

Stevens–Johnson syndrome and toxic epidermal necrolysis due to anticonvulsants share certain clinical and laboratory features with drug-induced hypersensitivity syndrome, despite differences in cutaneous presentations

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Summary

Background. Drug-induced hypersensitivity syndrome (DIHS)/drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is characterized by late disease onset, fever, rash, hepatic dysfunction, haematological abnormalities, lymphadenopathy and often, human herpesvirus (HHV) reactivation. The diagnosis of DIHS is based on the combined presence of these findings. Anticonvulsants are a major cause of DIHS and may also cause Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). We examined whether SJS/TEN due to anticonvulsants display similar clinical and laboratory features to those seen in DIHS.

Methods. Patients diagnosed with SJS or TEN due to anticonvulsants ($n = 8$) were examined and their clinical features and laboratory findings were compared with patients with anticonvulsant-related DIHS ($n = 6$).

Results. Seven of the eight patients with SJS/TEN developed symptoms > 3 weeks after starting anticonvulsants. Hepatic dysfunction was present in six patients with SJS/TEN and five patients with DIHS. Leucocytosis and/or eosinophilia was noted in seven patients with SJS/TEN and four patients with DIHS. Only one patient in the SJS/TEN group had atypical lymphocytosis; this was present in four patients with DIHS. Reactivation of HHV-6 was detected in one of the four patients tested in the SJS/TEN group, although it was seen in five of the six patients with DIHS.

Conclusions. SJS/TEN due to anticonvulsants may exhibit some clinical and laboratory features of DIHS. The nature of the cutaneous involvement should be emphasized in the diagnosis of DIHS.

Introduction

Drug-induced hypersensitivity syndrome (DIHS)/drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is a severe form of drug-induced reaction with multiorgan involvement.^{1–4} DIHS is characterized by fever, rash, hepatic dysfunction, haematological

abnormalities and lymphadenopathy. Reactivation of several herpesviruses, such as human herpesvirus (HHV)-6, often occurs in the course of the disease.^{3–6} This syndrome is associated with several drugs, including anticonvulsants (carbamazepine, phenytoin, phenobarbital, zonisamide), allopurinol, sulfasalazine, dapsone and mexiletine, and typically develops 3–6 weeks after commencement of the drug. Recently, diagnostic criteria for DIHS⁶ and a scoring system for determining the likelihood of DRESS⁷ have been proposed based on a combination of both clinical features and laboratory findings. However, there is confusion in the diagnosis of DIHS/DRESS syndrome vs. Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN),^{8–10} although

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the skin lesions in SJS/TEN are different from those in DIHS/DRESS.

Anticonvulsants are the most common cause of DIHS, and also represent a major cause of SJS/TEN.^{1,11,12} This raises the question of whether anticonvulsants cause similar clinical and laboratory features in both SJS/TEN and DIHS. We report the clinical and laboratory findings in patients with SJS/TEN and DIHS caused by anticonvulsants. The results indicate that anticonvulsant-induced SJS/TEN may display the clinical and laboratory features of DIHS, notwithstanding the difference in cutaneous features.

Methods

Eight patients with anticonvulsant-related SJS (three women) or TEN (three men, two women) (mean age 49.1 years; range 18–72) admitted to the Saitama Medical Center between 2003 and 2007 were examined. The diagnosis of SJS [skin detachment of < 10% of total body surface area (BSA)] and TEN (detachment of > 30% of total BSA) was made both clinically and histopathologically.¹

The anticonvulsant drugs responsible for SJS or TEN were: zonisamide ($n = 3$), carbamazepine ($n = 2$), phenytoin ($n = 2$) and phenobarbital ($n = 1$). Anticonvulsants were started in patients with the following diseases: psychiatric diseases ($n = 2$), cerebral infarction ($n = 1$), brain tumour ($n = 1$), cerebral haemorrhage ($n = 1$), brain surgery for cerebral aneurysm ($n = 1$) and unknown cause ($n = 2$). With respect to the management of SJS/TEN, seven patients were treated with systemic corticosteroids, and one patient was treated with intravenous immunoglobulin.

Cases of anticonvulsant-related DIHS (three men, three women; mean age 54.7 years, range 27–71) between 2006 and 2008 were examined. The anticonvulsant drugs responsible for DIHS were carbamazepine ($n = 5$) and zonisamide ($n = 1$). Anticonvulsants were started for the prevention of epilepsy ($n = 4$), headache ($n = 1$) and trigeminal neuralgia ($n = 1$). Systemic corticosteroids were given to five patients.

Any abnormal haematological, biochemical, microbiological and serological results were recorded. Skin biopsies and histopathological examination were performed in all cases of SJS/TEN and DIHS.

Results

Table 1 summarizes the clinical and laboratory findings in the eight patients with SJS/TEN (patients 1–8). The time elapsed between starting the drug and the onset of

symptoms was > 3 weeks (range 22–31 days) for all but one patient. All patients had fever of > 38.5 °C. Enlargement of lymph nodes was confirmed in one patient, but was unknown in the other cases. Results of laboratory examinations showed hepatic dysfunction (alanine aminotransferase > 100 U/L (normal range 4–43 U/L) and/or γ -glutamyl transferase > 100 U/L (10–47 U/L)] in six of the eight cases. There were seven patients with leucocytosis ($> 11 \times 10^9$ /L; normal range $3.3\text{--}8.6 \times 10^9$ /L) and four patients with eosinophilia ($> 0.7 \times 10^9$ /L; $0.07\text{--}0.45 \times 10^9$ /L). However, only one patient had atypical lymphocytosis (> 5% atypical lymphocytes; < 1%). HHV-6 IgG antibody titres were examined in four patients on admission and on recovery. In one patient, HHV-6 IgG titres increased from 1 : 10 to 1 : 1280, whereas no significant increases in HHV-6 IgG titres were seen in the other three patients. The lymphocyte transformation test (LTT) for drugs was performed in six patients; positive results were seen in four of the six patients, all of whom had positive LTTs after recovery.

Cutaneous lesions included diffuse erythema with target-like lesions, blisters and erosions (Fig. 1a). Hemorrhagic erosions on the lips and oral mucosa, and conjunctival injection were seen in all cases. Histopathologically, extensive eosinophilic necrosis of keratinocytes and subepidermal blisters were seen in all cases (Fig. 1b). The mean time from onset to resolution of skin lesions was 22.8 days (range 16–37 days). There were complications of sepsis ($n = 2$) and pneumonia ($n = 1$).

The clinical and laboratory findings of six patients with DIHS (patients 9–14) are also shown in Table 1. The mean interval between commencement of the drug and the onset of rash was 34.2 days (range 22–51). All patients with DIHS had a fever of > 38.5 °C. The enlargement of lymph nodes was seen in five of the six patients with DIHS. Hepatic dysfunction was seen in five patients. Haematological abnormalities, including leucocytosis, eosinophilia and/or atypical lymphocytosis were seen in four. Anti-HHV-6 IgG titres were increased in five patients with DIHS. In four of the five patients tested, HHV-6 DNA was detected in the peripheral blood by real-time quantitative PCR 17–55 days after the onset of the rash. The cutaneous lesions of patients with DIHS included erythroderma or exfoliative dermatitis with oedema on the face and limbs (Fig. 2a). Hemorrhagic mucocutaneous involvement was not seen in any patient. Histopathologically, focal liquefaction degeneration of the basal layer, exocytosis of lymphocytes and a superficial perivascular lymphocytic infiltrate, often with extravasation of erythrocytes, were

Table 1 Characteristics of patients with Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug-induced hypersensitivity syndrome (DIHS) due to anticonvulsants.

Case	Type	Age/ Sex	Drug	Duration,* day	ALT, γ -GTP, U/L	Total leucocytes, / μ L	Eosinophils, / μ L	Atypical lymphocytes, %	Anti-HHV-6 IgG (FA)	DBSA %	Lymph- node enlargement	Other organs involvement	Initial dose of corticosteroids, mg/day
1	SJS	29/F	Carbamazepine	12	215/132	13 200	303	0	ND	5	UN	–	PSL 30
2	SJS	72/F	Phenobarbital	31	72/28	15 800	416	0	40 $\rightarrow$ 20	5	UN	–	PSL 40
3	SJS	19/F	Phenytoin	26	90/436	12 800	896	0	80 $\rightarrow$ 80	10	+	–	PSL 60
4	TEN	59/M	Carbamazepine	22	306/149	15 900	788	1	ND	30	UN	Sepsis	Methyl-PSL 1000 $\rightarrow$ PSL 60
5†	TEN	71/M	Zonisamide	22	48/111	12 500	1018	0	10 $\rightarrow$ 1280	40	UN	Pneumonia	Not used
6	TEN	59/F	Zonisamide	30	210/302	12 700	127	3	ND	60	UN	–	Methyl-PSL 1000 $\rightarrow$ Bethamesasone 10
7	TEN	66/M	Zonisamide	25	58/61	10 100	277	ND	40 $\rightarrow$ 40	40	UN	–	Methyl-PSL 500 $\rightarrow$ PSL 30
8	TEN	18/F	Phenytoin	26	337/451	25 300	792	6	ND	55	UN	Sepsis	Methyl-PSL 1000 $\rightarrow$ Bethamesasone 4
9	DIHS	59/M	Carbamazepine	30	119/79	16 200	452	16	160 $\rightarrow$ 1280	–	+	–	PSL 40
10	DIHS	56/F	Carbamazepine	22	706/318	11 500	828	15	160 $\rightarrow$ 160	–	+	–	PSL 40
11	DIHS	62/F	Carbamazepine	51	9/40	7800	1155	8	10 $\rightarrow$ 640	–	+	Pneumonia	Bethamesasone 2
12	DIHS	53/F	Carbamazepine	26	327/108	6400	390	0	640 $\rightarrow$ 10240	–	+	–	Not used
13	DIHS	71/M	Carbamazepine	50	108/140	8100	500	0	10 $\rightarrow$ 160	–	+	–	PSL 30
14	DIHS	27/F	Zonisamide	26	401/220	21 300	660	49	40 $\rightarrow$ 1280	–	+	–	PSL 30

ALT, alanine aminotransferase; DBSA, detachment of the total body surface area; γ -GTP, γ -glutamyl transpeptidase; HHV-6, human herpesvirus-6; FA, fluorescent antibody; ND, not done; UN, unknown. Reference ranges are as follows: ALT (4–43 U/L), γ -GTP (10–47 U/L), total leucocytes (3300–8600/ μ L), eosinophils (70–450/ μ L). *Duration between initiation of the drug and onset of symptoms. †Case 5 has already reported in reference 13. Titres of HHV-6 IgG antibodies were performed during the active and recovery phase.



Figure 1 (a) Extensive epidermal detachment on the thigh in a patient with toxic epidermal necrolysis (TEN) (patient 8). (b) Numerous necrotic epidermal keratinocytes and a subepidermal blister in TEN (haematoxylin and eosin, original magnification $\times 100$).

commonly seen (Fig. 2b). The mean time from withdrawal of the causative drugs to resolution of skin eruptions was 28 days (range 16–53). DIHS was complicated by pneumonia in one case.

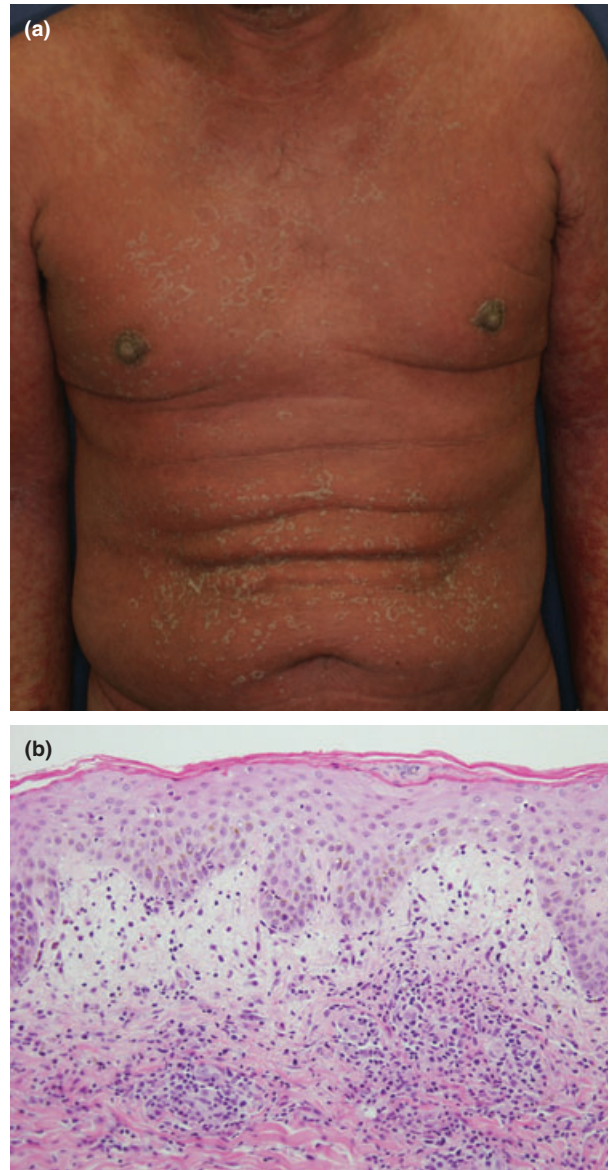


Figure 2 (a) Drug-induced hypersensitivity syndrome (DIHS) showing erythroderma (patient 9). (b) Exocytosis of lymphocytes, subepidermal oedema and superficial perivascular lymphocytic infiltration in DIHS (haematoxylin and eosin, original magnification $\times 100$).

Discussion

In this present study, we found that SJS/TEN due to anticonvulsants shared some clinical and laboratory features with DIHS, including delayed onset, fever, prolonged clinical course, hepatic dysfunction and haematological abnormalities such as leucocytosis and eosinophilia. These findings seen in patients with anticonvulsant-related SJS/TEN may differ from those

in SJS/TEN caused by other drugs. In seven of the eight patients with SJS/TEN, the time between starting the drug and onset of the rash was 3–4 weeks, although it has been reported that SJS/TEN usually occurs 1–3 weeks after treatment initiation.¹ Recently, an analysis of cases in Japan found that 67.6% of SJS cases and 80% of TEN cases developed within 2 weeks after starting the drug.¹⁴

Hepatic dysfunction and haematological abnormalities have often been described in SJS/TEN.^{14,15} However, the percentages of hepatic dysfunction (75%) and leucocytosis (88%) in our patients with SJS/TEN were greater than those in previous reports (31–55.6% and 31%, respectively).^{14,15} Thus, the delayed onset, hepatic and haematological abnormalities may be more common in anticonvulsant-related SJS/TEN. Although the delayed onset, prolonged clinical course, hepatic dysfunction and haematological abnormalities are considered characteristic of DIHS, they may also be seen in other adverse drug reactions caused by anticonvulsants. In contrast, atypical lymphocytosis was rarely seen in our cohort of patients with SJS/TEN. This may be related to the fact that reactivation of HHV-6 rarely occurs in patients with SJS/TEN.^{16,17} Indeed, reactivation of HHV-6 was seen in only one of the four patients tested, although it was detected in five of the six patients with DIHS. Thus, reactivation of HHV-6 and atypical lymphocytosis seem to be more specific to DIHS, as described previously.^{4–6}

As DIHS is characterized by the presence of several clinical and laboratory features, diagnostic criteria for DIHS have recently been proposed by a Japanese consensus group.⁶ Using this, some of our cases of anticonvulsant-related SJS/TEN satisfy five of the seven criteria for DIHS. If clinicians do not pay careful attention to the precise morphological features of the skin eruption, such cases may be regarded as atypical DIHS. In this regard, Wolf *et al.* pointed out that the confusion in the diagnosis of DRESS syndrome vs. SJS/TEN is due to a flaw in the classification of the drug eruptions.¹⁰ Although cutaneous drug-related reactions (SJS/TEN, fixed drug eruption and urticaria/angioedema) are classified according to their cutaneous features, the diagnosis of DIHS depends on a combination of clinical features and laboratory findings. In the criteria for DIHS, the rash is not fully defined. DIHS typically begins with a maculopapular rash, which progresses to an erythroderma or exfoliative dermatitis, often with oedema on the face and limbs.^{4,8} A bullous appearance, which is caused by subepidermal oedema and is not due to extensive necrosis of keratinocytes, may be seen in some cases. There is no haemorrhagic mucocutaneous involvement as seen in SJS/TEN. Thus, the nature of the skin involvement in

DIHS is quite different from those in SJS and TEN. Therefore, a clear description of the cutaneous feature of DIHS should be established in the diagnostic criteria to exclude SJS/TEN.

In conclusion, several of the clinical and laboratory features seen in DIHS may also be present in SJS/TEN due to anticonvulsants. Greater emphasis should be placed on the nature of the eruption in the diagnosis of DIHS.

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