Human Herpesvirus 6 Reactivation in Trichloroethylene-exposed Workers Suffering from Generalized Skin Disorders Accompanied by Hepatic Dysfunction

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Abstract: Human Herpesvirus 6 Reactivation in Trichloroethylene-exposed Workers Suffering from Generalized Skin Disorders Accompanied by Hepatic Dysfunction: Hanlin Huang, et al. Hospital for Occupational Diseases Control of Guangdong Province, P. R. of China—Idiosyncratic generalized skin disorders resembling serious drug hypersensitivities have reportedly occurred after occupational exposure to trichloroethylene. However, factors associated with the disorders remain unknown except for trichloroethylene exposure. This study aimed at clarifying whether infectious diseases contributed to the development of rash or hepatitis in patients with trichloroethylene-related generalized skin disorders. Fifty-nine patients consecutively hospitalized between March 2002 and December 2003 and 59 healthy exposed workers selected on an age-matched basis in the patients’ factories were enrolled in the study. Information on possible risk factors for rash and hepatitis was collected with structured checklists. Antibody titers were measured for hepatitis A, B and C viruses, Mycoplasma pneumoniae, herpes simplex viruses 1 and 2, Epstein-Barr virus, cytomegalovirus, human herpesvirus 6, measles and rubella virus. Thirty-six cases (59%) showed exfoliative dermatitis, 17 (28%) erythema multiforme, 4 (7%) Stevens-Johnson syndrome, and 4 (7%) toxic epidermal necrolysis. Before the onset of rash, 16 (27%) cases had received medication prescribed for the preceding fever, a main first symptom of the disorders. Marked increases in anti-human herpesvirus 6 IgG titer (≥256), which indicated viral reactivation, were noted in 14 (25%) patients, while no abnormal increase was detected in the controls (p<0.001). Anti-measles IgM titer was positive in 2 (7%) cases but not in the controls (p=0.49). The involvement of other known risk factors of rash or hepatitis was ruled out. These results suggest that part of trichloroethylene-related generalized cutaneous disorders occurring in China and drug-induced hypersensitivity syndrome overlap in terms of human herpesvirus 6 reactivation.

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Key words: Solvents, Trichloroethylene, Occupational exposure, Drug hypersensitivity, Dermatitis, Stevens-Johnson syndrome, Hypersensitivity syndrome, Hepatitis, Human herpesvirus 6, Reactivation

Generalized skin disorders, such as Stevens-Johnson syndrome, toxic epidermal necrolysis and hypersensitivity syndrome (HS) or drug rash with eosinophilia and systemic symptoms are infrequent but serious adverse reactions to medicines, and can result in death or disability1–3. The disorders are not caused solely by drugs. A close link between occupational solvent exposure, mostly trichloroethylene (TCE), and severe generalized skin disorders has been suggested by a series of case reports4–11. Recently, the number of patients suffering from TCE-related severe skin disorders has been increasing in Asia, especially the Philippines, Singapore, Taiwan and Guangdong Province, China10, 12, 13. In Guangdong, the Hospital for Occupational Diseases Control of Guangdong Province treated the first patient with the disorder in 1997, and 201 cases including 13 fatalities had been hospitalized by the end of 2005. Their clinical manifestations were in clear contrast to the irritating contact dermatitis caused by the solvent’s defatting action. Low incidence, a certain
period of exposure before disease onset, generalized rash, fever, lymphadenopathy, liver dysfunction and resulting fatalities, and recurrence just after minimal re-exposure exactly overlap characteristics of skin hypersensitive reactions to drugs.\textsuperscript{10, 14}

TCE is a ubiquitous solvent used worldwide, mostly for degreasing metals, and was in extensive use until the mid-80s, when its possible carcinogenicity for humans became a hotly debated issue after publication of rodent study results\textsuperscript{20}. The reason why the TCE-related skin disorders are growing in number recently in Asia is a mystery, though it could partly be attributable to the rapid industrialization of the area and the resulting increase in the use of TCE and the exposed populations\textsuperscript{10}, especially after the conclusion of the Montreal Protocol to phase out use and production of chlorofluorocarbons and 1,1,1-trichloroethane. To date, however, all publications on the clinical features of the disorders in the English literature have been confined to case reports of a single or a few cases, which have attracted only limited attention among clinicians and researchers worldwide. Factors associated with the disorders remain unknown except for trichloroethylene exposure. The possible involvement of infectious diseases, which can be expected from the analogy between the disorders and drug-induced HS, has never been explored.

In this study, we collected patients suffering from TCE-related generalized skin disorders, and clarified the prevalence of concomitant infection of viruses or bacteria in the cases. This is the first report showing that human herpesvirus 6 (HHV-6), the causative virus of exanthema subitum\textsuperscript{16–18}, the reactivation of which has been reported in the cases. This is the first report showing that human herpesvirus 6 (HHV-6), the causative virus of exanthema subitum\textsuperscript{16–18}, the reactivation of which has been reported in patients with drug-induced HS\textsuperscript{19–24}, can also be reactivated in those having developed skin disorders after occupational solvent exposure.

\textbf{Methods}

\textbf{Subjects}

This study was conducted according to the Declaration of Helsinki. All the subjects (or the responsible relatives in cases of physical incapacity) gave their written informed consent, and the Medical Ethics Committee of the Nagoya University Graduate School of Medicine approved the study protocols.

In principle, the Hospital for Occupational Diseases Control of Guangdong Province identified all patients with TCE-related generalized skin disorders occurring inside the province which has a population of over 79 million. Their skin manifestations were classified according to a diagnostic standard for occupational dermatoses (GBZ18-2002 4.1.5) defined by the Ministry of Health, People’s Republic of China. Between March 2002 and December 2003, 61 patients [22 males and 39 females; 22.8 ± 5.8 (mean ± standard deviation (SD)) years old] were hospitalized for treatment. Of them, all the males and 37 females whose serum was available (22.9 ± 5.9 yr old) were enrolled in the present study (Table 1). Fifty-nine control subjects (26 males and 33 females; 23.3 ± 5.3 yr old) were selected on an age-matched (± 3 yr old) basis among healthy TCE-exposed workers in the 12 factories where the disorders occurred. Sex could not be matched due to the limited number of female workers in these factories. All the patients and controls were Han Chinese.

\textbf{Serological assay}

The patients’ blood was taken on the 21st day of hospitalization, and the controls’ blood on the day of the factory visit. The serum was stored at −80°C until analysis. We measured nonspecific IgE and antibody titers against the following infectious diseases potentially causing rash or hepatitis, or relating to HS or Stevens-Johnson syndrome\textsuperscript{23, 25, 26}: measles, rubella, Mycoplasma pneumoniae, herpes simplex viruses 1 and 2, Epstein-Barr virus, cytomegalovirus, and HHV-6. IgG antibody titers against HHV-6 were measured by an indirect immunofluorescence assay as described previously\textsuperscript{20}. The antibody titer was defined as the reciprocal of the serum dilution showing specific fluorescence. Due to the limitation of serum volume, antibody titers against hepatitis A, B, and C viruses, measured by enzyme immunoassay (ELA), were examined only in the patients along with other routine blood tests. The serological ELAs for measles, rubella, Mycoplasma pneumoniae, herpes simplex viruses 1 and 2, and cytomegalovirus, and the IgE measurement were conducted in the consecutive first 30 cases and corresponding controls, and the ELAs for Epstein-Barr virus were conducted for the last 28 and their controls.

\textbf{Checklist}

Using the structured checklists, the patients (or their families in cases of physical incapacity) were asked during hospitalization about their alcohol consumption, smoking and the following possible risk factors for rash, hepatitis and other infectious diseases: medication(s) received within 2 wk before the appearance of rash, the use of marijuana, use of sanitary chemicals including anthelmintic and cosmetics, drinking of unsanitary water, past history of allergic, immunological or hepatocystic diseases, and family history of TCE-related skin disorders. The controls were asked the same at their factories.

\textbf{Statistical analyses}

The frequencies of possible risk factors including positive virus titers were compared between the cases and controls with the chi-square test. When the expectations in the cells were less than 5, Fisher’s exact probability test was used. Serum IgE concentrations were compared between the cases and the controls with
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Student's t-test. A two-tailed p value less than 0.05 was considered to indicate a statistically significant difference. The Bonferroni adjustment was applied to the p value for defining statistical significance of positive antibody titers against infectious diseases. All values were expressed as mean ± SD. JMP ver. 5.0.1 (SAS Institute Inc.) was used to analyze the data.

Results

Clinical manifestations of cases

More than half of the cases showed exfoliative dermatitis (Table 1, Fig. 1A). The remaining patients showed phenotypes of erythema multiforme spectrum: erythema multiforme minor or major, Stevens-Johnson syndrome and toxic epidermal necrolysis (Table 1, Figs. 1B, 1C and 1D). The typical clinical course started with fever and/or rash occurring on the extremities, face, neck or trunk after commencement of TCE use mostly as a degreasing solvent for 27.1 ± 9.8 days (range 4–53 d), and it showed little difference between phenotypes or sexes (Table 1). Liver dysfunction was the most frequently observed organ reaction other than skin at the time of hospitalization (Table 2), however serological tests for hepatitis A, B, and C viruses ruled out acute hepatitis or its recrudescence (data not shown). Lymphadenopathy was remarkable in 41 patients (69%). C-reactive protein or the erythrocyte sedimentation rate did not increase in most of the 59 cases, which ruled out severe bacterial infection or active autoimmune diseases. Marked eosinophilia (>1,000/ mm³) was observed in 5 patients (9%) out of 57 examined (Table 2). Serum IgE concentrations showed slight but significant (p=0.001) increase compared to controls [212.5 ± 88.0 IU/mL in the cases (n=30) and 137.6 ± 75.6 IU/mL in the controls (n=30)].

Table 1. Analyzed cases suffering from trichloroethylene-related generalized skin disorders (N=59)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
<th>Age (Mean ± SD)</th>
<th>Exposure duration until onset of the first symptoms (days) (range) (Mean ± SD)</th>
<th>Work</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male: Exfoliative dermatitis</td>
<td>15</td>
<td>24.4 ± 5.7</td>
<td>26.0 ± 12.2 (8–53)</td>
<td>Degreasing</td>
<td>14</td>
</tr>
<tr>
<td>EM spectrum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EM</td>
<td>5</td>
<td>22.2 ± 3.8</td>
<td>31.6 ± 8.7 (24–42)</td>
<td>Degreasing</td>
<td>5</td>
</tr>
<tr>
<td>SJS</td>
<td>1</td>
<td>20</td>
<td>8</td>
<td>Degreasing</td>
<td>1</td>
</tr>
<tr>
<td>TEN</td>
<td>1</td>
<td>33</td>
<td>9</td>
<td>Degreasing</td>
<td>1</td>
</tr>
<tr>
<td>(Total)</td>
<td>22</td>
<td>23.8 ± 5.2</td>
<td>25.7 ± 12.3 (8–53)</td>
<td></td>
<td>22</td>
</tr>
<tr>
<td>Female: Exfoliative dermatitis</td>
<td>19</td>
<td>21.4 ± 5.6</td>
<td>27.1 ± 9.3 (4–42)</td>
<td>Degreasing</td>
<td>14</td>
</tr>
<tr>
<td>EM spectrum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EM</td>
<td>12</td>
<td>22.2 ± 6.0</td>
<td>29.3 ± 7.4 (14–41)</td>
<td>Degreasing</td>
<td>10</td>
</tr>
<tr>
<td>SJS</td>
<td>3</td>
<td>24.7 ± 8.3</td>
<td>28.3 ± 6.7 (21–34)</td>
<td>Examining degreased products</td>
<td>1</td>
</tr>
<tr>
<td>TEN</td>
<td>3</td>
<td>26.7 ± 9.7</td>
<td>27.0 ± 6.2 (22–34)</td>
<td>Degreasing</td>
<td>3</td>
</tr>
<tr>
<td>(Total)</td>
<td>37</td>
<td>22.4 ± 6.2</td>
<td>27.9 ± 8.1 (4–42)</td>
<td></td>
<td>37</td>
</tr>
</tbody>
</table>

EM, Erythema multiforme; SJS, Stevens-Johnson syndrome; TEN, Toxic epidermal necrolysis.

Antibody titers relating to rash or hepatitis

We observed marked increases in anti-HHV-6 IgG titer (≥256) in 14 patients out of 57 (25%) but not in the controls. The difference in the frequency of its abnormal increase between the cases and the controls was significant (Tables 2 and 3). Anti-measles IgM titer was positive in 2 of the 30 cases examined but not in the corresponding controls (p=0.49). The serological tests for rubella, Mycoplasma pneumoniae, herpes simplex viruses 1 and 2, Epstein-Barr virus and cytomegalovirus revealed no significant differences between the cases and the controls (Table 3).

Medication, alcohol consumption, smoking, and other possible risk factors for rash or hepatitis

Forty-three cases (73%) did not receive medication...
Fig. 1. Typical skin manifestations of trichloroethylene-related generalized skin disorders. (A) Exfoliative dermatitis (IgG titer to HHV-6 was 1:8). (B) Erythema multiforme (HHV-6 titer <1:8). (C) Stevens-Johnson syndrome (HHV-6 titer >1:256). (D) Toxic epidermal necrolysis (HHV-6 titer 1:16).

Table 2. Clinical manifestations of cases with trichloroethylene-related generalized skin disorders (N=59)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Mucosal lesions</th>
<th>Lymphadenopathy</th>
<th>Eosinophil count*</th>
<th>ASTb (IU/L) (Mean ± SD)</th>
<th>ALTb (IU/L) (Mean ± SD)</th>
<th>C-reactive proteinb (mg/L) (Mean ± SD)</th>
<th>Erythrocyte sedimentation rateb (mm/h) (Mean ± SD)</th>
<th>Medication received before occurrence of rash</th>
<th>HHV-6 IgG titer ≥1:250c</th>
<th>Number of cases showing rash</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>(Mean ± SD)</td>
<td>(Mean ± SD)</td>
<td>(Mean ± SD)</td>
<td>(Mean ± SD)</td>
<td>Yes</td>
</tr>
<tr>
<td>Male: Exfoliative dermatitis</td>
<td>15</td>
<td>7</td>
<td>8</td>
<td>11</td>
<td>4</td>
<td>386 ± 457</td>
<td>262 ± 317</td>
<td>462 ± 390</td>
<td>8.27 ± 7.10</td>
<td>10.1 ± 11.6</td>
</tr>
<tr>
<td>EM spectrum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Mean ± SD)</td>
<td>(Mean ± SD)</td>
<td>(Mean ± SD)</td>
<td>(Mean ± SD)</td>
<td></td>
</tr>
<tr>
<td>EM</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>255 ± 287</td>
<td>229 ± 266</td>
<td>340 ± 289</td>
<td>4.53 ± 3.82</td>
<td>3.4 ± 1.1</td>
</tr>
<tr>
<td>SJS</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>264</td>
<td>21</td>
<td>10</td>
<td>5.09</td>
<td>35</td>
</tr>
<tr>
<td>TEN</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>66</td>
<td>181</td>
<td>210</td>
<td>5.41</td>
<td>18</td>
</tr>
<tr>
<td>(Total)</td>
<td>22</td>
<td>11</td>
<td>11</td>
<td>15</td>
<td>7</td>
<td>331 ± 396</td>
<td>240 ± 289</td>
<td>402 ± 360</td>
<td>7.15 ± 6.27</td>
<td>10.1 ± 11.6</td>
</tr>
<tr>
<td>Female: Exfoliative dermatitis</td>
<td>19</td>
<td>11</td>
<td>8</td>
<td>15</td>
<td>4</td>
<td>343 ± 343</td>
<td>290 ± 328</td>
<td>375 ± 425</td>
<td>6.52 ± 3.39</td>
<td>8.6 ± 6.6</td>
</tr>
<tr>
<td>EM spectrum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Mean ± SD)</td>
<td>(Mean ± SD)</td>
<td>(Mean ± SD)</td>
<td>(Mean ± SD)</td>
<td></td>
</tr>
<tr>
<td>EM</td>
<td>12</td>
<td>2</td>
<td>10</td>
<td>7</td>
<td>5</td>
<td>436 ± 632</td>
<td>146 ± 151</td>
<td>330 ± 333</td>
<td>4.04 ± 2.15</td>
<td>7.1 ± 5.2</td>
</tr>
<tr>
<td>SJS</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>308 ± 192</td>
<td>559 ± 529</td>
<td>548 ± 389</td>
<td>2.85 ± 1.06</td>
<td>10.5 ± 3.5</td>
</tr>
<tr>
<td>TEN</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>779 ± 886</td>
<td>252 ± 205</td>
<td>458 ± 371</td>
<td>4.68 ± 1.30</td>
<td>9.7 ± 4.2</td>
</tr>
<tr>
<td>(Total)</td>
<td>37</td>
<td>18</td>
<td>18</td>
<td>26</td>
<td>11</td>
<td>409 ± 493</td>
<td>262 ± 302</td>
<td>381 ± 380</td>
<td>5.27 ± 3.03</td>
<td>8.3 ± 5.7</td>
</tr>
</tbody>
</table>

EM, Erythema multiforme; SJS, Stevens-Johnson syndrome; TEN, Toxic epidermal necrolysis.

*Eosinophil counts were not available for two female patients with exfoliative dermatitis. #On hospitalization. ≥HHV-6 titer were not determined in one male patient with exfoliative dermatitis, and one female with erythema multiforme due to insufficiency of serum.  The number includes one patient whose HHV-6 titer showed 1:8 at the 3rd wk of hospitalization but >1:256 at the 12th wk.
before the onset of the rash while the remaining 16 (27%)
took medicines for cold, e.g. antipyretics, on account of
fever preceding rash. Although 4 female patients
suffering from erythema multiforme were from the same
factory, their periods on the job did not overlap.

Alcohol consumption, smoking and all the other
investigated possible risk factors did not reveal any
significant differences between the cases and the controls
(data not shown).

Discussion

The present study shows that there are a number of
patients in southern China suffering from idiosyncratic
generalized skin disorders similar to drug-induced
hypersensitivity reactions subsequent to occupational
TCE exposure. Though 27% of the patients had received
some medication before the onset of rash, the medications
were prescribed for the preceding fever, the main first
symptom of the disorders. Other risk factors or agents
possibly causing rash and/or hepatitis were generally not
detected in these patients. In general, the adverse skin
effects of solvents, responsible for as much as 20% of
occupational dermatitis cases, are attributable not to
allergic reaction but to irritation due to a local defatting
action. Thus, we are now attempting to determine the
impurities or stabilizers, which are usually contained in
the commercial TCE, in the solvent used in the patients’
factories. The exact TCE exposure level, i.e. environmental
TCE concentrations and urinary excretion of its metabolites, is also under investigation to establish
the best strategy to prevent the TCE-related generalized
skin disorders.

The main finding of this study is that, of the examined
titers against infectious diseases potentially causing rash
or hepatitis, or relating to HS or Stevens-Johnson
syndrome, only the frequency of HHV-6 reactivation
showed a significant difference between the patients
and the controls. This is the first report illustrating that HHV-
6 can be reactivated in patients with skin disorders that
had developed about 3–5 wk after commencement of
exposure to TCE. Other potential confounders were either
controlled or statistically equalized, though sex was not
matched between the groups. Since the controls worked
on the same factory lines as the patients before the disease
onset, both cases and controls received nearly equivalent
exposures. Thus, the HHV-6 reactivation was associated
with the occurrence of the TCE-related generalized skin
disorders, but maybe not with the level of TCE exposure.

HS, Stevens-Johnson syndrome and toxic epidermal
necrolysis are parts of a spectrum of severe skin reactions
to medicines such as nonsteroidal anti-inflammatory
drugs, antibacterial sulfonamides, anticonvulsants,
antibiotics and allopurinol. Of these reactions,
HHV-6 reactivation in adults has been reported in drug-
induced HS. However, in the present study, anti-
HHV-6 titers increased also in some female patients
suffering from diseases of erythema multiforme spectrum.
Since the diagnostic standard for skin disorders used in
this study was not exactly the same as Roujeau’s
classification, the diagnosis of future patients needs to

Table 3. Serum antibody titers for infectious diseases in patients with trichloroethylene-related
generalized skin disorders and healthy controls

<table>
<thead>
<tr>
<th>Antibodies</th>
<th>Case</th>
<th>Control</th>
<th>p-valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles virus IgM</td>
<td>+</td>
<td>2 (n=30)</td>
<td>0 (n=30)</td>
</tr>
<tr>
<td>Rubella virus IgM</td>
<td>+</td>
<td>0 (n=30)</td>
<td>0 (n=30)</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae IgM</td>
<td>+</td>
<td>0 (n=30)</td>
<td>0 (n=30)</td>
</tr>
<tr>
<td>Herpes simplex virus 1,2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgM</td>
<td>+ or ±</td>
<td>0 (n=30)</td>
<td>0 (n=30)</td>
</tr>
<tr>
<td>IgG</td>
<td>+ or ±</td>
<td>30 (n=30)</td>
<td>30 (n=30)</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG against early antigen</td>
<td>+ or ±</td>
<td>3 (n=28)</td>
<td>4 (n=28)</td>
</tr>
<tr>
<td>IgM against viral capsid antigen (VCA)</td>
<td>+ or ±</td>
<td>1 (n=28)</td>
<td>0 (n=28)</td>
</tr>
<tr>
<td>IgG against VCA</td>
<td>+ or ±</td>
<td>21 (n=28)</td>
<td>18 (n=28)</td>
</tr>
<tr>
<td>IgG against nuclear antigen (EBNA)</td>
<td>+ or ±</td>
<td>26 (n=28)</td>
<td>26 (n=28)</td>
</tr>
<tr>
<td>Primary infectionb</td>
<td></td>
<td>2 (n=28)</td>
<td>1 (n=28)</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgM</td>
<td>+ or ±</td>
<td>0 (n=30)</td>
<td>0 (n=30)</td>
</tr>
<tr>
<td>IgG</td>
<td>+ or ±</td>
<td>30 (n=30)</td>
<td>30 (n=30)</td>
</tr>
<tr>
<td>Human herpesvirus 6 IgG</td>
<td>≥1:256</td>
<td>14 (n=57)c</td>
<td>0 (n=57)</td>
</tr>
</tbody>
</table>

aBefore Bonferroni adjustment. bVCA-IgG (+ or ±) and EBNA-IgG (–). cHHV-6 titers were not determined
in two patients due to insufficiency of serum (see footnotes to Table 2).
be made according to his classification to discuss the involvement of HHV-6 in the development of each type of TCE-related skin disorders.

HHV-6 infects most children between 6 months and 2 yr of age causing exanthema subitum\(^{10}\). The virus remains latent after primary infection and is then reactivated during immunosuppressive conditions such as lymphoproliferative disorders\(^{31}\) and transplantation of bone marrow\(^{32, 33}\), kidney\(^{40}\) or liver\(^{35}\), often in relation to the rash\(^{33}\). In drug-induced HS, IgG titers against HHV-6 rise remarkably between the 3rd and 4th weeks after the onset of clinical manifestations, and active HHV-6 replication precedes the rise in antibody titers\(^{25}\). In our cases, the IgG titer of one patient out of 9 preliminarily measured in the serum obtained at the 12th wk of hospitalization increased markedly, not in serum from the 3rd wk (see footnotes to Table 2), suggesting that the virus reactivation would have occurred more in the present cases. Since the blood sampling on the 21st d was a little too early to detect the reactivation in cases of drug-induced HS\(^{40}\), sequential blood sampling and virological tests different from serological assays will also be required in future study to know the exact timing of the reactivation and the role of HHV-6 in the clinical manifestations. In addition, the effectiveness of treatment with anti-herpesvirus agents must be considered.

As for the other infectious diseases examined, 2 cases showed an increased IgM titer for measles. CD46, a receptor for the measles virus\(^{37, 38}\), is also a cellular receptor for HHV-6\(^{40}\). Thus, these cases might have been susceptible to both HHV-6 and measles virus as reported in simultaneously co-infected cases\(^{40}\).

In conclusion, the present study shows that at least part of the TCE-related generalized skin disorders in China overlap drug-induced HS in terms of HHV-6 reactivation. Solvent exposure histories possibly overlooked under medication histories must also be thoroughly reviewed in patients with drug-induced severe skin disorders.

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