Follow-up assessment of two cases of trichloroethylene hypersensitivity syndrome: A case report

YONG-SHUN HUANG[1], HAN-LIN HUANG[1,2], QI-FENG WU[1], LI-HUA XIA[1], MING HUANG[1], XIN-XIANG QIU[1] and SHAN-YU ZHOU[1]

[1]Department of Occupational Medicine, Guangdong Province Hospital for Occupational Disease Prevention and Treatment, Guangzhou, Guangdong 510300; [2]Department of Scientific Education, Guangdong Women and Children Hospital, Guangzhou, Guangdong 511442, P.R. China

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Abstract. The present study aimed to explore the stability, curability and sequelae of cases of Trichloroethylene (TCE) Hypersensitivity Syndrome (THS), and to investigate the causal allergens of THS. Two cases of THS were followed-up in the current study; both cases were healing following glucocorticoid therapy and were discharged >10 weeks prior to follow-up. A questionnaire investigation, health examination and patch test were performed. Allergens of TCE and its metabolites, including chloral hydrate, trichloroethanol (TCOH) and trichloroacetic acid, were applied in the patch test; 4 controls were included. The two subjects were experiencing itching, pigmentation and xerosis of the skin, and had abnormal results in the ophthalmology Schirmer I test and tear break-up time. The body temperature, liver function, superficial lymph nodes, blood, urine routine and autoimmune antibodies of two subjects were shown to be normal, and no new rashes had appeared. All mass concentration of chloral hydrate and TCOH were positive; 5.0% trichloroacetic acid was weakly positive, 0.5% trichloroacetic acid and all mass concentration of TCE were negative. All patch tests were negative in the 4 control subjects. The results suggest that THS was stable following treatment with glucocorticoid therapy. Dry eye syndrome may continue as a sequelae of THS. The patch test demonstrated that the mechanism underlying THS is delayed-type hypersensitivity induced by TCE. In addition, as the hypersensitivity state in a THS rehabilitee could be sustained over a long period of time, it suggests that the metabolites of TCE, not TCE itself, are responsible for THS. Therefore, patients with THS should avoid contact with TCE and its metabolites, and avoid using hypnotic and anticonvulsive drugs containing chloral hydra as the primary ingredient.

Correspondence to: Dr Han-Lin Huang, Department of Occupational Medicine, Guangdong Province Hospital for Occupational Disease Prevention and Treatment, 68 Haikang Street, Xingangxi Road, Haizhu, Guangzhou, Guangdong 510300, P.R. China
E-mail: huanghanlin_b@163.com

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Introduction

Trichloroethylene (TCE) is a ubiquitous chemical used occupationally for various production and manufacturing purposes; it is widely used in metal, electroplating, electronics and other industries. Since 1990, numerous patients with Trichloroethylene Hypersensitivity Syndrome (THS) were exposed to TCE; this has attracted much attention worldwide (1-3). THS was shown to occur in 1-13% of the TCE-exposed workers (3). In the Chinese prescribed occupational disease list, THS is known as occupational medicamentosa-like dermatitis induced by TCE. Concerns about THS have driven epidemiological and experimental studies investigating TCE exposure and risks associated with THS (1,4-6).

The genetic polymorphism of human leukocyte antigen HLA-B*1301 is strongly associated with THS among exposed workers (4). Although the mechanism underlying TCE toxicity remains the subject of debate, THS is suggested to be a type VI hypersensitivity (5), although types II and III hypersensitivity may also be associated with THS (7). Current treatment strategies for THS include hormonal therapy, administration of γ-globulin, protection of liver and reinforcement of skin care (8,9). THS can also be treated with glucocorticoid therapy, and the primary therapeutic principle is to prescribe an appropriate dosage of glucocorticoids early in the course of the disease, followed by a tapered reduction of the dose (8,9). Despite extensive research, studies are limited with regards to the stability, curability and sequelae of THS. Furthermore, the nature of the causative compound of THS was also questioned by some researchers. Therefore, by completing a follow-up assessment of two patients who had THS, the current study was designed to explore the stability, curability and sequelae of THS, and to investigate the causative compound.

Materials and methods

Subjects. The study protocol was conducted according to the principles of the Declaration of Helsinki and approved by the Medical Ethics Committee of the Guangdong Province

Hospital for Occupational Disease Prevention and Treatment (GDOH; Guangzhou, China). The subjects provided their written informed consent.

In March 2011, 2 male subjects (age, 42 years) with healing THS, who were discharged from the GDOH >10 weeks prior to the commencement of the study, were included. The two cases were diagnosed with THS by three occupational dermatologists of the hospital, based on the Chinese National Diagnostic Criteria of Occupational Disease (GBZ 185-2006; Ministry of Health, China, 2006; appendix A; http://www.moh.gov.cn/cmsresources/zwgkzt/wsbz/new/20080118111726.pdf). Four patients with occupational noise-induced hearing loss, without a history of dermatosis, served as controls for the patch tests.

Questionnaire. The contents of the questionnaire questioned whether the patients suffered from a cold, as well as skin, eye or liver abnormalities. The subjects were questioned on disease, medication and occupational history.

Health examination. The subjects were hospitalized for ~1 week. During the study, the subjects underwent a series of investigations, including the following: Physical examination; ophthalmic examination; electrocardiogram; X-ray; abdominal color ultrasound (liver, kidney and spleen); liver function tests (7080 Automatic Analyzer; Hitachi, Tokyo, Japan) including the analysis of total protein, albumin, total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, gamma glutamyl transferase, total bile acids, aspartate aminotransferase (AST) and alanine aminotransferase (ALT); routine blood tests (XT-1800i hematology analyzer; Sysmex Corp., Kobe, Japan); routine urinary tests (Mejer-600; Shenzhen Mejer Medical Science and Technology Co., Ltd., Shenzhen, China); autoimmune disease indicators including anti-nuclear antibody (ANA), anti-DNA antibodies and anti-double-stranded DNA (dsDNA); Schirmer I test (SIT) and tear break-up time (BUT) test. These examinations were performed on three occasions.

Patch test. TCE (purity, ≥99.5%; Sigma-Aldrich, St. Louis, MO, USA), chloral hydra (CH; purity ≥99.5%; Honeywell Specialty Chemicals Seelze GmbH, Seelze, Germany) and trichloroethanol (TCOH; purity ≥98.0%; Sigma-Aldrich) were added to olive oil (Sigma-Aldrich), and trichloroacetic acid (TCA; purity ≥99.5%; Tianjin Chemical Reagent Second Factory, Tianjin, China) was added to saline to prepare various concentrations of allergens. According to previous trial tests (10-14), TCE (50, 25, 10 and 5% in olive oil), chloral hydrate (15, 10 and 5% in olive oil), TCOH (5, 0.5 and 0.05% in olive oil) and TCA (5 and 0.5% in saline) were used in the patch test. Olive oil and normal saline served as controls. The allergen at the highest concentration was selected as the allergen in the control group, since it would induce the highest positive rate in the patch test.

The patch test method and interpretation followed the International Contact Dermatitis Research Group (ICDRG) criteria (15). Briefly, the patch test was performed as follows: Each well of the patch test apparatus (Finn chamber; Beijing Baiyi Yida Science and Technology Development Ltd., Beijing, China) was filled with 25 μl allergen, olive oil or saline, and the apparatus was numbered and patched to the back of the subjects. The edge of the apparatus was reinforced by 3 M micropore permeable medical tape (Minnesota Mining and Manufacturing Medical Equipment Co., Ltd., Shanghai, China). The subjects did not disturb the patch test for 48 h; showering was forbidden during the test. The patches were removed after 48 h. Observations and images were recorded by two occupational dermatologists of GDOH 0.5 h, 24 h and 48 h following the removal of the patch test. The results were observed, recorded and filed according to the ICDRG criteria by two professional dermatologists.

The 2 cases with THS and the 4 control subjects did not receive treatment with corticosteroids and other immunosuppressive drugs, or anti-infection drugs for 2 weeks prior to the patch test.

Results

Case one. The patient was exposed to TCE whilst working in a hardware products factory between August and September 2010. His duties included the cleaning of wax with organic solvents (90.857% TCE). The airborne concentrations of the time-weighted average in the working place of the subject ranged between 123.38 and 171.82 mg/m^3. The onset of THS occurred in September 2010, and the patient was transferred to the GDOH after 12 days. On admission, the body temperature of the patient was 39.8˚C. Physical examination revealed erythematous lesions over the whole body (Fig. 1). Dark erythematous lesions were present over the trunk, and the majority of the rash was confluent and resembled erythroderma. Scattered desquamated skin was also evident, the palms and soles were pigmented and hard to the touch, while the nature of the rash was similar to exfoliative dermatitis. Additionally, there was lymphadenectasis and tenderness of the submandibular, supraclavicular, inguinal and submental lymph nodes. The patient had conjunctival congestion, scleral icterus and itching of the eyes. The levels of ALT were 300 U/l (normal range, <40 U/l), those of AST were 133 U/l (normal range, <40 U/l) and the concentration of TCA in the urine was 14.10 mg/l. Methylprednisolone (500 mg/day; Pfizer Manufacturing, Puurs, Belgium) was administrated intravenously, and the patient also received diammonium glycyrrhizinate (Chia Tai Tianqing Pharmaceutical Group Co., Ltd., Lianyungang, China) for the protection of the liver and stomach. On day 3 after admission, the patient's body temperature returned to normal with no further spread of the rash and liver function test results were improved. Therefore, the methylprednisolone dose was reduced to 450 mg/day, and after 9 days of continued improvement, the dose was tapered to 300 mg/day and then progressively reduced by 50-150 mg/day. The total duration and dosage of methylprednisolone treatment was 81 days and 12,028 mg, respectively. When the skin recovered, the body temperature and liver function test results returned to normal, and the patient was discharged in January 2011. The patient returned for a follow-up assessment in March 2011.

Case two. The second subject had an employment history that was similar to the first case. In September 2010, a widespread pruritic rash appeared on the patient's legs and he was transferred to GDOH for further assessment 9 days after the appearance of the rash. On admission, the body temperature of the patient was 36.8˚C. Physical examination revealed dark erythematous skin

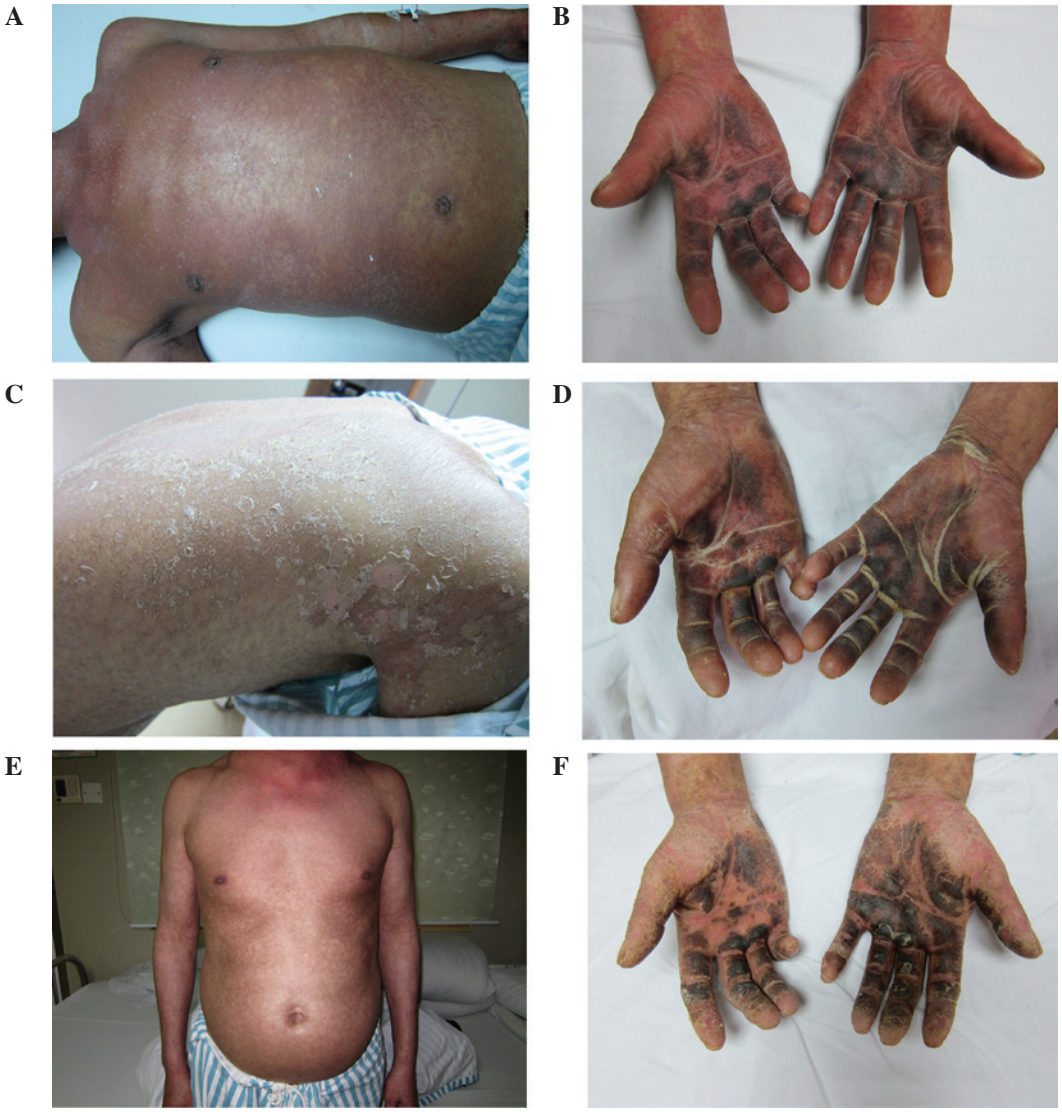

Figure 1. Case one. (A and B) The skin lesions of patient one when hospitalized at the acute stage. Dark erythematous lesions are present over the trunk. The majority of the rash was confluent and resembled erythroderma. Scattered desquamated skin was also evident. The palms and soles were pigmented and were hard to the touch. The nature of the rash was similar to exfoliative dermatitis. (C and D) The progressive stage; following treatment, the rash gradually disappeared although a large area of desquamated skin remained. The palms and soles exhibited increased pigmentation and became harder. (E and F) The healing stage; the skin disorder had recovered although pigmentation remained over the whole body. Skin was peeling on the back, palms and soles, with evidence of new skin formation.

lesions over the majority of the body (Fig. 2). The palms, fingers, soles and toes were swollen and tender, and the nature of the rash was similar to exfoliative dermatitis. Lymphadenectasis and tenderness was present in the submandibular, throat, axillary and inguinal lymph nodes. The levels of ALT were 343 U/l and those of AST were 153 U/l, and the concentration of TCA in the urine was 43.34 mg/l. Methylprednisolone (300 mg/day) was administrated intravenously, and the patient also received diammonium glycyrrhizinate for protection of the liver and stomach. On day 3 after admission, the results of liver function tests were improved. There was no further spread of the rash and the patient's temperature normalized. On the day 4, the methylprednisolone dose was reduced to 250 mg/day; the patient's condition continued to improve and the dose was tapered progressively. The total duration and dosage of methylprednisolone administration was 64 days and 5,237 mg, respectively. When the skin recovered, the body temperature and liver function returned to normal, and the patient was discharged in December 2010. The patient returned for a follow-up assessment in March 2011.

Follow-up assessment

Survey findings. Skin itching and xerosis were the primary complaints of both patients; no other symptoms were reported.

Health examination findings. The body temperature of both patients was normal. Skin examination revealed that spread pigmentation, but no new rashes or lymphadenectasis were apparent. The abdominal color ultrasound (liver, kidney and spleen), electrocardiogram and X-ray did not detect any abnormal changes. The blood tests, urinary test and liver function test were normal. Autoimmune disease indicators including ANA, anti-DNA antibodies and dsDNA were negative. The SIT results for patient one were as follows: Right eye 8.0 mm/5 min and left eye 18.0 mm/5 min; the SIT results for patient two were as follows: Right eye 2.0 mm/5 min and left eye 5.0 mm/5 min. A normal result is <10 mm/5 min. The BUT

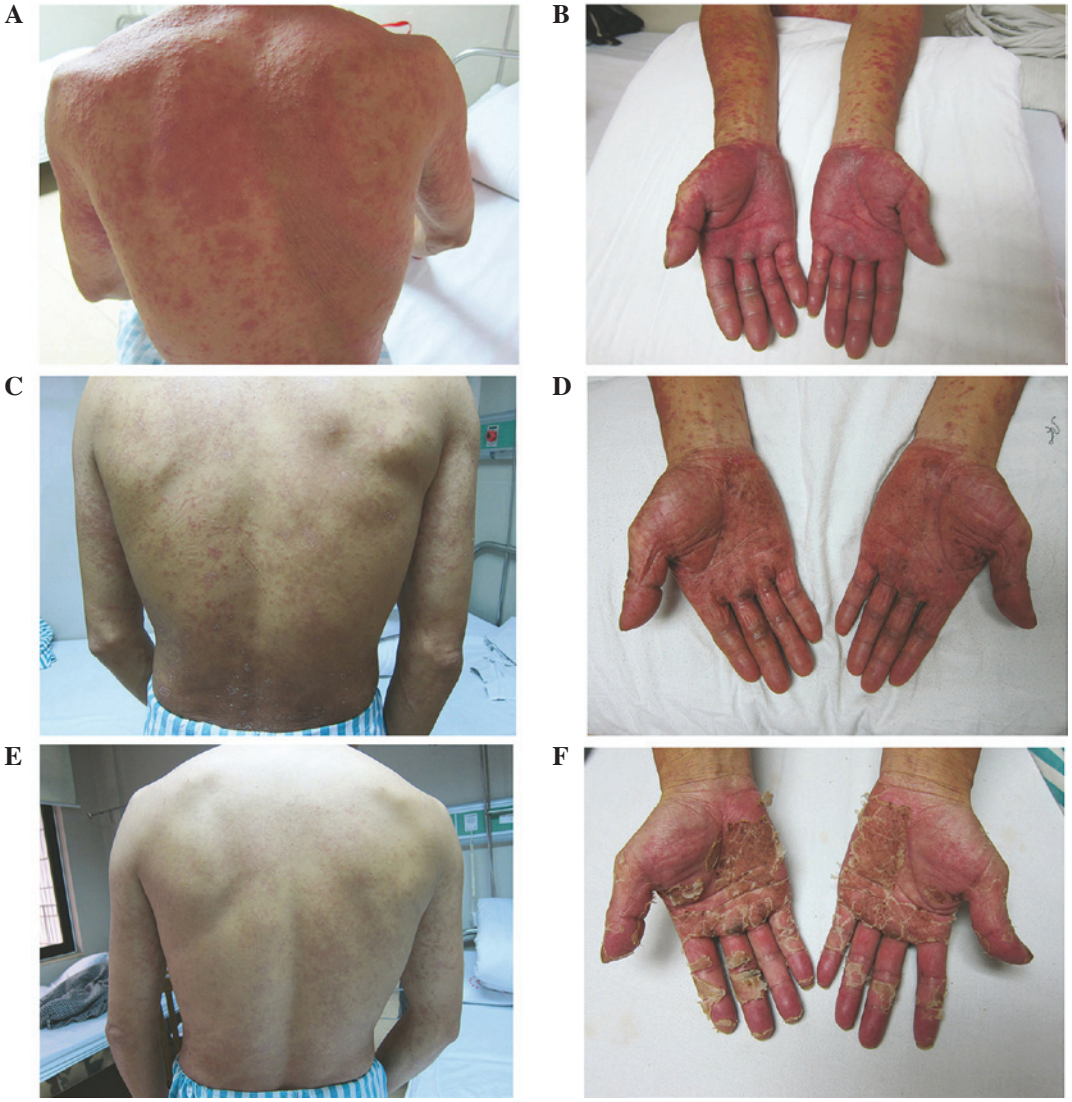

Figure 2. Case two. (A and B) The skin lesions of patient two when hospitalized at the acute stage. Dark erythematous lesions were widespread with confluent areas. The palms, fingers, soles and toes were swollen and tender. The nature of the rash was similar to exfoliative dermatitis. (C and D) The progressive stage; following treatment, the rash gradually disappeared while desquamated skin remained on some areas of the body. Skin swelling resolved and scattered pigmentation remained on the palms. (E and F) The healing stage; the skin disorder recovered although pigmentation remained over the whole body. Increased skin thickness and swelling changed to skin desquamation, with evidence of new skin formation.

results for patient one were as follows: Right eye 4.0 sec and left eye 5.0 sec; the BUT results for patient two were as follows: Right eye 3.0 sec and left eye 4.0 sec. A normal result is >10 sec.

Patch test results. No adverse reactions were observed during the patch test. Patches of skin with olive oil, saline and adhesive paste did not show abnormal changes such as reddening of the skin and swelling. The patch tests were positive for all mass concentrations of CH and TCOH, were weakly positive for 5.0% TCA, and were negative for 0.5% TCA and all mass concentrations of TCE. The four control patches also returned negative results. The results are presented in Table I and Fig. 3.

Discussion

In the present study, THS was caused in both patients by exposure to TCE without any previous history. To the best of our knowledge, this is the first study to describe the simultaneous THS onset in two patients that were exposed to the same work environment (same factory), and to perform follow-up assessment in THS cases. The patients presented predominantly with symptoms of skin involvement, as well as fever, lymphadenectasis and liver dysfunction (2,3,16,17). The primary therapeutic principle was to prescribe an appropriate dosage of glucocorticoid early in the course of the disease, followed by a tapered dose reduction. However, it is important to protect the liver and stomach from adverse effects during the treatment of THS (9). In the present study, the symptoms of the patients markedly improved when glucocorticoid therapy was administered. Following the discharge of patients one and two for 11 and 15 weeks, respectively, health examinations demonstrated that both patients were healthy. However, skin examination revealed pigmentation, itching and xerosis, but no new rash. These results suggested that the curative effect of glucocorticoid therapy is stable and that patients do not relapse following healing.

SIT and BUT are critical dry eye tests (18). The SIT and BUT results were abnormal in both patients, suggesting that dry eye syndrome may be a sequelae for THS. It has previously

Table I. Patch test results for TCE and its metabolites.

Patch test no.	Chemical and concentration	Reactions at 48 h		Reactions at 72 h	
		Case one	Case two	Case one	Case two
1	Control (NS)	-	-	-	-
2	Control (OO)	-	-	-	-
3	TCA 5% in NS	+	+	+	+
4	TCA 0.5% in NS	-	-	-	-
5	TCOH 5% in NS	++	++	++	++
6	TCOH 0.5% in NS	++	++	++	++
7	TCOH 0.05% in NS	++	++	++	++
8	CH 15% in NS	++	++	++	++
9	CH 10% in NS	++	++	++	++
10	CH 5% in NS	++	++	++	++
11	TCE 50% in OO	-	-	-	-
12	TCE 25% in OO	-	-	-	-
13	TCE 10% in OO	-	-	-	-
14	TCE 5% in OO	-	-	-	-

TCA, TCOH, CH, TCE had a purity of >99%. OO, olive oil; NS, normal saline; TCA, trichloroacetic acid; TCOH, trichloroethanol; CH, chloral hydra; TCE, trichloroethylene.

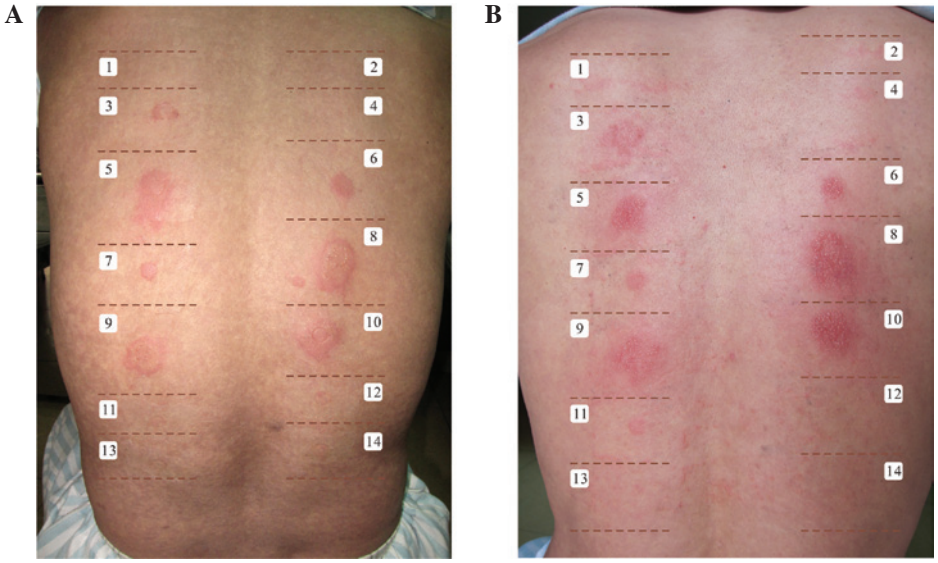

Figure 3. Patch testing results in (A) case one and (B) case two, of the chemicals mentioned in Table I. Positive reactions were observed for trichloroethanol (5, 0.5 and 0.05% in normal saline), chloral hydrate (15, 10 and 5% in normal saline) and trichloroacetic acid (5% in normal saline) in both cases. However, trichlorethanol and trichloroacetic acid (0.5% in normal saline) were negative.

been reported that Stevens-Johnson syndrome results in a lack of lacrimal gland secretion, resulting in various severe ocular surface disorders manifesting dry eye (19,20). Considering that the clinical manifestations and mechanism underlying THS resemble those of Stevens-Johnson syndrome, dry eye syndrome may be one of the primary sequelae of THS; this requires further study.

TCE is predominantly metabolized by cytochrome P450 (10). Two active metabolic compounds of TCE are chloral and CH; these metabolites have similar biological properties as the former metabolite hydrates rapidly to CH. CH is easily reduced to TCOH (a reversible reaction) and then to TCA (21). A patch test is now considered to be a recognized method for confirming an allergic contact dermatitis diagnosis and distinguishing the causal allergen(s), as well as identifying a type IV (cell delayed) hypersensitivity reaction (22-24). In the present study, the patch test was positive for CH, TCOH and TCA, but negative for all mass concentrations of TCE, in both patients, results which were consistent with those of previous investigations (11-14,16,25). This suggested that the causal allergens for THS were metabolites of TCE, not TCE itself; it can be hypothesized that the mechanism underlying

THS is cell delayed-type hypersensitivity induced by TCE exposure.

It has been reported that THS patients may relapse following re-exposure to TCE (8). The patch test was positive for CH, TCOH and TCA following healing for >10 weeks, illustrating that the hypersensitivity state in patients who had THS may be sustainable over a long period of time. Therefore, in order to avoid a relapse, patients who previously had THS should be advised to avoid re-exposing themselves to TCE and its metabolites. However, as the study period was short in the follow-up assessment in the present study, the sustainable period of hypersensitivity state remains unclear.

In conclusion, the follow-up assessment in the current study suggested that THS does not recur following healing, and that the curative effect of glucocorticoid therapy is stable; however, the results suggested that dry eye syndrome may continue as sequelae for THS. The mechanism underlying THS may be cell delayed-type hypersensitivity induced by TCE exposure; the fact that the hypersensitivity state in patients with THS remained over a long period of time indicates that the causal allergens for THS were the metabolites of TCE. Therefore, it can be suggested that patients who previously had THS do not re-expose themselves to TCE and its metabolites, and avoid receiving antipyretic, hypnotic or anticonvulsive medicines in which CH is a primary ingredient. Due to the sample and follow-up period limitations in the present study, further studies are required to verify these conclusions.

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