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Clinical Significance of Serum Vascular Endothelial-Cadherin Levels in Inflammatory Skin Diseases

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Dear Editor:

Inflammatory skin diseases are sometimes accompanied by vascular abnormalities; e.g. Auspitz phenomenon in psoriasis or white dermographism in atopic dermatitis (AD)[1,2]. However, the detailed mechanism(s) and role of such vasculopathy in the pathogenesis of each disease are still unclear.

Vascular endothelial (VE)-cadherin is one of the major components of adherens junctions between endothelial cells. The critical role of VE-cadherin is vascular morphogenesis during embryogenesis. Such function of VE-cadherin is regulated by vascular endothelial cell growth factor (VEGF) signaling through the VEGF receptor leads to the increased detachment of endothelial cells and transendothelial permeability by promoting VE-cadherin internalization[3]. On the other hand, VE-cadherin limits the

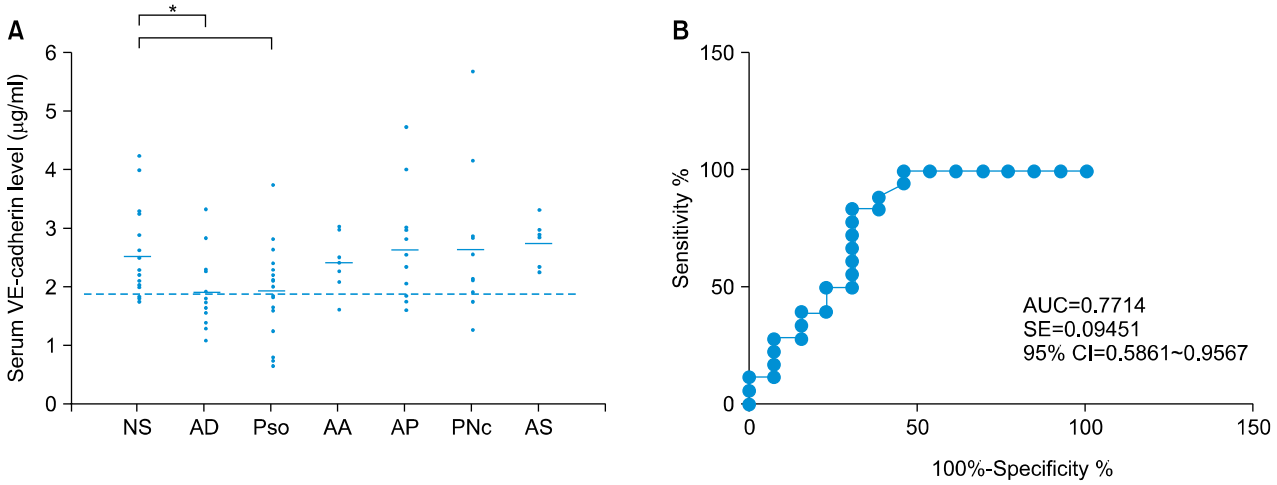

Fig. 1. (A) Serum soluble VE-cadherin levels in patients with various skin diseases. The serum levels of VE-cadherin determined by using ELISA are shown on the ordinate; the horizontal bars show the mean value in each group. The dotted line indicates the cutoff. VE: vascular endothelial, NS: normal subjects. AD: atopic dermatitis, Pso: psoriasis, AA: alopecia areata, AP: anaphylactoid purpura, PNc: cutaneous polyarteritis nodosa, AS: angiosarcoma. *$p<0.05$ by using the Mann-Whitney U-test. (B) Receiver operating characteristic curve for serum VE-cadherin levels in patients with AD. AUC: areas under curves, SE: standard error, CI: confidence interval.

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proliferation of endothelial cells by preventing the internalization of the VEGF receptor[4]. However, the role of VE-cadherin in the vascular abnormalities of inflammatory skin diseases has not been investigated. Full-length VE-cadherin is an insoluble transmembrane protein, whereas the extracellular domain of VE-cadherin is secreted as a soluble protein through a metalloproteinase-dependent mechanism[5]. Soluble VE-cadherin may function as an antagonist of full-length VE- cadherin, which is suggested by its inhibitory effect on tumor angiogenesis and tumor growth *in vivo*[6]. To date, although soluble VE-cadherin has been detected in serum *in vivo*, the clinical significance of serum soluble VE- cadherin levels is still unknown. Therefore, in this study, we attempted to evaluate the possibility that the serum VE-cadherin level can be a useful marker for inflammatory skin diseases. Serum samples were obtained from 13 patients with AD, 33 patients with psoriasis, and 7 patients with alopecia areata. Control serum samples were also collected from 18 healthy volunteers. Sera of 12 patients with anaphylactoid purpura, 11 patients with cutaneous polyarteritis nodosa, and 6 patients with angiosarcoma were also included as the disease controls. This research was approved by the Ethics Review Committee in Kumamoto University (No. 177). Written informed consents were obtained before patients and healthy volunteers were enrolled into this study according to the Declaration of Helsinki.

Table 1. Association of serum VE-cadherin levels with clinical and serological features

	VE-cadherin	
	Normal	Reduced
Patients with atopic dermatitis		
Mean duration of disease (yr)	15.3	20.3
Mean SCORAD (score)	56.1	47.4
Mean eosinophil (%)	11.9	9.3
Mean serum LDH (U/L)	321.0	237.4
Mean serum TARC (pg/ml)	9,428.0	4,386.0
Mean serum IgE (ng/ml)	539.3	881.8
Total	5	8
Patients with psoriasis		
Mean duration of disease (yr)	5.9	3.9
Mean PASI (score)	16.6	15.7
Mean BSA (%)	40.3	31.0
Arthritis (%)	25.0	28.6
Nail change (%)	53.8	21.4*
Total	17	16

SCORAD: scoring atopic dermatitis, LDH: lactate dehydrogenase, TARC: thymus and activation-regulated chemokine, IgE: immunoglobulin E, PASI: psoriasis area and severity index, BSA: body surface area of the involved skin.
*$p<0.05$ vs. patients with normal VE-cadherin levels by using the Fisher exact probability test.

The serum soluble VE-cadherin levels were measured with a specific enzyme-linked immunosorbent assay kit (R&D Systems, Minneapolis, MN, USA)[7] (Fig. 1A). The mean serum VE-cadherin level tended to be lower in patients with AD (1.903 μg/ml) and those with psoriasis (1.915 μg/ml) in comparison to normal subjects (2.511 μg/ml). We found a statistical significance in these decreases ($p=0.01$ in patients with AD, and $p=0.04$ in patients with psoriasis). The serum VE-cadherin levels in patients with alopecia ($p=0.81$), anaphylactoid purpura ($p=0.90$), cutaneous polyarteritis nodosa ($p=0.96$), or angiosarcoma ($p=0.13$) were similar to those in normal subjects. When the cutoff value was set at 1.880 μg/ml on the basis of the normal range provided by the manufacturer, reduced serum VE-cadherin levels were found in 3 of the 18 healthy volunteers (16.7%), 8 of the 13 patients with AD (61.5%), 16 of the 33 patients with psoriasis (48.5%), 1 of the 7 patients with alopecia (14.3%), 4 of the 12 patients with anaphylactoid purpura (33.3%), 2 of the 11 patients with cutaneous polyarteritis nodosa (11.2%), and 0 of the 6 patients with angiosarcoma. Thus, the low serum VE-cadherin levels may be more specific to AD or psoriasis than cutaneous vasculitis or vascular tumor.

In the receiver operating characteristic curve analysis of patients with AD (Fig. 1B), the area under curve (AUC) was 0.77 (95% confidence interval [95% CI], 0.59~0.96). An AUC of >0.7 indicates that the serum VE-cadherin levels can effectively distinguish patients with AD from normal subjects. On the other hand, the AUC was 0.67 (95% CI, 0.53~0.82) in patients with psoriasis, indicating that serum VE-cadherin is less useful in diagnosing psoriasis. Accordingly, serum VE-cadherin may be more effective for diagnosing AD than psoriasis.

Next, we determined the association of serum VE-cadherin levels with the clinical and serological features of patients with AD (Table 1); 5 disease activity markers (SCORAD, percentage of eosinophil counts, serum lactate dehydrogenase levels, serum thymus and activation-regulated chemokine levels, and serum immunoglobulin E level) and the duration of the disease (between symptom onset and the first visit to the hospital) were evaluated. However, we could not find a significant difference in these factors between patients with reduced VE-cadherin levels and those with normal levels. On the other hand, in patients with psoriasis, when 4 activity indicators (psoriasis area and severity index score, body surface area of the involved skin, arthritis, and nail change) and disease duration were evaluated (Table 1), patients with reduced VE-cadherin levels showed a significantly lower prevalence of nail change ($p=0.03$). Thus, serum VE-cadherin

levels are correlated with clinical symptom in patients with psoriasis but not in patients with AD. Taken together, our results suggest that the serum VE-cadherin level in patients with AD can be the diagnostic marker rather than the disease activity marker, whereas that in patients with psoriasis may be more useful as the marker for disease activity.

This is the first report measuring serum VE-cadherin levels in patients with various skin diseases. Furthermore, as far as we searched, decreased serum VE-cadherin levels have not been reported in human diseases. Although the role of VE-cadherin in skin diseases is unknown, skin erythema, for example, is one of the common features of AD and psoriasis and is caused by dilated vessels. As described above, soluble VE-cadherin may function as an antagonist of full-length VE-cadherin. Thus, lower serum soluble VE-cadherin levels may activate transmembrane full-length VE-cadherin, which may contribute to the pathogenesis of AD and psoriasis through erythema formation. Clarifying the mechanism by which VE-cadherin-mediated vascular abnormality contributes to the pathogenesis may lead to the understanding of these diseases and to novel therapeutic strategies. However, this study has a limitation; although the VE-cadherin levels were lower in patients with psoriasis than in healthy volunteers, the nail change is less frequent in patients with psoriasis with decreased VE-cadherin levels. This paradoxical finding may be due to the small number of patients. A larger study with an increased number of patients is needed in the future.

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