

Short communication

Amount of pollen has an effect on the systemic and local levels of soluble ICAM-1 in patients with seasonal allergic rhinitis

Kato M, Hattori T, Ikeda R, Yamamoto J, Yamashita T, Yanagita N, Nakashima I. Amount of pollen has an effect on the systemic and local levels of soluble ICAM-1 in patients with seasonal allergic rhinitis. *Allergy* 1996; 51: 128–132. © Munksgaard 1996.

We investigated whether the amount of antigen has an effect on the systemic and local levels of soluble ICAM-1 (sICAM-1) in patients with pollinosis, and assessed its biologic significance. The levels of subjective symptoms and sICAM-1 in sera and nasal epithelial lining fluids (ELF) from 14 subjects with pollinosis (allergic group) and eight healthy subjects (control group) were measured from pre- to postseason in 1993 (total pollen count: 10 854/cm²) and 1994 (total pollen count: 415/cm²), and the results were compared with each other among the four groups. The levels of subjective symptoms and sICAM-1 in ELF from the allergic group significantly increased during the season in both 1993 and 1994. However, there was a significant difference ($P < 0.01$) between the levels of those in 1993 and those in 1994 during the season. The levels of sICAM-1 in sera from the allergic group were significantly upregulated during the seasons and postseasons only in 1993, and there was a significant difference ($P < 0.05$) between the levels in 1993 and those in 1994 during the postseason. We conclude that amount of pollen has an influence on the local and systemic levels of sICAM-1, as well as the scores of subjective symptoms, in patients with seasonal allergic rhinitis.

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Key words: amount of allergen; natural allergen;
seasonal allergic rhinitis; soluble intercellular
adhesion molecule-1.

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Accepted for publication 19 October 1995

Mediators derived from eosinophils are believed to have an effect on allergic diseases (1–4). However, it is not well understood how eosinophils and other inflammatory cells are recruited to tissues in these diseases. Recently, it was reported that leukocyte-endothelial cell interaction is an early step in the cascade of events leading to cellular extravasation and development of the inflammatory response (5). Intercellular adhesion molecule-1 (ICAM-1) is involved in adhesion of leukocytes through LFA-1 and Mac-1, which are members of the β_2 family of integrins (6, 7). The soluble form of this adhesion molecule is present in human serum, and is assumed to have biologic actions (8–10). The soluble ICAM-1 (sICAM-1) levels in sera obtained from atopic asthmatic patients were higher than those from normal control subjects (11, 12). This suggested that sICAM-1 may contribute to the pathogenesis of allergic disease. However, the precise biologic function of sICAM-1 remains unclear.

In this study, we have measured the levels of sICAM-1 in sera and epithelial lining fluid (ELF) from subjects with seasonal allergic rhinitis and normal subjects throughout the pre- to postpollen seasons in both 1993, which had high pollen counts, and 1994, which had low pollen counts. From these data, we analyze the correlation between systemic and local levels of sICAM-1 and amount of antigen, and discuss the biologic significance of sICAM-1 in the pathogenesis of allergic rhinitis.

Material and methods

Pollen counts

The Aichi Prefecture Department of Health reported the airborne Japanese cedar pollen counts for 1993 (total: 10 854/cm²) and 1994 (total: 415/cm²) of Nagoya, Japan (Fig. 1; B5, C5).

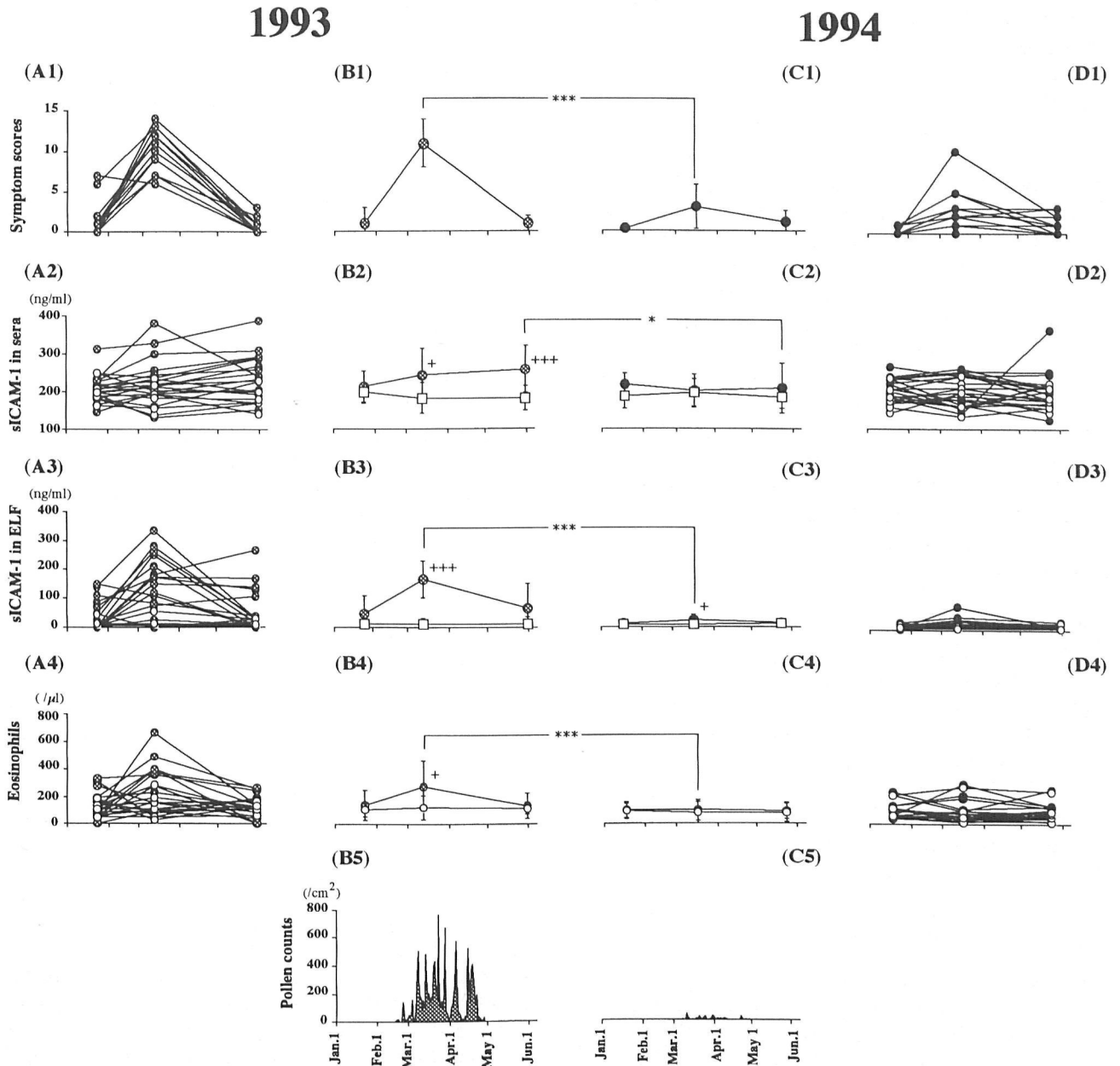


Fig. 1. Levels of total subjective symptom scores, sICAM-1 in sera and nasal epithelial lining fluids (ELF), and blood eosinophil counts and pollen counts in 1993 and 1994. Panels A1–4 and D1–4: patient-by-patient levels of total subjective symptom scores, sICAM-1 in sera and ELF, and blood eosinophil counts from control group (□) and allergic group (● 1993, ● 1994). Panels B1–4 and C1–4: mean $\pm$ standard deviation levels of subjective symptom scores, sICAM-1 in sera and ELF, and blood eosinophil counts from control group (□) and allergic group (● 1993, ● 1994). Panels B5 and C5 show Japanese cedar pollen counts in city of Nagoya during periods 1 January – 10 June 1993 (B5) and 1994 (C5). Values marked + ($P < 0.05$) and +++ ($P < 0.01$) represent significant difference between control group and allergic group. Values marked * ($P < 0.05$) and *** ($P < 0.01$) represent significant difference between allergic group in 1993 (●) and allergic group in 1994 (●).

Study design

The allergic group (1993: $n = 14$, mean age = 36 years; 1994: $n = 14$; mean age = 37 years) consisted of patients who had histories of only Japanese cedar pollen-induced rhinitis. They all showed single sensitization to Japanese cedar pollen by several kinds

of radioallergosorbent test (RAST). They had no other organic manifestations of their allergic disease during the study. There was little difference between members of the allergic group in 1993 and those in 1994, and no statistical difference in the levels of subjective symptom scores, sICAM-1 in sera and ELF, and blood eosinophil counts between these

two groups during the preseason. The control group (1993: $n=8$, mean age = 36 years; 1994: $n=8$; mean age = 35 years) consisted of volunteers who had no history of allergic or nasal disease. There was also little difference between members of the control group in 1993 and those in 1994. No drugs were permitted for the allergic and control groups during the study, including a period of 3 weeks before the study. Scores of subjective symptoms, the level of sICAM-1 in sera and nasal lavage fluids, and blood eosinophil counts were examined during the preseason (25 January 1993 [pollen count: $0/\text{cm}^2$] and 19 January 1994 [pollen count: $0/\text{cm}^2$]), season (12 March 1993 [pollen count: $97/\text{cm}^2$] and 16 March 1994 [pollen count: $3/\text{cm}^2$]), and postseason (2 June 1993 [pollen count: $0/\text{cm}^2$] and 25 May 1994 [pollen count: $0/\text{cm}^2$]), in all groups, and were compared with each other among the four groups. Kaulbach et al. have reported that the plasma, interstitial, glandular, and ELF urea concentrations are invariable, whether or not allergic rhinitis was induced by challenge test (13). Therefore, we used urea as a reliable marker for correction of the parameters measured in nasal lavage fluid. The levels of sICAM-1 in nasal lavage fluids were compared after those were multiplied by the dilution factor ($[\text{urea}]_{\text{serum}}(\text{mg/dl})/[\text{urea}]_{\text{nasal}}(\text{mg/dl})$) and revised to the levels in ELF. Collections of nasal lavage were performed by the technique described by Kato et al. (9). The scores of subjective symptoms (full mark: 15 points) were estimated by the method described by Kato et al. (9).

Analytic assays

sICAM-1 in sera and ELF was measured by the sICAM-1 ELISA kit (Bender MedSystems, Austria; lower limits of detection: 0.625 ng/ml), according to the manufacturer's instructions. We did not need to concentrate nasal lavage fluids for detection of sICAM-1. Urea in sera and nasal lavage fluids was measured with the Merck Auto UN Kit (Kanto Chemical Co., Inc., Tokyo, Japan) by the method of Hallett & Cook (14). The blood eosinophil count was done with an automated hematology analyzer NE-8000 (Sysmex TOA Medical Electronics Co., Ltd, Kobe, Japan).

Statistical analysis

For individual subjects, all parameters during the preseason, season, and postseason were analyzed with the Wilcoxon matched-pairs signed-ranks test

(intragroup analysis). Analysis of all parameters during the preseason, season, and postseason among the 1993 allergic group and the 1993 control group in 1993 and 1994 was done with the Mann-Whitney U test (intergroup analysis).

Results

Intergroup analysis between the allergic group and the control group

The patient-by-patient (A1–4, D1–4) and mean $\pm$ standard deviation (B1–4, C1–4) data in the levels of total subjective symptom scores, sICAM-1 in sera and ELF, and blood eosinophil counts during the pre- to postseason in 1993 and 1994 are shown in Fig. 1. There was no statistical difference between the allergic group and the control group in the levels of sICAM-1 in sera and ELF and blood eosinophil counts during the preseason in 1993 and 1994 (B2–4, C2–4). The levels of sICAM-1 in sera during the season ($P<0.05$) and postseason ($P<0.01$) and sICAM-1 in ELF ($P<0.01$) and blood eosinophil counts ($P<0.05$) during the season in the allergic group were significantly higher than those from the control group in 1993 (B2–4). However, only the levels of sICAM-1 in ELF during the season ($P<0.05$) in the allergic group were significantly higher than those in the control group in 1994 (C2–4).

Intergroup analysis between 1993 and 1994 in the allergic group

The levels of subjective symptoms ($P<0.01$), sICAM-1 in ELF ($P<0.01$), and blood eosinophil counts ($P<0.01$) during the season and sICAM-1 in sera ($P<0.05$) during the postseason in the allergic group in 1993 were significantly higher than those in the allergic group in 1994 (B1–4, C1–4). In fact, the levels of subjective symptom scores during the season in 1993 were 3.7 times higher than those in 1994. The levels of sICAM-1 in sera during the postseason in 1993 were 1.2 times higher than those in 1994. The levels of sICAM-1 in ELF during the season in 1993 were about seven times higher than those in 1994. The levels of blood eosinophil counts during the season in 1993 were about 2.8 times higher than those in 1994.

Intragroup analysis in the allergic group and the control group

The levels of subjective symptoms and sICAM-1 in ELF during the season were significantly higher than those during the preseason in the allergic group in 1993 (symptom: $P<0.01$; sICAM-1: $P<0.05$)

and 1994 (symptom: $P < 0.01$; sICAM-1: $P < 0.02$). The levels of sICAM-1 in sera during the season ($P < 0.05$) and postseason ($P < 0.01$) and blood eosinophil counts during the season ($P < 0.05$) were significantly higher than those in sera during the pre-season in the allergic group in 1993, whereas there was no statistical difference among the levels of sICAM-1 in sera and blood eosinophil counts throughout the pre- to postseason in the allergic group in 1994. There was no statistical difference among the levels of subjective symptom scores, sICAM-1 in sera and ELF, and blood eosinophil counts throughout the pre- to postseason in the control group in 1993 and 1994.

Discussion

Recently, we reported that the sICAM-1 levels in sera from patients with seasonal allergic rhinitis were upregulated during the season and postseason in 1993, which had high pollen counts (9). Since then, we have found that these levels were not upregulated during the same periods in 1994, which had low pollen counts. In addition, there was a statistical difference between those in 1993 and those in 1994 during the postseason. Moreover, although the levels of sICAM-1 in ELF from the allergic subjects were upregulated in both 1993 and 1994, those in 1993 was about seven times higher than those in 1994.

Montefort et al. have reported that ICAM-1 is upregulated on the mucosal vascular endothelium in perennial allergic rhinitis, and this is associated with a significant increase in LFA-1-positive cells within the tissue (15). Together with their results on perennial allergic rhinitis, our results demonstrating systemic and/or local upregulation of sICAM-1 in patients with pollinosis might suggest that increase of soluble forms of ICAM-1 simply reflects the consequence of inflammation and tissue damage. However, sICAM-1 retains the ability to bind specifically LFA-1 (10). ICAM-1 is a receptor for rhinovirus (16), and recombinant sICAM-1 blocks rhinovirus infections *in vitro* (17). These data may suggest that sICAM-1 could have some biologic function. In fact, sICAM-1 is increased in acute exacerbation of asthma and does not return to normal by 28 days after these episodes (12). The systemic levels of sICAM-1 in the patients with pollinosis was also upregulated during the post-season in our results. These data indirectly suggest that sICAM-1 plays a role in regulating allergic inflammation. However, further experiments are needed to define the function and significance of ICAM-1 shedding.

In our results, the dynamics of the "local" levels of sICAM-1 is similar to that of the scores of

subjective symptoms in both 1993 and 1994. In contrast, the "systemic" levels of sICAM-1 did not parallel changes in the scores of subjective symptoms in both 1993 and 1994. These data suggest that local presence of sICAM-1 is more sensitive than determinations in circulation, and directly corresponds to severity of subjective symptoms. They also suggest that the sources of sICAM-1 are, at least in part, different between serum and ELF.

We conclude that the amount of antigen has an effect on the systemic and local levels of sICAM-1 from patients with seasonal allergic rhinitis during the season and postseason.

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