

ORIGINAL ARTICLE

The clinical severity score of chronic actinic dermatitis correlates with *in vivo* photoallergic reactions and the immunologic parameters related to a shift towards Th2 immunity from the Th2/Th1 balanced status in patients with chronic actinic dermatitis

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SUMMARY**Background**

Chronic actinic dermatitis (CAD) has a more complicated pathogenetic basis than others. The clinical grading system and its correlations with the clinical and immunological parameters still remained to be investigated to define the nature of CAD in a more detailed manner.

Objectives

We investigated correlations of the clinical severity score of CAD (CSS-CAD) with the clinical and immunological parameters.

Methods

We evaluated 72 patients with CAD and classified them into three groups according to the CSS-CAD. We analysed total IgE level, peripheral blood (PB) eosinophil count, the ratio of Th2cell (CCR4 + CD4 +) percentage over Th1 cell (CXCR3 + CD4 +) percentage (Th2/Th1) and/or the sum of suppressor/cytotoxic T cells.

Results

The total IgE levels and the percentage of PB eosinophils were higher in the severer group than other groups. A shift towards Th2 from Th2/Th1 balanced status may be affected by total counts of suppressor T cells, and the patient with higher Th2/Th1 ratio than balanced status had the more proportion in the severer CSS-CAD group than other groups.

Conclusion

The CSS-CAD correlates with total IgE level, PB eosinophil count and a shift towards Th2 immunity from Th2/Th1. So we suggest the Th1/Th2 dysbalance may be affected by the CSS-CAD.

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INTRODUCTION

Chronic actinic dermatitis (CAD) is an uncommon eczematous photosensitive disorder by which elderly men are more often affected, and its disease spectra range from the mildest photosensitive eczema to the severest actinic reticuloid and even to the exanthematous variant of polymorphic light eruption (PLE) (1, 2). It is characterized by an abnormal broad-spectrum photosensitivity in the UVB and/or UVA spectra and even in the visible light range (2).

CAD had been regarded as a contact dermatitis-like reaction based on the facts that allergic contact dermatitis to various allergens was common and that most of the patients with CAD improved with appropriate avoidance of sunlight and allergen (1). Now, the spectra of CAD have been widened because it may affect normal skin but mostly arise in those with pre-existing dermatoses such as allergic contact dermatitis and atopic dermatitis and HIV infection and photodermatoses such as photoallergic contact dermatitis, drug or chemical systemic photosensitivity, even long-standing PLE (3).

Among the pathogenetic factors, the contact allergy is the most frequent component of the syndrome (2–4). And the persistence of photoallergens in the skin might contribute to it as so-called persistent light reactor state in the pathogenesis of CAD (5, 6), but on the other hand, it was proposed that few PLE patients exhibited UV-induced immune tolerance to topical-specific allergen and thus the diminished propensity might be the salient feature of PLE in terms of pathogenesis (7).

And so, we cannot always claim these states as reasonable interpretations because UV-induced type I regulatory T cells suppress Th2-type immune responses after immunization via secretion of IL-10 (8). Taken together, the exact mechanism of CAD is remained to be elucidated in clinical and immunopathogenetic aspects.

We suppose the multiplicity of photoallergens and/or allergens may be uniquely implicated in the pathogenesis and clinical severity in patients with CAD whereas the immune tolerance is usually observed in other chronic photosensitivity disorders. So, in consideration to the inflammatory nature of CAD, we planned to investigate in a more detailed manner the correlations between the clinical severity score and the clinical and immunological parameters in this study as a further work than the previous report (9).

MATERIALS AND METHODS

Seventy-two patients with CAD were enrolled at the Department of Dermatology in Dong-A University

Hospital between 2008 and 2013. The patients satisfied the following criteria; clinically, a patient who frequently showed an eczematoid skin lesion on sun-exposed areas, rarely extending into sun-protected areas, and lasting for longer than 3 months, photobiologically, a patient whose minimal erythemogenic doses (MEDs)-UVB or -UVA after phototestings were measured below a certain value ($\text{MED-UVB} \leq 80 \text{ mJ/cm}^2$, $\text{MED-UVA} \leq 10 \text{ J/cm}^2$), and histologically, a patient who showed a finding of intraepidermal spongiosis and perivascular lymphocytic infiltration and basophilic degeneration in the dermis or a pseudolymphomatous finding in the skin biopsy.

We performed phototestings to certain action spectra of UV radiations (broad-spectrum UVB and broad-spectrum UVA) and visible light (VL) to establish the presence of photosensitivity. We stopped the uses of any immunosuppressive agents, irrespective of topical and systemic, ideally for 2 weeks before phototesting. Phototesting was carried out on to the sun-protected skin areas, with F85/100W (Waldmann, Villingen-Schwenningen, Germany) as the UVA source and TL 20W/12RS (Philips, Roosendaal, the Netherlands) as the UVB source. Visible light (VL) was irradiated from a Kodak projector (Eastman Kodak Co., New York, NY, USA) 25 cm apart from the tested skin site. Eight or 10 round holes of 1 cm in diameter were engraved at 1 cm away to each other on a UV opaque aluminium tape and were closed by plaster after each hole was exposed to the wanted dose for UV testings, or four pieces of transiently sticking plasters were attached serially for VL testing, at different time points of 5, 15, 30 and 45 min by the desired doses. We determined MED sat 24 h after UVB ($10\text{--}200 \text{ mJ/cm}^2$) or UVA ($1\text{--}25 \text{ J/cm}^2$) irradiations, respectively, and erythema responses were read immediately at each VL dose.

Photopatch testing was performed if the history and physical findings were disclosed or suggested to be related to the development of cutaneous lesions by photoallergen or sun exposure. We applied duplicated sets of the Scandinavian photopatch test allergen series (Chemotechnique, Malmö, Sweden) onto the mid-back while covered by an UV opaque material. One panel was uncovered 24 h later and irradiated a dose of 1/2 MED-UVA. Photopatch testing results were evaluated at 48 h (R2) and at 96 h (R4). Positive reactions were recorded in a similar manner to the ICDRG scoring system also with photography (10).

To find any associated contact hypersensitivity, patch testing was accomplished with the commonly detectable contact allergens. Twenty-two allergens in a European standard patch test allergen series (Chemotechnique,

Malmö, Sweden) were applied onto the back skin in aluminium chambers on Scanpor tape. A first reading at 48 h (D2) or at 72 h (D3) was taken after the removal of patches and the next reading at 96 h (D4) or at 120 h (D5). Positive responses were recorded according to the International Contact Dermatitis Research Group (ICDRG) scoring system, and the patch testing sites were photographed.

We assessed various clinical parameters including sex, age, skin phototypes, duration of disease before treatment, and treatment duration which was defined as the duration from the diagnosis time to the resolution of photosensitivity.

Seventy-two patients were evaluated for the clinical signs and symptoms of CAD and classified into mild, moderate, or severe groups according to the clinical severity scores of CAD (CSS-CAD) we designed by following out the system of the PLE-severity assessment score (PLE-SAS)(9, 11). The scoring system is based on the intensity of four clinical signs and the extent of involvement of those signs in the skin. Firstly, the extent of skin involvement was calculated at each anatomical site (face, upper chest, dorsa of the hands and scalp), and gradings were determined for the percentage of body surface area involved at each location (%BSA), and then, the affected area at each location was given a score from 0 to 5 (0, 0%; 1, 1–20%; 2, 21–40%; 3, 41–60%; 4, 61–80%; and 5, 81–100%) based on the % BSA of clinical signs. Next, the intensity of 4 clinical signs (erythema, vesiculation, excoriation and lichenification) was graded as followed: 0, no skin changes; 1, mild degree; 2, moderate degree; and 3, severe degree. Lastly, the % BSA was multiplied by the intensity grade of clinical signs, resulting in the total sum ranged 0–240 points. As a result, each patient was classified into mild (score 0–80), moderate (score 81–160) or severe (score 161–240) group, respectively (Figs 1a,b).

Total IgE levels and percentages of peripheral blood eosinophils were obtained in blood samples from 72 patients with CAD. One-way analysis of variance was performed on the following parameters: CSS-CAD, total IgE level and eosinophil percentage. Each parameter was compared with the others using statistical program, SPSS version 17.0 (SPSS Inc., Chicago, IL, USA), to determine any significant covariance. Th1 cells (CXCR3 + CD4 +), Th2 cells (CCR4 + CD4 +), and Tc cells (suppressor/cytotoxic T cell, the sum of CXCR3 + CD8 + Tc1 cell and CCR4 + CD8 + Tc2 cells) were measured in the peripheral blood of 72 patients with CAD using flow cytometry. We also analysed any correlations of the CSS-CAD with the ratio of Th2 cell (CCR4 + CD4 +)

percentage over Th1 cell (CXCR3 + CD4 +) percentage (Th2/Th1) and/or the sum of suppressor/cytotoxic T cells from CXCR3 + CD8 + Tc1 cell percentage & CCR4 + CD8 + Tc2 cell percentage (Tc = Tc1 + Tc2).

RESULTS

According to the CSS-CAD, 72 patients were divided into three groups; 25 patients in the mild group, 26 patients in the moderate group and 21 patients in the severe group. Sixty-six of 72 patients (91.6%) showed UVB photosensitivity overall; a combined photosensitivity of UVB and UVA in 43 patients (59.7%), and UVB photosensitivity alone in 23 patients (31.9%); only four patients (5.5%) showed UVA photosensitivity alone. Eight patients (11%) showed broad-spectrum photosensitivity throughout UVB, UVA and VL (Fig. 2). Most patients (90.5%, 19 of 21 patients) in the severe group showed a broad-spectrum photosensitivity; meanwhile, a smaller proportion of patients in the mild and moderate groups exhibited a combined photosensitivity of UVB and UVA (46.2%, 12 of 26 patients in the moderate group; 20.0%, five of 25 patients in the mild group, respectively).

We could find a significant difference in the number (multiplicity) of detected photoallergens among the divided groups. However, in the number (multiplicity) of contact allergens, there was merely as light difference among them. In photopatch test reactions, the severe group showed more multiplicity of photoallergens than the mild group or moderate group. In severe group, 47.6% of patients had three or more photoallergen whereas 30.8% in the moderate group, 16.0% in the mild group, respectively ($P = 0.019$, Fig. 3). The severe group patients had a propensity for more multiplicity to contact allergens than the mild and moderate groups. In the severe group, 36.4% of patients had three contact allergens or more, and 24.0% and 15.4% in the mild and moderate groups, respectively ($P = 0.409$, Fig. 4). Most frequently detected photoallergens were balsam of Peru (33/72, 45.8%), promethazine HCl (17/72, 23.6%) and perfume mix (11/72, 15.3%). Among them, some patients showed combined contact and photoallergies to balsam of Peru and perfume mix. Most frequently detected contact allergens were balsam of Peru (25/72, 34.7%), Nickel (20/72, 27.8%) and Perfume mix (13/72, 18.1%).

In disease duration, we found a noticeable difference among the mild (3.785 ± 3.217), moderate (4.014 ± 4.055) and severe (4.728 ± 5.510) groups ($P = 0.04$).

Lastly, the longer treatment duration was needed or it would take the longer duration from the diagnosis time to the resolution of photosensitivity, as the higher CSS-CAD was ($P = 0.035$).

The total IgE levels were measured at higher values in 35 of the 72 patients with CAD (48.6%) (normal range <200 IU/ml) and well correlated with the CSS-CAD. Patients in the severe CAD group ($n = 21$) had higher values in total IgE levels (405.3 ± 329.5) than those in the moderate group ($n = 26$, 286.0 ± 272.5) or those in the mild group ($n = 25$, 168.6 ± 135.3) ($P = 0.002$).

Higher eosinophil counts were measured in 50 (69.4%) of 72 patients (normal range $<4.0\%$ of WBC), and a significant correlation was observed between the percentage of peripheral blood eosinophils and the CSS-CAD; the severe group ($n = 21$) had higher levels of eosinophilia (7.79 ± 6.58) than those of the moderate group ($n = 26$, 6.52 ± 3.08) or the mild group ($n = 25$, 4.54 ± 2.48) ($P = 0.038$).

We compared a ratio of Th2 cell (CCR4 + CD4 +) percentage over (CXCR3 + CD4 +) Th1 cell percentage (Th2/Th1) in 72 patients with CAD according to the

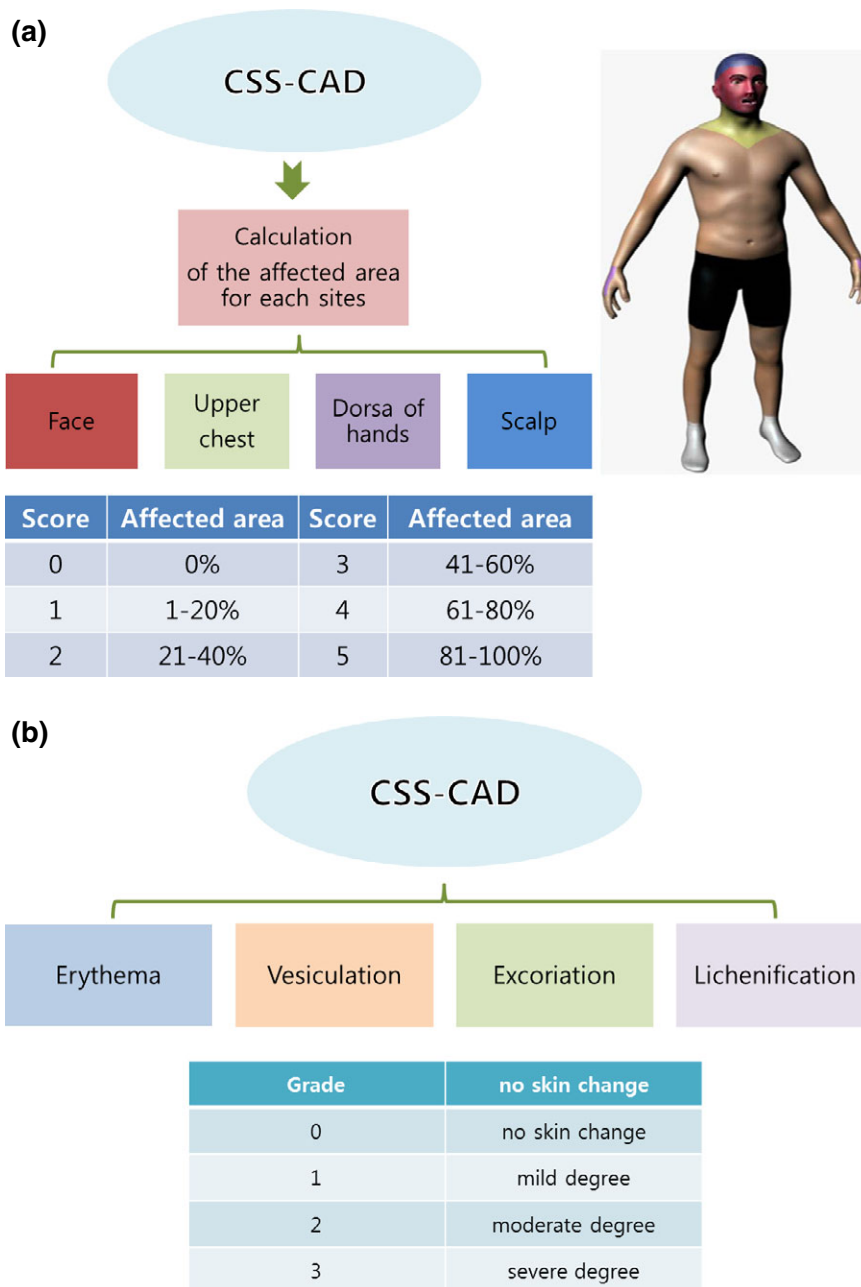


Fig. 1. Evaluation of clinical severity score of CAD (CSS-CAD).

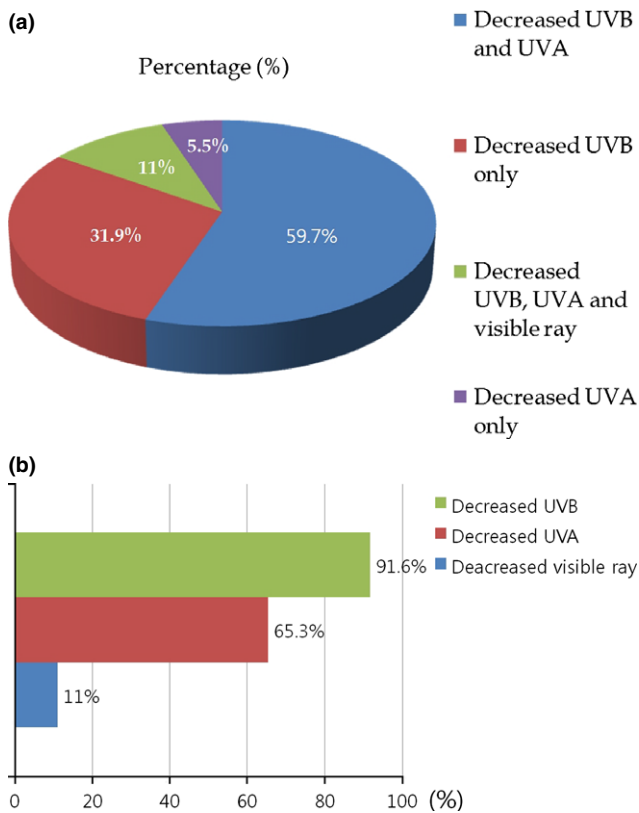


Fig. 2. Results of phototests. Proportion of the patient showing decreased MED according to each wavelength

CSS-CAD. All patients (100.0%) in the severe group showed a higher Th2/Th1 ratio, compared to that of the Th2/Th1 balanced status in normal control group (Th2/Th1 ratio 0.63 ± 0.27 , $n = 20$), and all patients in the moderate group (100.0%), compared to the mild group (92.0%) showed another higher ratio, too (Fig. 5). We could not find the significant correlation between Tc cell (%) and Th2/Th1 ratio among each group of patient with CAD (data not shown). But a shift towards Th2 from the Th2/Th1 balanced status may be affected by the sum of suppressor/cytotoxic T cells ($T_c = T_{c1} + T_{c2}$) as the CSS-CAD increases.

DISCUSSION

CAD has many clinical and laboratory characteristics which are suggestive of an immunological disorder. Clinically, it appears an allergic contact dermatitis-like reaction or pseudolymphomatous eruption with chronic persistent pruritic lichenified patches/plaques on sun-exposed areas (1, 2). Although some etiological conditions such as phototoxicity, photoallergy and PLE are proposed, CAD is not as exactly known to date as far as

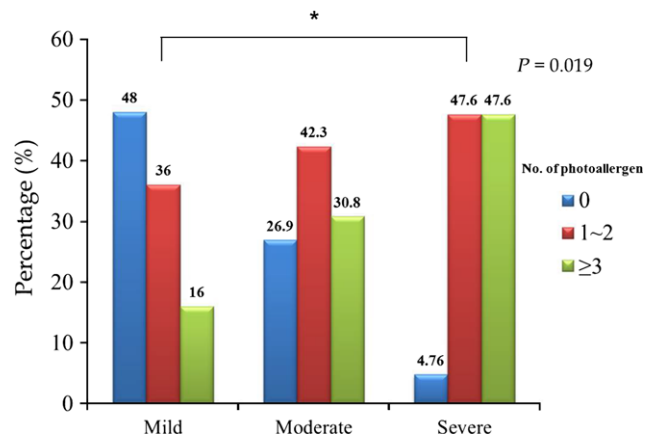


Fig. 3. Multiplicity of photoallergens. *, $P < 0.05$.

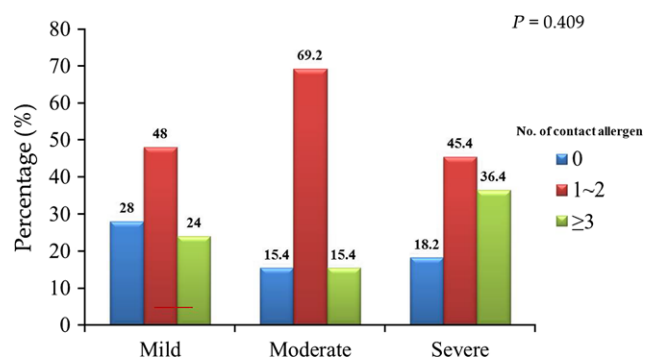
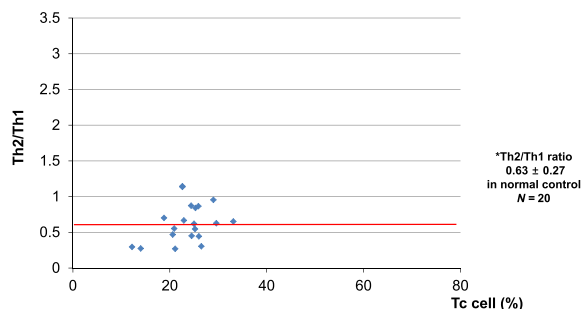
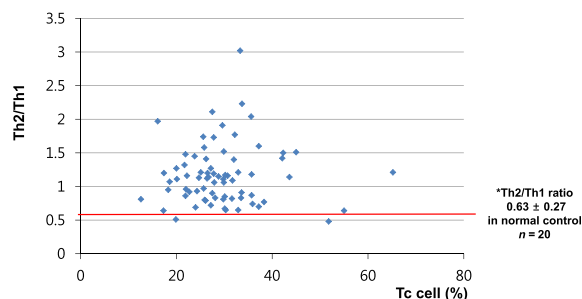
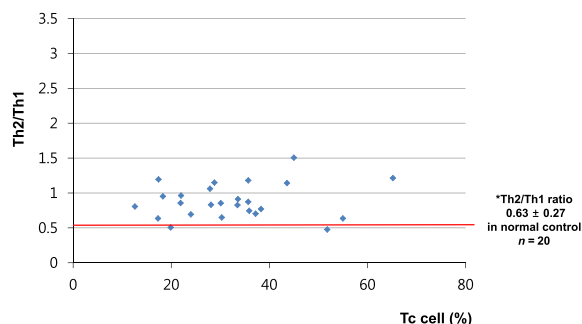
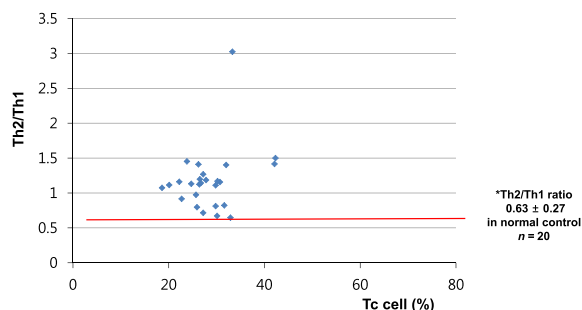
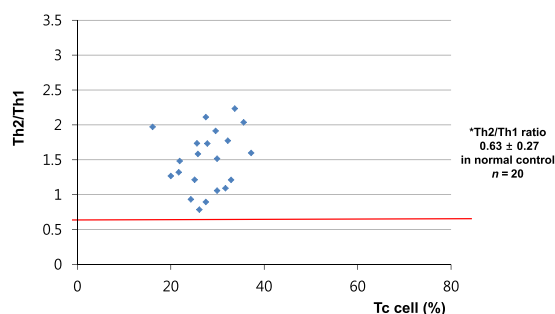


Fig. 4. Multiplicity of contact allergens.

the pathogenesis is concerned. But, a delayed-type hypersensitivity to a UV-induced autoantigen or a contact allergy to exogenous allergens may be involved in its pathogenesis (1, 3, 12).

A number of immune-regulatory factors are produced in the skin in response to UV, including platelet-activating factor, histamine, serotonin, PGE2 and cytokines including IL-10, IL-6 and TNF- α (13, 14). However, the cells and inflammatory mediators involved in the initial step towards immune suppression and tolerance are still unknown.

Photoimmunosuppression serves as a physiologic role as an adaptive response of the skin to UV-induced modifications of proteins and an immunologic response to so-called neoantigen, and consequently leading to chronic inflammation (15). UVB-induced CD3⁺, CD4⁺ and CD8⁻ regulatory T (UV-induced Ts) cells mediate their suppressive effects by releasing the immune-regulatory cytokines, IL-4 and IL-10 (16). And UV irradiation suppresses the antigen presentation to Th1 cells but enhance that to Th2 cells, experimentally (17). And so, UVB-induced immunosuppression can be explained by a shift into the Th2 immunity.

(a) Th2/Th1 ratio by Tc cell (%) in normal control**(b) Th2/Th1 ratio by Tc cell (%) in CAD patient (overall, $n = 72$ in tot.)****(c) Th2/Th1 ratio by Tc cell (%) in CAD patient (mild group, $n = 25$)****(d) Th2/Th1 ratio by Tc cell (%) in CAD patient (moderate group, $n = 26$)****(e) Th2/Th1 ratio by Tc cell (%) in CAD patient (severe group, $n = 21$)****Fig. 5.** Th 2 shift by Tc count. (a) normal control group, (b) overall group, (c) mild group, (d) moderate group, (e) severe group

Our study showed a tendency of shift into Th2 immunity from the Th1/Th2 balanced status was the more apparent and might be affected by suppressor T cells counts as the CSS-CAD was worsened; 100.0% of the Th2 shift responders are affected by suppressor T cells in the severe and moderate groups, compared to 92.0% in the mild group. And total IgE and the percentage of peripheral blood eosinophils were significantly correlated with the CSS-CAD, too. So, we need to explain why Th2 shift develops under the CAD condition. Moreover, it is needed to clarify the correlation of hyper-IgE-aemia or eosinophilia with the CSS-CAD, in aspect of the classic concept of Th2 immunity.

Nevertheless, some evidences have been recently discovered that UV radiation drives host into Th2 immunity through various mechanisms in addition to the known immune-regulatory factors. Firstly, IL-33 could be involved in allergic skin conditions (contact hypersensitivity or drug allergy), Th2-mediated inflammatory skin diseases (atopic dermatitis, autoimmune bullous diseases), and skin malignancies, and even in UV immunosuppression. IL-33, an IL-1 family member other than 'classical' ones, with its receptor ST2 produces Th-2-associated cytokines and/or their mRNAs and leads to blood eosinophilia and increased IgE (18). After UV radiation in the dermis, mast cells accumulate

rapidly and migrate to the B-cell follicles within draining lymph nodes, and then, IL-33 appears to attract mast cells and neutrophils into the dermis. Therefore, UVB-induced IL-33 production may act similarly as an early danger signal 'alarmin' in response to trauma and infection (19). Secondly, thymic stromal lymphopoietin (TSLP) is another candidate to explain Th2 shift under the influence of UV radiation. TSLP may have a key role in the initiation and maintenance of allergic inflammatory diseases, including atopic dermatitis (20). The UVB radiation could upregulate TSLP expression in a hypoxia-inducible factor-1 α (HIF-1 α)-dependent manner in human keratinocytes and a human skin equivalent model, and stimulate dendritic cells to produce Th2-attracting chemokine ligand (CCL17), resulting in T helper 2 polarization (21). Thirdly, a switch of expression pattern from type 1 to type 2 cytokines was observed in dermal T cells from psoriatic lesional skin as well as in those from normal skin, because less IFN- γ and more IL-4 were expressed after a single UVB irradiation in human skin experiments (22, 23).

Furthermore, we need to relate our results with this phenomenon of Th2 shift in respect that many clinical factors are correlated with the CSS-CAD in our series, in fact.

By the fact that patients in the severe CSS-CAD group have a tendency for the more multiplicity of photoallergens in a significant manner rather than contact allergens (Figs 3 and 4), we think that CAD is not simply an enhanced state of delayed-type hypersensitivity in skin immune system, but other factors than contact allergens may contribute to a photosensitivity in the patients with CAD (1).

And by the fact that the CSS-CAD correlated significantly with the peripheral blood eosinophilia or total Ig-

E level, we can explain that patients with CAD show a Th2 polarization as the CSS-CAD becomes severer as in most of allergic diseases, where some correlations existed between tissue eosinophilia and disease severity (24). The chronic UV photosensitivity would be in favour of an accelerated IgE overproduction and the eosinophilia from the circuit of UV-sensitized mast cells – dendritic cells – Th0 cells/Th2 cells – plasma cells in series of the patients with CAD (25).

In the patients with CAD, UV-induced immunosuppression is diminished although the exact mechanism had not yet been proven. In this study, the increased multiplicity of photoallergens in photopatch test results may be related to photoaugmentation rather than photosuppression in the patient with CAD. To explain how 'so-called' the reduced UV-induced immunosuppression can occur in the patients with CAD, photoaugmentation may occur in the UVA-irradiated set of photopatch series in some patients, as a result of an additive effects of subclinical UV-induced erythema to subclinical irritancy or contact allergy, instead of a photosuppression of contact allergy or irritancy can occur (26).

In summary, we investigated in this study a correlation between CAD and Th2 response. From our study results about the correlations between the CSS-CAD and various parameters in clinical and immunological items, we proved a shift towards Th2 immunity from the Th2/Th1 balanced status as the higher CSS-CAD were. We suggest Th1/Th2 dysbalance may be affected by 'suppressor T cells (Tc)' and may affect the CSS-CAD and vice versa.

In future, further study would be conducted about the exact mechanism that Th2 immunity work in the generation of CAD.

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