

# Soluble E-selectin as a Marker of Disease Activity in Pustulosis Palmaris et Plantaris

TETSUNORI KITAMURA<sup>1</sup>, YASUHIKO TAMADA<sup>1</sup>, MASASHI KATO<sup>3</sup>, TAKASHI YOKOCHI<sup>2</sup> and TOSHIHIKO IKEYA<sup>1</sup>

Departments of <sup>1</sup>Dermatology and <sup>2</sup>Microbiology and Immunology, Aichi Medical University, Nagakute, Aichi and <sup>3</sup>Department of Immunology, Nagoya University School of Medicine, Nagoya, Japan

**In this study, we investigated a possible correlation between adhesion molecules and activity of pustulosis palmaris et plantaris (PPP). Serum levels of soluble E-selectin (sE-selectin), soluble intercellular adhesion molecules 1 (sICAM-1) and tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ) in 30 untreated PPP patients were examined, and compared with those in 20 healthy subjects. Values in 10 PPP patients were re-examined after treatment. Serum levels of sE-selectin and TNF- $\alpha$  in untreated PPP patients were significantly higher than those in healthy subjects. There was a statistically significant correlation between the disease activity and serum levels of sE-selectin in untreated PPP patients. Furthermore, disease activity of PPP was higher in patients who smoked and during the summer, with elevation of serum sE-selectin levels. Serum levels of sE-selectin were downregulated with the recovery from PPP. These results suggest that sE-selectin may play a role in the pathogenesis of PPP and could be a reliable marker of its disease activity. *Key words: soluble intercellular adhesion molecule 1; tumour necrosis factor  $\alpha$ .***

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Tetsunori Kitamura, MD, Department of Dermatology, Aichi Medical University, Nagakute, Aichi 480-1195, Japan.

It is well known that leukocyte-endothelial cell interaction is an early step in a cascade of events leading to cellular extravasation and development of an inflammatory response (1, 2). Adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1) and E-selectin are involved in adhesion of leukocytes and their soluble form is found in human serum (3, 4). Recently, it was reported that there was an elevation of both soluble ICAM-1 (sICAM-1) and soluble E-selectin (sE-selectin) in serum from bronchial asthma patients (5). In allergic rhinitis patients, however, the levels of sICAM-1, but not of sE-selectin, were increased (6–8). In atopic dermatitis patients, only serum levels of sE-selectin were elevated, suggesting that it may be a good marker of disease activity (9, 10). In this study, we demonstrate that sE-selectin is involved in the pathogenesis and disease activity of pustulosis palmaris et plantaris (PPP).

## MATERIALS AND METHODS

### Study design

The PPP patient group comprised 15 men (mean age 48 years) and 15 women (mean age 49 years). The healthy control group comprised 10 men (mean age 45 years) and 10 women (mean age 49 years). The trial was approved by Aichi Medical University and each PPP patient and healthy subject gave written informed consent before entering the

study. In addition, sera from the 10 PPP patients who were treated only with internal betamethasone 0.5 mg/day and external tacalcitol ointment for a period of 4 weeks were used for the estimation of sE-selectin level.

Disease activity in PPP was estimated by the number of pustules in bilateral palms and soles. The levels of sE-selectin, sICAM-1 and tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ) in sera were examined in both the PPP patients and healthy subjects. They were then subjected to intragroup or intergroup comparative analyses.

### Analytical assays

sE-selectin, sICAM-1 and TNF- $\alpha$  in sera were measured as triplicates by a commercial enzyme-linked immunosorbent assay (ELISA) kit (sE-selectin: Bender Med Systems, Vienna, Austria; sICAM-1 ELISA kit: Genzyme Corporation, Cambridge, MA, USA; Human TNF- $\alpha$  Immunoassay kit: Genzyme Corporation), according to the method described previously (2, 4, 7, 8).

### Statistical analysis

For individual subjects, all parameters (disease activity, sE-selectin, sICAM-1 and TNF  $\alpha$ ) were analysed with the Wilcoxon's matched-pairs signed-rank test (intragroup analysis). The changes in all parameters in the PPP group compared with that of control group

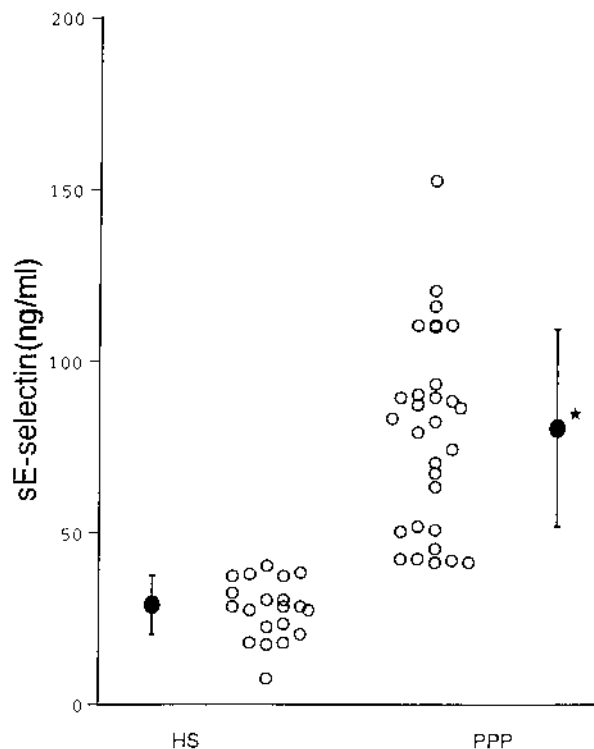


Fig. 1. Serum levels of soluble E-selectin in PPP patients and healthy subjects (HS), showing (○) individual values and (●) mean  $\pm$  SD. \* $p < 0.0001$ .

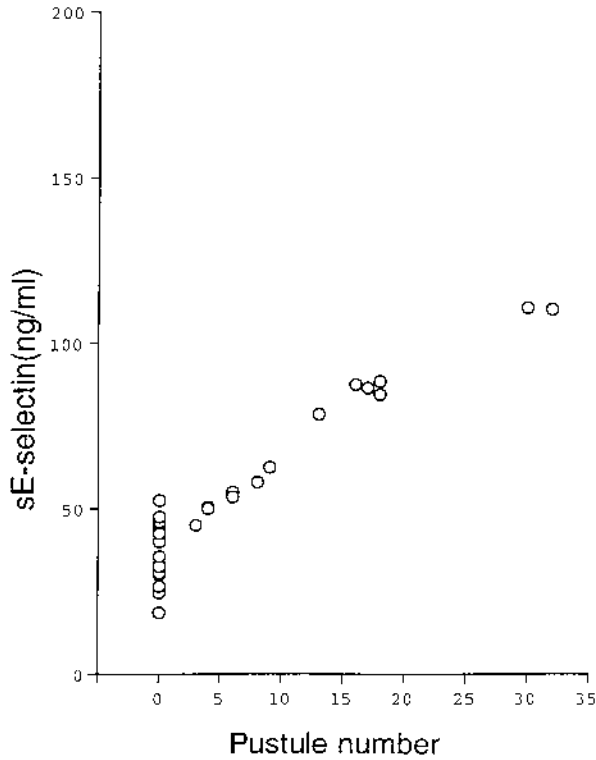


Fig. 2. Correlations between disease activity and serum levels of sE-selectin in PPP patients.

were analysed with the Mann-Whitney U test (intergroup analysis). Correlations among the parameters were determined using Spearman's rank correlation coefficient.

## RESULTS

The serum levels of sE-selectin in untreated PPP patients were about 3 times higher ( $p < 0.0001$ ) than those of healthy subjects (Fig. 1). However, there were no differences between serum levels of sICAM-1 in PPP patients ( $474 \pm 185$  ng/ml) and those in healthy subjects ( $420 \pm 119$  ng/ml).

As shown in Fig. 2, there was a statistically significant correlation ( $r = 0.905$ ,  $p < 0.0001$ ) between the disease severity and sE-selectin in untreated PPP patients. However, there was no statistical correlation ( $r = 0.212$ ) between sICAM-1 and the disease severity.

Serum levels of TNF- $\alpha$  in untreated PPP patients ( $37.0 \pm 30.6$  pg/ml) were higher ( $p < 0.05$ ) than those in healthy subjects ( $21.5 \pm 10.1$  pg/ml). No correlation was found between the disease activity and serum levels of TNF- $\alpha$  ( $r = 0.230$ ).

The levels of sE-selectin ( $92.2 \pm 18.8$  ng/ml,  $n = 15$ ) in untreated patients who smoked (20–40 cigarettes/day) were higher ( $p < 0.005$ ) than in those ( $66.9 \pm 31.8$  ng/ml,  $n = 15$ ) who did not smoke.

As shown in Fig. 3, the number of pustules increased during summer as well as the levels of sE-selectin.

In the 10 patients treated with betamethasone and tacalcitol

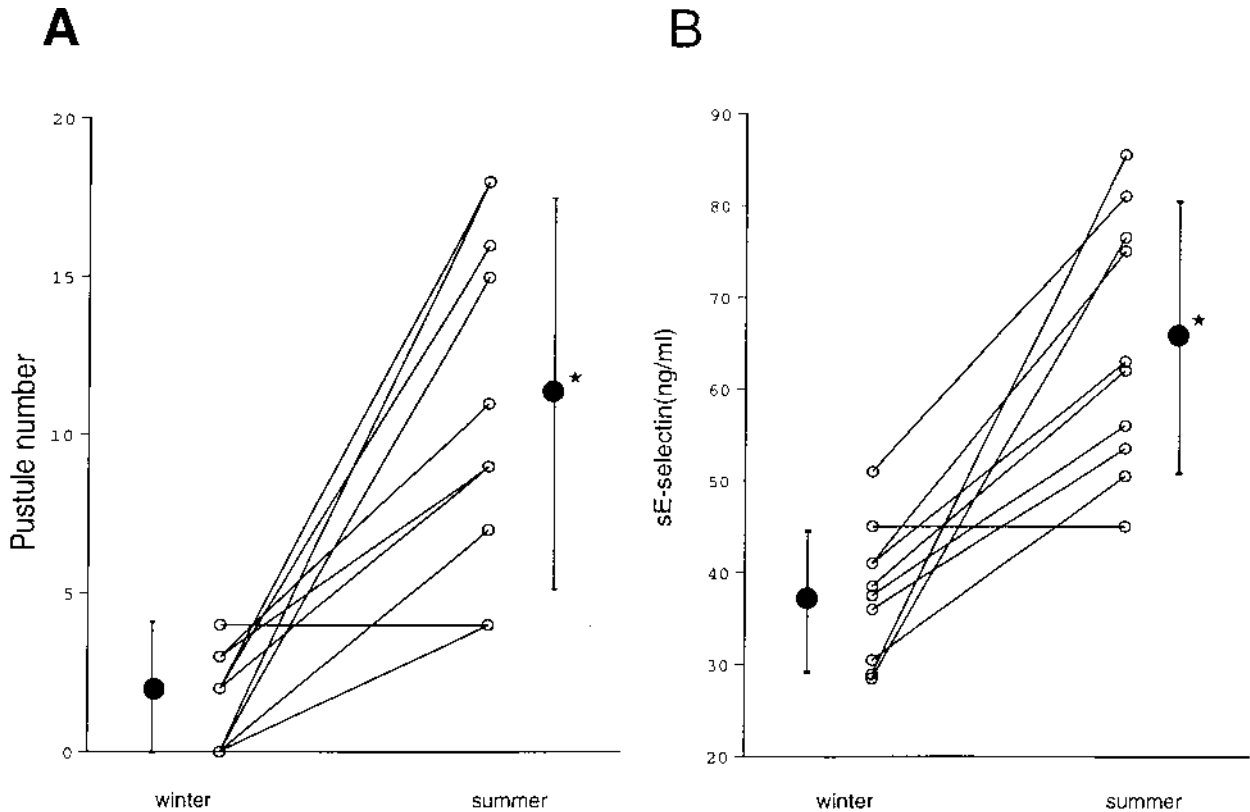


Fig. 3. Effect of season on the levels of sE-selectin in PPP patients. Number of pustules (A) and sE-selectin values (B) in untreated PPP patients in summer and winter.  $*p < 0.01$ .

ointment, sE-selectin levels were again measured when they no longer had pustules. The levels of sE-selectin ( $38.1 \pm 19.5$  ng/ml) were statistically significantly lower ( $p < 0.01$ ) than before ( $73.3 \pm 39.0$  ng/ml).

## DISCUSSION

Our results suggest that sE-selectin could be a reliable marker of PPP. Earlier studies have shown that inflammatory cytokines, such as IL-1 $\beta$  and TNF- $\alpha$ , activate endothelial cells *in vitro* and increase the expression of adhesion molecules (2, 11–15). The increased TNF- $\alpha$  levels in our patients might play a role in the upregulation of sE-selectin. Cigarette smoke condensate has been shown to increase the expression of E-selectin in endothelial cells *in vitro* (16). The increased levels of sE-selectin and disease activity in our patients who smoked strengthen the earlier-described effect of smoking in PPP (17).

In fact, increased levels of sE-selectin, sICAM-1 and TNF- $\alpha$  in patients with psoriasis were reported (18–20). PPP is thought to be a type of psoriasis, but in our patients with PPP only elevation of sE-selectin and TNF- $\alpha$  were observed. This discrepancy may depend on a difference of disease area.

Previously, we reported that the expression level of E-selectin and sialyl Lewis<sup>x</sup> were increased in lesional palm skin and polynuclear leukocytes from peripheral blood from PPP patients (21). It was also reported that EG2+ eosinophils as well as neutrophils were involved in the pathogenesis of PPP (17). E-selectin might be important in leukocytes homing into the skin.

Eriksson et al. reported that there were numerous mast cells, which are rich in TNF- $\alpha$  (22), in the upper dermis and destruction of the intraepidermal sweat duct in PPP skin (17). Together with our findings of increased levels of sE-selectin, but not sICAM-1 in PPP patients, these results suggest the possibility that TNF- $\alpha$  released from mast cells infiltrating the upper dermis might enhance the sE-selectin level more than the sICAM-1 level in the inflammatory process in PPP.

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