Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms due to lamotrigine differs from that due to other drugs

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Running Head

DIHS by lamotrigine versus other drugs

CONFLICT OF INTEREST

The authors state no conflict of interest.

Abstract

Background: Drug-induced hypersensitivity syndrome (DIHS), also referred to as drug reaction with eosinophilia and systemic symptoms (DRESS), is a multi-organ systemic drug reaction characterized by hematologic abnormalities and reactivation of human herpesvirus-6 (HHV-6). DIHS/DRESS is typically associated with a limited number of drugs, such as the anticonvulsants. Our group has treated 12 patients for DIHS/DRESS due to lamotrigine (LTG), but their presentation differed from that of patients with DIHS/DRESS caused by other drugs.

Objectives: To identify significant differences between DIHS/DRESS caused by LTG versus other drugs.

Methods: We retrospectively reviewed data of 12 patients with DIHS/DRESS caused by LTG and 32 patients with DIHS/DRESS due to other drugs.

Results: The increase in alanine aminotransferase level was significantly milder in the LTG group than in the group with DIHS/DRESS due to other drugs ($P<0.01$). The percentage of atypical lymphocytes in the blood during DIHS/DRESS was significantly lower in the LTG group ($P<0.05$). Serum levels of lactate dehydrogenase and thymus and activation-regulated chemokine were also significantly lower in the LTG group ($P<0.05$). There were fewer DIHS/DRESS patients with HHV-6 reactivation in the LTG group than in the group treated with other drugs ($P<0.01$). Lymphocyte transformation after DIHS/DRESS onset was significantly faster in the LTG group ($P<0.05$). The two groups did not differ with respect to the interval from first drug intake to rash, white blood cell count, blood eosinophilia, or DRESS score. There were no significant histopathological differences between the two groups.

Conclusions: The features of LTG-associated DIHS/DRESS and DIHS/DRESS due to other drugs differ.

Introduction

Drug-induced hypersensitivity syndrome (DIHS), [1-3] also referred to as drug reaction with eosinophilia and systemic symptoms (DRESS), [4-6] is characterized by severe skin eruption, fever, lymphadenopathy, hepatitis, hematologic abnormalities with eosinophilia and atypical lymphocytes and, in some cases, the involvement of other organs.[1-6] Recent reports have shown that HHV-6 reactivation contributes to the development of DIHS/DRESS.[1,2] Compared with other types of drug eruptions, the onset of DIHS/DRESS tends be late (2–8 weeks or more after drug exposure).[1-7] Human HHV-6 DNA is detected in the serum 3–5 weeks after the onset, followed by a dramatic rise in anti-HHV-6 IgG titers.[3,7] According to published data, among patients with DIHS/DRESS, 75–95% have leukocytosis,[4,8] 18.2–90% show atypical lymphocytes,[8,9] 52–95% have eosinophilia,[5,6] and 75–100% develop hepatic abnormalities.[5,8]

A limited number of drugs cause DIHS/DRESS; namely, anticonvulsants, such as carbamazepine, phenytoin, phenobarbital and zonisamide, as well as allopurinol, diaphenylsulfone, salazosulfapyridine and mexiletine.[1-7] Lamotrigine (LTG) is an antiepileptic drug that is also effective for the treatment of bipolar disorder.[10] In Japan, LTG was approved as add-on therapy for patients with recalcitrant epilepsy in 2008. In 2011, approval was granted for its use for suppression of recurrent/relapsed mood episodes in patients with bipolar disorder, and in 2014 as monotherapy in epileptic patients.[11] The primary safety concern with LTG is drug eruption, with ordinary eruption occurring in ~10% of patients and serious eruption in ~0.1%.[12] To date, our group has treated 12 patients with DIHS/DRESS due to LTG. The presentation in these patients, such as liver dysfunction, differed from that in patients treated with other drugs. Therefore, in this study we investigated differences in DIHS/DRESS between 12 patients treated with LTG and 32 patients receiving other drugs.

Patients and Methods

This study was approved by the Ethics Committee of Showa University School of Medicine, Nara Medical University School of Medicine, Kyorin University School of Medicine, and Shimane University School of Medicine (all Japan), and was conducted according to the Helsinki Declaration. Informed consent for all diagnostic and research procedures was obtained from all participating patients.

DIHS was diagnosed according to the criteria established by the Japanese consensus group:[13] High fever, widespread eruption, lymphadenopathy, leukocytosis with atypical lymphocytosis and/or eosinophilia, and liver dysfunction. The data of 44 patients seen at our hospital for DIHS/DRESS between April 1, 2000 and August 31, 2018, and who satisfied the full criteria for DIHS were retrospectively evaluated. There were 12 patients with DIHS/DRESS caused by LTG. There were 32 patients with DIHS/DRESS due to other drugs; data on 20 of these patients were also used in other studies.[8]

Time from disease onset to the first visit to our hospital, the results of blood examinations, the presence/absence of HHV-6 reactivation, and the results of lymphocyte transformation tests (LTTs) were evaluated. Biopsy specimens were available for 28 of the 44 patients.

White blood cell (WBC) counts (normal range: 3,500–9,000/μL) were determined both at the initial examination and at the time of maximum disease severity. Eosinophils, serum lactate dehydrogenase (LDH: normal range: 105–220 U/L), and serum alanine aminotransferase (ALT, normal range: 5–25 IU/L) levels were determined at the time of maximum disease severity. The serum thymus and activation-regulated chemokine (TARC/CCL17: (normal range: < 450 pg/mL) level was measured using a chemiluminescent enzyme immunoassay with the HISCL system (Sysmex, Hyogo, Japan) with a TARC assay kit (Shionogi, Osaka, Japan). The highest value of TARC during DIHS/DRESS was included in the analysis in this study.

HHV-6 infection was evaluated by serological tests of serum samples upon patient admission and at various times thereafter. Titers of immunoglobulin (Ig) G and IgM antibodies to HHV-6 were determined in all DIHS/DRESS patients using an

indirect immunofluorescence antibody assay. Serum HHV-6 DNA was measured using real-time polymerase chain reaction (PCR), as described previously.[1,14] HHV-6 reactivation as evidenced by the increase in HHV-6 IgG titers and HHV-6 DNA levels commonly occurs 2–3 weeks after onset.[13]

LTTs are commonly performed in Japan because the test is covered by health insurance agencies as a method for diagnosing cutaneous adverse drug reactions (ADRs). All patients (12 patients with DIHS/DRESS caused by LTG and 32 patients with DIHS/DRESS due to other drugs) were examined by LTTs. LTTs were performed as described previously.[14] Briefly, peripheral mononuclear cells separated by density-gradient centrifugation were cultured with each possible causative drug for 7 days and the stimulation index (SI), obtained by measuring lymphocyte proliferation, was compared with that of a control. SI > 1.8 was considered a positive result.

The RegiSCAR scoring system[15] was developed to more clearly define DIHS/DRESS, and patient scores were evaluated in this study.

Histopathological features were investigated by hematoxylin and eosin (H&E) staining of skin biopsy samples obtained from the 28 DIHS/DRESS patients for whom biopsy data were available. The histopathological features of DIHS/DRESS were classified into four patterns, as described by Ortonne et al.:[16] Interface dermatitis (ID), eczematous, acute generalized exanthematic pustulosis (AGEP)-like, and erythema multiforme (EM)-like. Briefly, the ID pattern was defined as basal lymphocyte exocytosis with keratinocyte vacuolization and/or apoptosis; the eczematous pattern as a grade 2 or 3 spongiosis with lymphocytes exocytosis; AGEP-like as a multilocular subcorneal or intracorneal pustulosis; and EM-like as slight to moderate acanthosis with orthokeratotic hyperkeratosis and perivascular infiltrations in the upper dermis.[16] The presence of apoptotic keratinocytes in the epidermis was also examined. The histopathological findings were examined by three experts in dermatopathology (M.I., H.S, and H.W).

Data analysis

The Mann-Whitney *U* test and Fisher's exact test were used to identify significant differences between groups. The data are expressed as means ± standard error. A *P*-value of <0.05 was considered to indicate statistical significance in all tests.

Results

Patient data

The data of 44 patients who satisfied all criteria for DIHS[13] were retrospectively evaluated. In 32 patients (21 males and 11 females), DIHS/DRESS occurred due to the usual causative drugs: carbamazepine (n = 15), allopurinol (n = 4), phenobarbital (n = 3), salazosulfapyridine (n = 2), mexiletine (n = 2), zonisamide (n = 2), and dapsone, febuxostat, phenytoin, and trichloroethylene (n = 1 each).[17] Twelve patients (5 males and 7 females) developed DIHS/DRESS due to LTG use. The mean age in the group treated with the usual drugs (UD group) and the LTG group was 49.3 and 40.9 years, respectively (Table 1). A previous report[18] showed a greater predominance of women (66.67% female and 33.33% male patients [F:M = 2:1]) with DIHS/DRESS due to LTG, and 68.42% of patients were over 18 years of age. We did not observe significant gender differences, but 11 out of 12 DIHS/DRESS cases due to LTG were over 18 years of age. However, only a small number of cases were included in this report, and further studies are required.

Liver dysfunction in DIHS/DRESS is significantly milder in patients treated with lamotrigine than with other drugs

An essential feature in the diagnosis of DIHS/DRESS is liver dysfunction,[3,7] which is the most characteristic finding of this drug eruption. In this study, all 44 patients had hepatic abnormalities, as evidenced by their serum ALT levels being above the normal range (5–25 IU/L). However, liver dysfunction was significantly milder in the LTG group (mean, 110.6 ± 26.1 IU/L) compared with the UD group (mean, 328.1± 61.4 IU/L; $p<0.01$) (Fig. 1). In previous reports,[18] 57.89% of DIHS/DRESS patients experienced liver dysfunction (ALT > 100 IU/L) due to LTG. In our study, liver dysfunction (ALT > 100 IU/L) was found in 33.3% of patients in the LTG group and 75% (ALT > 100 IU/L) in the UD group. Therefore, liver dysfunction from DIHS/DRESS due to LTG appears milder compared with that caused by other drugs.

The percentage of atypical lymphocytes, but not white blood or eosinophil counts, are significantly lower in patients treated with lamotrigine than with other drugs

Because leukocytosis with atypical lymphocytes of varying amounts is a prominent feature of DIHS/DRESS,[3,7] we investigated whether the two groups differed in their blood examination results. WBC counts exceeding 11,000/μL (normal range: 3,500–9,000/μL) during the clinical course were found in 9 of the 12 patients (75.0%) in the LTG group and in 27 of the 32 patients (84.4%) in the UD group. There was no significant difference in WBC count between the two groups during the course of the disease. Atypical lymphocytes were found in 10 patients (83.3%) in the LTG group and 30 patients (93.8%) in the UD group. The mean percentage of atypical lymphocytes (maximum value during the disease course) was significantly lower in the LTG group than in the UD group (mean 3.38 ± 1.03% vs. 9.83 ± 1.65%, respectively; $P<0.05$). (Fig. 2). Eosinophilia (≥ 1,500/mm^3; normal range: 70–440/μL) was noted in 6 of 12 patients (50.0%) in the LTG group and in 21 of 32 patients (65.6%) in the UD group during the clinical course of DIHS/DRESS. There was no significant difference between the LTG and UD groups in the incidence of eosinophilia or the mean eosinophil count in WBCs (2,391.4 ± 574.3 mm^3 vs. 3 448.6 ± 569.4 mm^3, respectively) during the disease course.

DIHS/DRESS-related serum LDH levels are significantly lower in patients treated with lamotrigine versus other drugs

Mean serum LDH levels were significantly lower in cases with DIHS/DRESS caused by LTG (453.1 ± 54.2 U/L) than in those caused by other drugs (639.6 ± 78.2 U/L; $P<0.05$) (Fig. 3a).

DIHS/DRESS-related serum TARC/CCL17 levels are significantly lower in patients treated with lamotrigine versus other drugs

A previous report demonstrated a correlation between serum TARC levels of patients in the acute stage of DIHS/DRESS and disease activity.[19,20] In our patients, mean serum TARC levels were significantly lower in the LTG group than in the UD group (4,442.0 ± 1,027.8 pg/mL vs. 14,736.3 ± 3,334.6 pg/mL; $P<0.05$) (Fig. 3b).

HHV-6 reactivation

DIHS/DRESS is a multi-organ systemic reaction closely associated with the reactivation of herpes virus, especially HHV-6.[1-3] Among the 44 patients in this study, HHV-6 reactivation was detected in 1 of the 12 LTG patients and 23 of the 32 UD patients with DIHS/DRESS; there were fewer DIHS/DRESS patients with HHV-6 reactivation in the LTG group than in the UD group ($P<0.01$: Fisher's exact test). DIHS/DRESS patients with HHV-6 reactivation also had significantly higher levels of serum LDH and TARC (both $P<0.01$).

Onset of a positive lymphocyte transformation test

Drug-specific T cell responses are often diagnosed using LTTs. In DIHS/DRESS patients, a high rate of positive LTT results 4 weeks after disease onset (after the disappearance of eruptions) has been reported.[21] We examined all patients (12 patients with DIHS/DRESS caused by LTG and 32 patients with DIHS/DRESS due to other drugs) and observed positive results in 8 of 12 patients caused by LTG and 23 of 32 patients due to other drugs. In the present study, the mean time from disease onset to a positive LTT result was shorter in the LTG group than in the UD group (12.0 ± 3.89 days vs. 69.3 ± 19.9 days; $P<0.05$) (Fig. 4).

Histopathological features are not associated with HHV-6 reactivation

The histopathological features of DIHS/DRESS were investigated in the 28 patients for whom skin biopsy samples were available. The histopathological findings were classified as described in a previous study: [16] eczematous, ID, AGEP-like, or EM-like. The most common histological pattern on biopsy was ID (n = 8, Fig. 5a), followed by an EM-like pattern (n = 7, Fig. 5b) and an AGEP-like pattern (n = 1, Fig. 5c). While an eczematous pattern alone was not seen in any of the specimens, it did occur together with other patterns. In addition to the four patterns listed above, a lichenoid-tissue reaction was seen alone in a single biopsy specimen (n = 2, Fig. 5d) but co-occurred with other findings in other samples.

The co-occurrence of two or more patterns in a single skin specimen was common (10 out of 28 patients; 35.7%), similar to previous reports.[16, 22,23] A report from Taiwan

showed that patients with both histological patterns tended to have a higher rate of HHV-6 reactivation.[23] However, none of the histological patterns (including the co-existence of two or more patterns) was statistically associated with HHV-6 reactivation. HHV-6 reactivation was noted in 6 of 7 patients with an EM-like pattern alone, but there was no significant difference in prevalence between an EM-like pattern and other patterns (P=0.0604: Fisher's exact test). Moderately apoptotic keratinocytes were observed on the biopsies of 11 of the 28 patients (Fig. 5d), but did not correlate with HHV-6 reactivation.

Other findings

There was no significant difference in the interval from first drug intake to skin rash, or in skin manifestations such as a purpuric erythematous rash and/or periorbital and facial edema, which are characteristic of DIHS/DRESS, between the LTG and UD groups. In addition, there was no difference in DRESS score. The DRESS score is used for classification of DIHS/DRESS; neither DIHS caused by LTG nor DIHS caused by other drugs affected the diagnosis of DIHS/DRESS. In the UD group, 3 of 32 patients showed reactivations of both HHV-6 and Epstein-Barr virus (EBV) and 5 of 32 patients showed reactivation of both HHV-6 and cytomegalovirus (CMV). There were no patients who showed reactivation of HHV-6, EBV, and CMV. In the LTG group, one patient showed only CMV reactivation and another showed only EBV reactivation. There were no differences in the DIHS/DRESS relapse rate between LTG and other drugs.

Discussion

Lamotrigine is one of the causative drugs of DIHS/DRESS, and it can also cause other types of severe drug eruptions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).[10,24,25] In Japan, there is a system managed by the Pharmaceuticals and Medical Devices Agency (PMDA) designed to aid those suffering from ADRs. Saeki et al. reported that 92 out of 309 patients (29.8%) with LTG-related ADR reported to the PMDA had DIHS/DRESS.[11] However, whether DIHS/DRESS due to LTG differs from DIHS/DRESS due to other drugs is unclear and was investigated in this study.

The main feature of DIHS/DRESS is a cutaneous rash that develops after exposure to the causative drug, and is associated with fever and organ involvement.[3,7] Hepatic failure, including elevation of serum transaminases, is a common finding.[5,8] In this study, all 44 patients had liver dysfunction, but it was milder in the LTG group than in the UD group. The reason for this difference in DIHS/DRESS due to LTG versus other drugs, including anticonvulsants such as carbamazepine and phenytoin, remains unclear. Carbamazepine and phenytoin are typical cytochrome P450 (CYP) substrates. Whereas LTG is mainly metabolized by UDP-glucuronosyltransferase (UGT), carbamazepine is metabolized to the toxic metabolite carbamazepine-10, 11-epoxide, by the enzyme CYP3A4,[26] while phenytoin is mainly metabolized to 4'hydroxylated phenytoin by CYP2C9, and to a minor extent by CYP2C19.[27] Generally, unstable reactive metabolites metabolically activated by CYP enzymes induce hepatotoxicity. LTG contains a triazine ring that is metabolized at the 2-position by UGT to form a quaternary ammonium glucuronide.[28] A significant pharmacokinetic interaction exists between valproate and LTG that increases the risk of LTG-related drug rash due to the inhibition of UGT by valproate.[29] It has therefore been hypothesized that unmetabolized LTG is the cause of the ADR. A direct interaction between LTG and macromolecules, such as human leukocyte antigen (HLA), also triggers ADR. However, this does not explain the difference between DIHS/DRESS due to LTG versus other anticonvulsants; therefore, further studies are required.

TARC/CCL17, a member of the CC family of chemokines[30], is a ligand for CC chemokine receptor (CCR) 4, expressed on type 2 helper T (Th2) lymphocytes.[31-33] TARC plays important roles in Th2-type immune responses, by selectively incorporating CCR4+ Th2-polarized memory/effector T cells into inflamed tissues, such as those seen in atopic dermatitis.[34] Ogawa et al. determined a correlation between serum TARC levels and disease activity in patients in the acute stage of DIHS/DRESS, consistent with our finding of significantly lower serum TARC levels in DIHS/DRESS due to LTG than that due to other drugs.[19] Moreover, both previous investigations[19,20] and our own suggest that elevated serum TARC levels during the early stage of disease is a useful marker for early recognition of HHV-6 reactivation. Our results also showed higher serum LDH levels in patients with DIHS/DRESS than in those without HHV-6 reactivation, in agreement with a previous study.[8] Thus, both serum TARC and serum

LDH levels in patients with DIHS/DRESS may be biomarkers of HHV-6 reactivation. Moreover, serum TARC levels may be an indicator of DIHS/DRESS severity.
LTT positivity after disease onset occurred significantly earlier in the LTG group than in the UD group in this study. Previous reports noted that positive LTT reactions during the acute, but not the recovery, stage of maculopapular drug eruptions and SJS/TEN, while the opposite situation characterized DIHS/DRESS.[21] In this study, a positive LTT was also observed in patients during the recovery stage of DIHS/DRESS. The time to LTT was faster in the LTG group than in the UD group, although patients in both groups suffered from the same syndrome; DIHS/DRESS. Thus, it may be possible to identify causative drugs by performing LTTs at an early stage when DIHS/DRESS is suspected due to LTG. Hanafusa et al.[35] detected drug-specific $CD8^+$ cytotoxic T lymphocytes in the acute stages of DIHS/DRESS and SJS, whereas $CD4^+$ T-cell proliferation predominated in most patients in the recovery stage of DIHS/DRESS, and in those with maculopapular-type drug eruption or EM. Moreover, during the course of DIHS/DRESS, there was a dramatic switch in the predominant drug-specific proliferating T-cell population, in which first $CD8^+$ CTLs, but later $CD4^+$ T cells, predominated, followed by proliferation of drug-specific $CD4^+$ $CD25^+$ $Foxp3^+$ regulatory T cells during the recovery stage of DIHS/DRESS.[35] These findings are suggestive of a predominant drug-specific proliferating T-cell population in the acute stage of LTG-related DIHS/DRESS. LTTs are also used to diagnose drug-induced liver injury; therefore, we examined the relationship between LTT positivity and liver dysfunction. There were no significant differences in LTT results between patients with ALT$\geqq$100 IU/L and those with ALT < 100 IU/L. In addition, there was no significant difference in ALT value between the LTT-positive and LLT-negative groups.

Among the four histopathological patterns of DIHS/DRESS identified by Ortonne et al.,[16] i.e., eczematous, ID, AGEP-like and EM-like patterns, ~54% of our patients had ID or an EM-like pattern. Only one patient had an AGEP-like pattern. In addition, the eczematous pattern also occurred together with one or more of the other types of pattern. We further identified lichenoid tissue reaction as a characteristic feature of DIHS/DRESS, occurring alone and with other histopathological patterns. A

recent study demonstrated that patients with certain histological patterns tended to have a higher rate of HHV-6 reactivation.[23] However, none of the histological patterns (including cases with co-existence of two or more patterns) was statistically associated with HHV-6 reactivation. Interestingly, among the seven biopsy specimens with only an EM-like pattern, six were obtained from patients with HHV-6 reactivation, but the incidence did not differ between study groups. Two studies reported a correlation between apoptotic keratinocytes in skin biopsies and severe DIHS/DRESS,[16,22] whereas in our study scattered apoptotic keratinocytes were seen in 39.3% of the DIHS/DRESS samples. However, there was no correlation between the presence of these cells in the epidermis and DIHS/DRESS severity. Histological differences between the LTG and UD groups were not observed.

In conclusion, DIHS/DRESS due to LTG seems to be characterized by symptoms that are milder than those occurring in DIHS/DRESS due to other drugs, including liver dysfunction and the percentage of atypical lymphocytes, but there was no difference in the DRESS score between our UD and LTG groups. Fewer patients in the LTG group had HHV-6 reactivation than was the case in the UD group, with both TARC and LDH levels correlating with HHV-6 reactivation. Moreover, the time to LTT positivity after DIHS/DRESS onset was significantly faster in the LTG group. However, histological differences between the two groups were not observed.

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Table 1. Characteristics of the patients

	Other drugs	Lamotrigine
Numbers of patients	32	12
Sex (male/female)	21/11	5/7
Age (years, mean ± SE)	49.3±2.81	40.9±4.37
Causative drug (numbers of patients)	Carbamazepine (15) Allopurinol (4) Phenobarbital (3) Mexiletine (2) Salazosulfapyridine (2) Zonisamide (2) Dapsone (1) Febuxostat (1) Phenytoin (1) Trichloroethylene (1)	Lamotrigine (12)

Table 2. Histological features of patients with DIHS/DRESS

Histological pattern	Lamotrigine	Other drugs	Total	Apoptotic cells	DRESS score (mean)	HHV-6 reactivation
EM	0	7	7	2	6.29	6
ID	3	5	8	3	5.38	3
Eczema	0	0	0	-	-	-
AGEP	0	1	1	-	8	1
LTR	1	1	2	1	5	1
EM+ID	0	3	3	2	6.67	1
EM+Eczema+AGEP	0	1	1	-	5	-
EM+AGEP+ID	1	1	2	-	7.5	1
EM+AGEP+LTR	0	1	1	1	7	1
ID+AGEP	0	1	1	1	7	-
ID+LTR	0	2	2	1	6.5	1

Data are numbers of patients unless otherwise stated

ID, interface dermatitis; AGEP, acute generalized exanthematic pustulosis; EM, erythema multiforme, LTR, lichenoid-tissue reaction

Figure 1. Serum alanine aminotransferase (ALT) levels in drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS) caused by lamotrigine (LTG group) and the usual drugs (UD group). Patients in both groups had hepatic abnormalities, based on serum ALT levels that were above the normal range (5–25 IU/L). However, mean liver dysfunction was significantly milder in the LTG group than in the UD group (110.6 ± 26.1 IU/L vs. 328.1 ± 61.4 IU/L; **P<0.01).

Figure 2. Atypical lymphocytes in the two groups. Atypical lymphocytes were detected in 83.3% of the patients in the LTG group and 93.8% of those in the UD group. The mean percentage of atypical lymphocytes (maximum value during the disease) was significantly lower in the LTG than in the UD group (3.38 ± 1.03% vs. 9.83 ± 1.65%; *P<0.05).

Figure 3. Serum lactate dehydrogenase (LDH) and thymus and activation-regulated chemokine (TARC) levels in DIHS/DRESS. (a) The mean serum LDH levels were significantly lower in patients with DIHS/DRESS caused by LTG (453.1 ± 54.2 U/L) than in those with DIHS/DRESS caused by other drugs (639.6 ± 78.2 U/L) (*P<0.05). (b) Mean serum TARC levels were also significantly lower in the LTG than in the UD group (4,442.0 ± 1,027.8 pg/mL vs.14,736.3 ± 3,334.6 pg/mL; P<0.05). DIHS/DRESS patients with HHV-6 reactivation had significantly higher serum LDH (P<0.01) and TARC (**P<0.01) levels.

Figure 4. Lymphocyte transformation test (LTT) results. We performed LTT in all patients and obtained positive results for 8 of 12 patients with DIHS/DRESS caused by LTG, and for 23 of 32 patients with DIHS/DRESS due to other drugs. The mean time from disease onset to a positive LTT result was shorter in the LTG group than in the UD group (12.0 ± 3.89 days vs. 69.26 ± 19.9 days; *P<0.05).

Figure 5. Histopathological features of DIHS/DRESS. (a) Interface dermatitis. Spongiosis and ballooning degeneration are seen in the epidermis together with

perivascular inflammation in the upper dermis. Bar = 200 μm (b) An erythema-multiforme-like pattern featuring moderate acanthosis with orthokeratotic hyperkeratosis and perivascular infiltrations in the upper dermis. Bar = 200 μm (c) Acute generalized exanthematic pustulosis, characterized by subcorneal pustules, papillary dermal edema, and infiltration by lymphocytes, eosinophils and neutrophils, is seen in the upper dermis. Bar = 200 μm (d) Lichenoid tissue reaction, characterized by hyperkeratosis, focal acanthosis, and a dense infiltration, is seen in the upper dermis, together with liquefaction degeneration between the epidermis and dermis. The rete ridges are irregularly elongated. Bar = 200 μm (e) In some specimens, apoptotic keratinocytes are scattered within the epidermis. Apoptotic cells (arrow) in the epidermis were seen to some extent in samples from 11 of the 28 DIHS/DRESS patients for whom biopsy tissue was available. Bar = 200 μm

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