2.2 (3.1)	>.05
Direct bilirubin, mg/dL	1.7 (3.4)	1.6 (2.9)	>.05
Admission, d	31.1 (33.5)	14.5 (8.0)	>.05
Parameters	**Anticonvulsants**	**Antibiotics**	***P* Value**
Eosinophils/L	2465.1 (2607.9)	570.9 (559.0)	<.05
Atypical lymphocytes/μL	935.4 (2088.8)	57.6 (152.3)	>.05
AST, IU/L	205.1 (226.9)	241.7 (304.2)	>.05
ALT, IU/L	188.5 (147.0)	273.0 (353.8)	>.05
Total bilirubin, mg/dL	1.1 (0.8)	1.5 (2.4)	>.05
Direct bilirubin, mg/dL	0.6 (0.5)	1.1 (2.0)	>.05
Admission, d	23.1 (9.5)	11.4 (4.7)	<.05

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a]Values are expressed as mean (SD).

Discussion

The results of this study show that several drugs can cause DIHS/DRESS. Consistent with the findings of previous reports, anticonvulsants were the most common causative agents. Antibiotics, especially ß-lactams, were also common causative agents. Some patients with liver damage, even those presenting with hyperbilirubinemia, showed a good response to conservative treatment without systemic corticosteroids.

Several authors have proposed diagnostic criteria for DIHS/DRESS [3,4,12,13]. However, there is no consensus on the of use of these criteria. In the present study, we used the findings of cutaneous eruption and fever (>38°C) as 2 essential criteria for a diagnosis of DIHS/DRESS. Eosinophilia was defined as more than 10% of total white blood cells or more than 500/μL [14]. Other studies use different criteria for eosinophilia, for example >1500 cells/μL [4,13], although generally only in more severe cases. All of the study patients had at least 1 internal organ involved and hematological abnormalities, and all of the findings were compatible with DIHS/DRESS.

Objective methods of detecting the association between a culprit drug and DIHS/DRESS have been recommended. The in vitro lymphocyte toxicity assay, lymphocyte transformation test, and the in vivo patch test might be helpful [12,15-17]. These objective diagnostic tests were not applied in our study, due to poor cooperation and unsuccessful follow-up of study patients. However, withdrawal of the culprit drug and subsequent improvement in clinical manifestations proved to be the most reliable and practical means of making this diagnosis in the clinical setting.

Consistent with previous reports, anticonvulsants were the drugs most commonly associated with DIHS/DRESS, and almost 20% of patients had DIHS/DRESS associated with antibiotics. Few authors report DIHS/DRESS caused by ß-lactam antibiotics [18,19], probably because DIHS/DRESS is commonly thought to develop after taking anticonvulsants and sulfonamide [6,7]. Another possible explanation for this finding was the incorrect diagnosis of a simple drug eruption by doctors not familiar with DIHS/DRESS. In addition, the clinical manifestations of patients with antibiotic-induced DIHS/DRESS were less severe than those of patients with hypersensitivity to anticonvulsants (Table 3). The increased number of quinolones available may also have contributed to antibiotic-induced DIHS/DRESS [20].

As the prevalence of tuberculosis is high in South Korea, the role of antituberculosis agents in DIHS/DRESS must be studied.

Genetic factors could play a role in the pathogenesis of the anticonvulsant hypersensitivity syndrome, and familial cases have been reported [8,21]. The HLA-B*1502 allele has been shown to be closely associated with severe cutaneous reactions in Asians induced by antiepileptic drugs (carbamazepine, phenytoin, and lamotrigine) [22]. However, further studies could prove useful for determining the genetic factors associated with antibiotic-induced DIHS/DRESS.

DIHS/DRESS has a variable latency period after ingestion of the offending drug. In the case of anticonvulsants, the latency period is between 1 week and 3 months after the initial exposure [6,9,23]. The results of the present study showed that anticonvulsants had the longest latency period; the differences were significant when compared with antibiotics and NSAIDs, possibly as a result of different drug metabolites and variable individual sensitivity to these metabolites. However, further studies are required to evaluate these differences objectively.

Hematological abnormalities in patients with DIHS/DRESS have included leukocytosis with eosinophilia and atypical lymphocytosis. Agranulocytosis, aplastic anemia, and thrombocytopenia are rare [24]. Three patients had no eosinophilia, 2 had leukopenia, and 1 had thrombocytopenia. Eosinophilia in this study was more common than in previous reports [14]. We thought this might be associated with differences in the definition of eosinophilia. All patients had a variable degree of hepatitis, ranging from mild elevations of serum transaminase levels to progressive deterioration of liver damage. More than 70% of patients with DIHS/DRESS have liver damage, and this could be a cause of death [18]. Liver damage in patients with DIHS/DRESS could be caused by eosinophilic infiltration driven by interleukin (IL) 5 [8,9,25]. Significant correlations were noted between peripheral blood eosinophil counts and liver function test results (liver enzyme and bilirubin) in our patients. Lymphadenopathy was observed in 20 patients (52.6%); this was lower than in previous reports [9,14]. This difference might have been due to the fact that not all patients were examined at admission or they were not described accurately. Nephritis was observed in 6 patients (15.8%). Kidney involvement can range from mild hematuria to nephritis to renal function impairment. However, in our study, the only abnormalities observed (hematuria and proteinuria) were in the urinalysis, and these improved rapidly after withdrawal of the culprit drugs. One patient had rhabdomyolysis, which is a very rare finding in patients with DIHS/DRESS [26]. Autoimmune thyroiditis has been identified as a long-term complication [27]. Other rare autoimmune manifestations are type I diabetes mellitus [28], systemic lupus erythematosus [29], and syndrome of inappropriate antidiuretic hormone secretion [30]. Unfortunately, long-term follow-up was not performed in most of the patients with DIHS/DRESS in this study. Further studies are required to determine the long-term autoimmune sequelae of DIHS/DRESS.

Systemic corticosteroids have been considered the treatment of choice, especially in patients with internal organ involvement [31]. These drugs can reduce the systemic symptoms of delayed hypersensitivity reactions and are known to inhibit the effects of IL-5 on eosinophil accumulation in vivo [32]. However, the initial dose is high (1.0 g/kg) and must be tapered over 6 to 8 weeks to prevent the relapse of DIHS/DRESS symptoms [6], with the consequent increase in the risk of infectious complications. The use of systemic corticosteroids could promote viral reactivation, a potential risk factor for increased lymphocyte sensitivity to reactive drug metabolites [33,34]. In addition, systemic corticosteroids have been associated with long-lasting, corticosteroid-dependent DIHS/DRESS [31]. Nevertheless, as the incidence of this disease is very low and the disease is potentially life-threatening, there is no evidence based on randomized controlled trials. In our study, more than 50% of patients (22 patients, 57.9%) were treated conservatively (ie, without systemic corticosteroids) and made

a complete recovery. This difference in outcome between conservative treatment and systemic corticosteroids could have been due to differences in clinical severity between the 2 patient groups. The group treated with systemic corticosteroids had more severe clinical manifestations than the group that received conservative treatment (Table 3). However, some patients (patients 30 to 38) had interesting clinical courses. Although they had severe liver damage including hyperbilirubinemia, they recovered completely without complications. Therefore, it seems reasonable to evaluate the detailed indications for systemic corticosteroids in the treatment of patients with DIHS/DRESS. However, as this study is not a randomized controlled trial, conclusions are limited.

In conclusion, the drugs associated with DIHS/DRESS were anticonvulsants, ß-lactam antibiotics, and NSAIDs. DIHS/DRESS was more common than expected. Systemic corticosteroids can be used in cases with organ damage or in patients with life-threatening abnormalities. However, additional studies are needed to evaluate the detailed clinical indications for systemic corticosteroids in the treatment of patients with DIHS/DRESS. Early recognition and withdrawal of the causative agent are the most important steps in the treatment of DIHS/DRESS.

Acknowledgments

This work was supported by Dong-A University research fund 2009.

References

1. Shiohara T, Inaoka M, Kano Y. Drug-induced hypersensitivity syndrome (DIHS): A reaction induced by complex interplay among herpes viruses and antiviral and antidrug immune responses. Allergol Int. 2006;55:1-8.
2. Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (Drug Rash with Eosinophilia and Systemic Symptoms: DRESS). Semin Cutan Med Surg. 1996;15:250-7.
3. Peyrière H, Dereure O, Breton H, Demoly P, Cociglio M, Blayac JP, Hillaire-Buys D, Network of the French pharmacovigilance centers. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol. 2006;155:422-8.
4. Shiohara T, Iijima M, Ikezawa Z, Hashimoto K. The diagnosis of a DRESS syndrome has been sufficiently established on the basis of typical clinical features and viral reactivations. Br J Dermatol. 2007;156:1083-4.
5. Chaiken BH, Goldberg BI, Segal JP. Dilantin sensitivity; report of a case of hepatitis with jaundice, pyrexia and exfoliative dermatitis. N Engl J Med. 1950;242:897-8.
6. Tennis P, Stern RS. Risk of serious cutaneous disorders after initiation of use of phenytoin, carbamazepine, or sodium valproate: a record linkage study. Neurology. 1997;49:542-6.
7. Vittorio CC, Muglia JJ. Anticonvulsant hypersensitivity syndrome. Arch Intern Med. 1995;155:2285-90.
8. Tas S, Simonart T. Drug rash with eosinophilia and systemic symptoms (DRESS syndrome). Acta Clin Belg. 1999;54:197-200.
9. Roujeau JC. Clinical heterogeneity of drug hypersensitivity. Toxicology. 2005;209:123-9.
10. Ganeva M, Gancheva T, Lazarova R, Troeva J, Baldaranov I, Vassilev I, Hristakieva E, Tzaneva V. Carbamazepine-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: report of four cases and brief review. Int J Dermatol. 2008;47:853-60.
11. Arellano F, Sacristan JA. Allopurinol hypersensitivity syndrome: a review. Ann Pharmacother. 1993;27:337-43.
12. Eshki M, Allanore L, Musette P, Milpied B, Grange A, Guillaume JC, Chosidow O, Guillot I, Paradis V, Joly P, Crickx B, Ranger-Rogez S, Descamps V. Twelve-year analysis of severe cases of drug reaction with eosinophilia and systemic symptoms: a cause of unpredictable multi-organ failure. Arch Dermatol. 2009;145:67-72.
13. Chiou CC, Yang LC, Hung SI, Chang YC, Kuo TT, Ho HC, Hu S, Hong HS, Chung WH. Clinicopathological features and prognosis of drug rash with eosinophilia and systemic symptoms: a study of 30 cases in Taiwan. J Eur Acad Dermatol Venereol. 2008;22:1044-9.
14. Ben m'rad M, Leclerc-Mercier S, Blanche P, Franck N, Rozenberg F, Fulla Y, Guesmi M, Rollot F, Dehoux M, Guillevin L, Moachon L. Drug-induced hypersensitivity syndrome clinical and biologic disease patterns in 24 patients. Medicine (Baltimore). 2009;88:131-40.
15. Romano A, Blanca M, Torres MJ, Bircher A, Aberer W, Brockow K, Pichler WJ, Demoly P, ENDA, EAACI. Diagnosis of nonimmediate reactions to ß-lactam antibiotics. Allergy. 2004;59:1153-60.
16. Tchen T, Reguai Z, Vitry F, Arnoult E, Grange A, Florent G, Bernard P. Usefulness of skin testing in cutaneous drug eruptions in routine practice. Contact Dermatitis. 2009;61:138-44.
17. Devos SA, Van Der Valk PG. Epicutaneous patch testing. Eur J Dermatol. 2002;12:506-13.
18. Suswardana, Hernanto M, Yundani BA, Pudjiati SR, Indrastuti N. DRESS syndrome from cephadroxyl confirmed by positive patch test. Allergy. 2007;62:1216-7.
19. Akcam FZ, Ayqun FO, Akkaya VB. DRESS like severe drug rash with eosinophilia, atypic lymphocytosis and fever secondary to ceftriaxone. J Infect. 2006;53:51-3.
20. Son CH, Kim HI, Kim KN, Lee KN, Lee CU, Roh MS, Kim KH, Yang DK, Lee SK. Moxifloxacin-associated drug hypersensitivity syndrome with drug-induced hypersensitivity pneumonitis. J Investig Allergol Clin Immunol. 2008;18:72-3.
21. Sullivan JR, Shear NH. The drug hypersensitivity syndrome: What is the pathogenesis? Arch Dermatol. 2001;137:357-64.
22. Man CB, Kwan P, Baum L, Yu E, Lau KM, Cheng AS, Ng MH. Association between HLA-B*1502 allele and antiepileptic drug-induced cutaneous reactions in Han Chinese. Epilepsia 2007;48:1015-8.
23. Bocquet H, Bagot M, Roujeau JC. DIDMOHS: A proposed consensus nomenclature for the drug-induced multiorgan hypersensitivity syndrome. Arch Dermatol. 1998;134:875.
24. Kaminsky A, Moreno M, Diaz M, Charas V, Bravo G, Kien C. Anticonvulsant hypersensitivity syndrome. Int J Dermatol. 2005;44:594-8.
25. Callot V, Roujeau JC, Bagot M, Wechsler J, Chosidow O, Souteyrand P, Morel P, Dubertret L, Avril MF, Revuz J. Drug-induced pseudolymphoma and hypersensitivity syndrome: Two

different clinical entities. Arch Dermatol. 1996;132:1315-21.
26. Kim YH, Lee CU, Kim KH, Kim SH, Shin BC, Seo HR, Kim BK, Heo JH, Yang DK, Lee SK, Son CH. Rhabdomyolysis as a manifestation of phenytoin-induced anticonvulsant hypersensitivity syndrome. Korean J Asthma Allergy Clin Immunol. 2007;27:66-9 [Article in Korean].
27. Gupta A, Eggo M, Uetrecht JP, Cribb AE, Danemon D, Rieder MJ, Shear NH, Cannon M, Spilberg SP. Drug-induced hypothyroidism; The thyroid as a target organ in hypersensitivity reactions to anticonvulsants and sulfonamides. Clin Pharmacol Ther. 1992;51:56-67.
28. Sommers LM, Schoene RB. Allopurinol hypersensitivity syndrome associated with pancreatic exocrine abnormalities and new-onset diabetes mellitus. Arch Intern Med. 2002;162:1190-2.
29. Aota N, Hirahara K, Kano Y, Fukuoka T, Yamada A, Shoihara T. Systemic lupus erythematosus presenting with Kikuchi-Fujimoto's disease as a long-term sequela of drug-induced hypersensitivity syndrome. Dermatology. 2009;218:275-7.
30. Sakuma K, Kano Y, Fukuhara M, Shiohara T. Syndrome of inappropriate secretion of antidiuretic hormone associated with limbic encephalitis in a patient with drug-induced hypersensitivity syndrome. Clin and Exp Deramtol. 2007;33:287-90.
31. Roujeau JC. Treatment of severe drug eruptions. J Dermatol. 1999;26:718-22.
32. Hellman C, Lönnkvist K, Hedlin G, Hallden G, Lundahl J. Down-regulated IL-5 receptor expression in peripheral blood eosinophil from budesonide-treated children with asthma. Allergy. 2002;57:323-8.
33. De Vries A, Philippe J, Van Renterghem D, De Cuyper CA, Hindryckx PH, Matthys EG, Louagie A. Carbamazepine hypersensitivity syndrome: Report of 4 cases and review of the literature. Medicine. 1995;74:144-51.
34. Descamps V, Bouscarat F, Laglenne S, Aslangul E, Veber B, Descamps D, Saraux JL, Grange MJ, Grossin M, Navratil E, Crickx B, Belaich S. Human herpesvirus 6 infection associated with anticonvulsant hypersensitivity syndrome and reactive haemophagocytic syndrome. Br J Dermatol. 1997;137:605-8.

Manuscript received July 2, 2009; accepted for publication March 18, 2010.

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