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Relationship Between Squamous Cell Carcinoma Antigen and the Clinical Severity of Allergic Rhinitis Caused by *Dermatophagoides farinae* and Japanese Cedar Pollen

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Objectives: Allergic rhinitis is known to be related to the Th2-type immune response, but no sensitive biomarker of severity yet exists. Serum squamous cell carcinoma antigen (SCCA) is clinically used as a popular tumor biomarker. We have demonstrated that SCCA is related to allergic diseases such as asthma. The purpose of the present study was to clarify the relationship between allergic rhinitis and SCCA, which had not yet been investigated.

Methods: We compared the serum SCCA levels in patients with allergic rhinitis due to Japanese cedar pollen and *Dermatophagoides farinae* with those in normal subjects. Thereafter, the correlations between the clinical severity of allergic rhinitis and the serum levels of SCCA were investigated. Furthermore, the influence of 8 variables (serum levels of SCCA, immunoglobulin E, eosinophil cationic protein, and eosinophils; age; gender; oral administration of antiallergic or antihistaminic agents; and use of nasal drops) in regard to the severity of allergic rhinitis was studied by a multiple regression analysis.

Results: The SCCA levels of the *D farinae* group were statistically higher than those of the control group, and they correlated with the severity of rhinitis. Among the 8 variables, only the SCCA level was found to be a predictive factor of severity on a multiple regression analysis. No relationship between SCCA level and Japanese cedar pollen allergy was demonstrated.

Conclusions: These results suggest that the serum SCCA level may be a useful biomarker to evaluate the severity of allergic rhinitis caused by *D farinae*.

Key Words: house dust mite, perennial allergic rhinitis, pollen, seasonal allergic rhinitis, severity, squamous cell carcinoma antigen.

INTRODUCTION

Allergic rhinitis is known to be related to the T helper 2 (Th2)-type immune response, but there is presently no sensitive clinical biomarker available reflecting its severity. Squamous cell carcinoma antigen (SCCA) was purified from cervical squamous cell carcinoma cells¹ and developed into a tumor biomarker. The antigen is also present and expressed in the normal epithelium. The elevation of SCCA has been reported in several benign lesions, including lung and skin diseases. It has therefore become evident that SCCA is related to type I allergy, such as asthma² and allergic dermatitis, and that it also correlates with its severity.^{3,4} The present study was aimed at clarifying the correlation between SCCA and allergic rhinitis by evaluating the serum SCCA levels in patients with allergic rhinitis, in reference to the severity of the disease, and examining the dif-

ference in causative allergens (Japanese cedar pollen versus *Dermatophagoides farinae*, which is the major antigen in house dust mites and thus causes perennial allergic rhinitis in Japan).

METHODS

Patients. This study included 134 adult patients with allergic rhinitis due to Japanese cedar pollens and/or *D farinae*. All patients completely satisfied the following conditions: 1) a well-documented history of typical allergic rhinitis; 2) Japanese cedar pollen-specific immunoglobulin (Ig) E and/or *D farinae*-specific IgE in sera, greater than the lower limit of detection and quantitatively detectable; and 3) no history of malignant diseases.

The patients were divided into 3 groups: 1) a pollen group (46 patients) with Japanese cedar pollen allergy only; 2) a *D farinae* group (26 patients) with

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TABLE 1. CHARACTERISTICS OF GROUPS

Group	Total	Asthma		Smoker		Age >40 y	
		No.	%	No.	%	No.	%
Control	60	3	5.0	9	1.50	34	56.7
Pollen allergy	46	4	8.7	6	1.30	26	56.5
<i>D farinae</i> allergy	26	6	23.1	9	34.6	10	38.5
Pollen and <i>D farinae</i> allergy	62	9	14.5	17	27.4	20	32.3
Total	194	22	11.3	41	21.1	90	46.4

D farinae allergy only; and 3) a pollen and *D farinae* group (62 patients) with both allergies.

As controls, 60 healthy adult volunteers (control group) were chosen according to the following criteria: 1) no history of allergic rhinitis diagnosed at a medical institution; 2) negative serum IgE antibodies specific to the major allergens in Japan, namely, *D farinae* and Japanese cedar pollen; 3) no history of dermatosis such as psoriasis or atopic dermatitis; and 4) no history of malignant diseases.

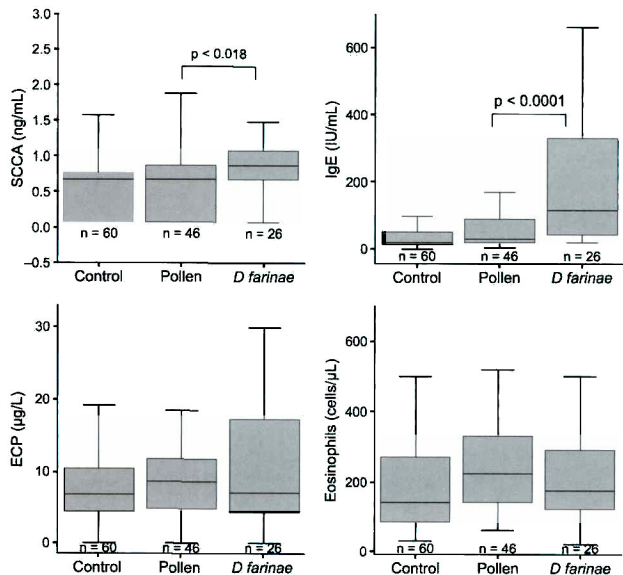
All subjects lived in Saga Prefecture, and included 126 women and 68 men (age range, 18 to 82 years). None of the subjects had skin disease. The asthma prevalence, smoking history, and ages of each group are shown in Table 1.

Study Design. The period for pollination of Japa-

nese cedar in 2005 was from the third week of February to the fourth week of April. Peripheral blood was collected at Saga University during that cedar pollen season (first week of March 2005). The serum SCCA levels were measured with a commercially available double-antibody radioimmunoassay (SRL Inc, Tokyo, Japan). The levels of IgE, serum-specific IgE (Japanese cedar pollen or *D farinae*), eosinophil cationic protein (ECP), and eosinophils were measured at the same time. The severity of nasal symptoms in daily life, which were defined according to the Practical Guidelines for the Management of Allergic Rhinitis in Japan, was divided into 5 grades through the use of a questionnaire. Age (under 40 years of age or over 40 years of age), gender, oral administration of antiallergic agents or antihistaminic agents, use of nasal drops, history of asthma, and smoking were examined as background factors.

The median levels of SCCA, IgE, ECP, and eosinophils of the nasal allergy groups (pollen group and *D farinae* group) were each compared with those of the control group. We investigated the correlation rate between the severity of nasal symptoms and the median levels of SCCA, IgE, ECP, and eosinophils in the pollen group and the *D farinae* group. The Mann-Whitney U test or Pearson correlation coeffi-

Fig 1. Serum levels of squamous cell carcinoma antigen (SCCA), immunoglobulin E (IgE), eosinophil cationic protein (ECP), and eosinophils of allergic rhinitis groups (pollen group, *Dermatophagoides farinae* group) compared with those of control group. Data are presented as ranges, interquartile ranges (boxes), and medians (horizontal lines in boxes). Median level of SCCA in *D farinae* group was significantly higher than that of control group.



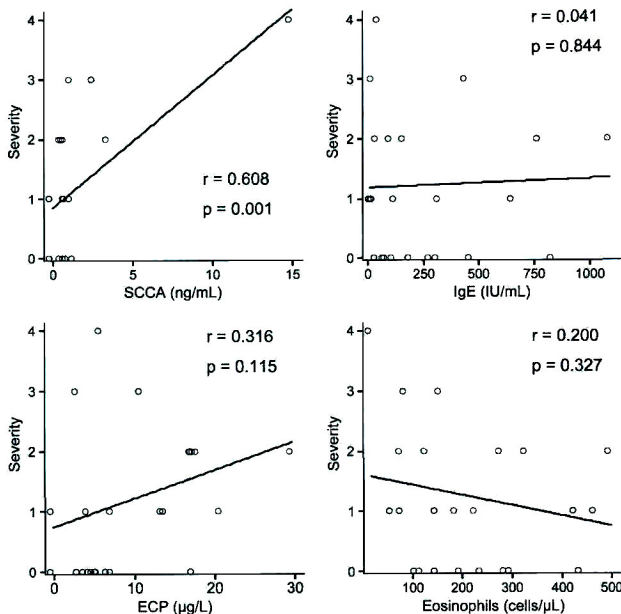


Fig 2. Correlations between severity of allergic rhinitis in *D farinae* allergy group and SCCA, IgE, ECP, and eosinophils. SCCA levels were observed to correlate with severity ($r = 0.608$; $p = 0.001$).

cient was applied for each set of data. Furthermore, to predict independent factors for severity, we performed a multiple regression analysis in each antigen group. Variables that were significant in these analyses — ie, SCCA, IgE, ECP, eosinophils, age, gender, oral administration of antiallergic agents or antihistaminic agents, use of nasal drops, history of asthma, and smoking — were included as explanatory variables. A statistical analysis was performed with SPSS software (version 11.0J for Windows, SPSS Japan Inc, Tokyo). A p value of less than 0.05 was considered significant. Informed consent was obtained from all subjects, and this study was approved by our Institutional Review Board. The design of this study followed the principles outlined in the Declaration of Helsinki.⁵

RESULTS

Comparison of Median Levels of SCCA, IgE, ECP, and Eosinophils in Allergic Rhinitis Groups With Those in Control Group. The median levels of SCCA, IgE, ECP, and eosinophils of the allergic rhinitis groups (pollen group and *D farinae* group) were each compared with those of the control group (Fig 1).

The median level of SCCA in the *D farinae* group

was 0.80 ng/mL, showing a significantly higher value than the 0.60 ng/mL in the control group ($p < 0.018$). It was 0.6 ng/mL in the pollen group, which was not significantly different from the level in the control group ($p = 0.724$). The median level of IgE in the *D farinae* group was 115.0 IU/mL — a significantly higher value than the 21.0 IU/mL in the control group ($p < 0.0001$). It was 30.5 IU/mL in the pollen group, and thus not significantly different from the level in the control group ($p = 0.194$). The median levels of ECP in the *D farinae* group and the pollen group showed no significant difference from that in the control group. The median number of eosinophils per microliter in the pollen group was 225 — a significantly higher value than the 140 in the control group ($p = 0.012$). It was 175 in the *D farinae* group, ie, higher than in the control group, but the difference was not significant ($p = 0.271$).

Correlation Between Severity of Nasal Symptoms and Levels of SCCA, IgE, ECP, and Eosinophils. We investigated the correlation rate between the severity of nasal symptoms and the levels of SCCA, IgE, ECP, and eosinophils in each antigen group (Figs 2 and 3). The levels of IgE, ECP, and eosinophils did not show any correlation with severity in any group.

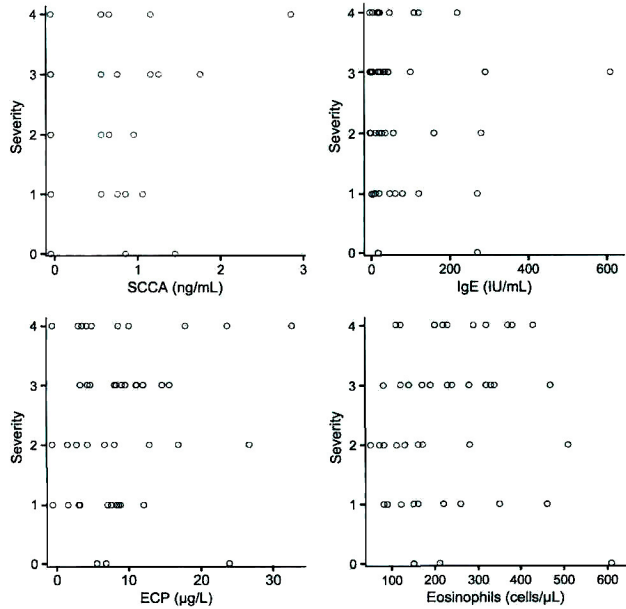


Fig 3. Correlations between severity of allergic rhinitis in pollen allergy group and SCCA, IgE, ECP, and eosinophils. SCCA levels did not correlate with severity ($r = 0.134$).

The SCCA levels were observed to correlate with the severity in the *D farinae* group ($r = 0.608$; $p = 0.001$; Fig 2), but they did not correlate with the severity in the pollen group ($r = 0.134$; Fig 3).

Multiple Regression Analysis of Predictive Factors for Severity. In a multiple regression analysis, we found that only SCCA ($p = 0.017$) was a predictive factor for severity in the *D farinae* group (Table 2). In addition, use of an oral antiallergic or antihistaminic agent ($p < 0.001$) alone was determined to be predictive factor for severity in the pollen group.

DISCUSSION

As indicated previously, SCCA production is induced by interleukin (IL)-4 and IL-13 in human

bronchial epithelial cells and keratinocytes.^{2,6} It has also become evident that SCCA is related to type I allergies such as asthma and allergic dermatitis, and that it also correlates with the disease severity.^{3,4} Allergic rhinitis is also a type I allergy disease; therefore, we consider that a common mechanism in the Th2-type immune response may be the reason why a significant increase in the serum SCCA level was thus observed.

In the pollen group, however, even though there were significantly more severe cases than in the *D farinae* group, the serum SCCA level did not increase, and no correlation with severity was observed. We therefore considered 2 potential reasons for these phenomena.

The first is the difference in the duration of expo-

TABLE 2. SEVERITY ACCORDING TO VARIABLES

Group	SCCA	IgE	ECP	Eosinophils	Age	Gender	Medication	Nasal Drops	Asthma	Smoking
Control	0.924	0.720	0.718	0.906	0.648	0.530	0.395	None	0.968	0.613
Pollen allergy	0.210	0.913	0.666	0.934	0.493	0.913	<0.001	0.696	0.863	0.640
<i>D farinae</i> allergy	0.017	0.856	0.062	0.228	0.628	0.494	0.590	0.533	0.758	0.683

Data are p values.

SCCA — squamous cell carcinoma antigen; IgE — immunoglobulin E; ECP — eosinophil cationic protein; Medication — oral administration of antiallergic agents or antihistaminic agents; None — no subjects used nasal drops.

sure to the antigen. In the pollen group, the duration of exposure to the antigen was limited to a certain season, but the *D farinae* group is continuously being exposed to antigen stimuli throughout the year, and this phenomenon may have affected the results.

Second, the cedar pollen antigen may have a lower capacity to induce a Th2-type immune response than does the mite antigen. In other words, the mite antigen may have a greater capacity to induce a Th2-type immune response. For example, Ishii et al⁷ reported that the production of IL-4 from peripheral mononuclear cells after stimulation with mite antigen was significantly higher in house dust mite-allergic rhinitis patients than in a normal group. In that report, IL-4 in the culture supernatants was determined by enzyme-linked immunosorbent assay. In contrast, in another report, IL-4 was not detected by similar methods in patients with allergic rhinitis caused by Japanese cedar pollen.⁸ However, in the same experiment, when reverse transcription-polymerase chain reaction was used to detect IL-4 messenger RNA, the IL-4 gene expression was found to be significantly elevated.⁸ We consider that in patients with allergic rhinitis caused by cedar pollen, the expression of IL-4 was the same as in patients with allergic rhinitis caused by mites, but it was speculated that such an expression was only observed when a reverse transcription-polymerase chain reaction method with a high degree of detectability was used, because there was little quantity of IL-4. This therefore means that the capacity of inducing a Th2-type immune response is lower in patients with seasonal allergic rhinitis due to Japanese cedar pollen.

Serum SCCA levels have been reported to be in-

creased in Japanese patients with asthma or atopic dermatitis. House dust mites are the major causative antigens in pediatric asthma and pediatric atopic dermatitis. Therefore, it is suggested that the serum SCCA levels might increase in patients with allergic disorders caused by house dust mites.

Presently, no sensitive clinical biomarker is available reflecting the severity of allergic rhinitis. As reported previously, eosinophils in nasal smears^{6,9} and serum allergen-specific IgE^{6,10} were correlated with the severity of allergic rhinitis. However, the former assay is not often performed in general practice, and the utility of the latter in the assessment of the severity of allergic rhinitis is controversial.^{10,11} In this study, multiple regression analysis found a correlation between SCCA and the severity of allergic rhinitis due to *D farinae*. Screening for SCCA levels requires an extra cost; however, this cost is not very great. Because the method of measurement of serum SCCA is simple and easy, we consider that it may become a useful biomarker reflecting the severity of allergic rhinitis due to *D farinae*.

CONCLUSIONS

In the present study, the patients with perennial allergic rhinitis due to *D farinae* were found to have higher serum SCCA levels than did normal subjects, thereby showing a correlation with the severity of allergic rhinitis. Furthermore, in a multiple regression analysis, only SCCA was found to be a predictive factor for the severity of allergic rhinitis. These results suggest that SCCA is therefore a useful biomarker for evaluating the severity of allergic rhinitis due to house dust mites.

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