

ORIGINAL ARTICLE

Serum soluble CD26 levels: diagnostic efficiency for atopic dermatitis, cutaneous T-cell lymphoma and psoriasis in combination with serum thymus and activation-regulated chemokine levels

T. Miyagaki, M. Sugaya,* H. Suga, S. Morimura, M. Kamata, H. Ohmatsu, H. Fujita, Y. Asano, Y. Tada, T. Kadono, S. Sato

Department of Dermatology, Faculty of Medicine, University of Tokyo, Tokyo, Japan

*Correspondence: M. Sugaya. E-mail: sugayam-der@h.u-tokyo.ac.jp

Abstract

Background CD26 is a multifunctional type II transmembrane glycoprotein, which also exists as a secreted isoform, soluble CD26 (sCD26). The CD26 expression on circulating T cells is decreased in some skin diseases such as cutaneous T-cell lymphoma (CTCL) and psoriasis. It remains to be determined whether sCD26 can be used as a marker of skin diseases or not.

Objective To investigate utility of sCD26 as a diagnostic marker of skin diseases in combination with thymus and activation-regulated chemokine (TARC).

Methods Serum sCD26 levels were measured using enzyme-linked immunosorbent assay in 130 participants including 32 patients with atopic dermatitis (AD); 45 patients with CTCL; 26 patients with psoriasis; and 27 healthy controls.

Results Serum sCD26 levels in patients with CTCL and psoriasis (162.1 ± 80.2 ng/mL and 125.4 ± 82.1 ng/mL respectively) were significantly lower than those of healthy controls (392.6 ± 198.7 ng/mL; $P < 0.01$ and 0.01 respectively). In patients with CTCL, serum sCD26 levels of patients with advanced stage were 135.0 ± 51.5 ng/mL and they were significantly lower than those with early stage (193.1 ± 96.0 ng/mL; $P < 0.05$). When we used serum sCD26 and TARC levels for diagnostic criteria, sensitivity, specificity, positive predictive value and negative predictive value for AD, CTCL and psoriasis were 65.2–73.7%, 81.4–97.6%, 65.2–94.4%, and 81.4–88.9% respectively.

Conclusion Serum sCD26 levels, combined with serum TARC levels, are helpful in diagnosis of AD, CTCL and psoriasis.

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Conflicts of interest

The authors have declared no conflicts of interest.

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Introduction

CD26, exhibiting dipeptidyl peptidase IV enzyme activity, is a multifunctional type II transmembrane glycoprotein, which belongs to a serine protease family.¹ It is expressed on a variety of tissues including epithelial cells, endothelial cells, natural killer cells and the subset of T cells.^{2–6} It is up-regulated after T cells and natural killer cells get activated.^{5,7} CD26 acts to selectively remove the N-terminal dipeptide from peptides with proline or alanine in the penultimate position.^{1,8,9} Several gastrointestinal hormones, neu-

ropeptides, integrins and chemokines have been demonstrated to be cleaved by this enzymatic activity.¹⁰ CD26 also exhibits a co-stimulatory function. It can bind adenosine deaminase and mediate signalling by direct interaction with the cytoplasmic domain of CD45.^{11–13} A new model for CD26 costimulatory function suggests that, at least in activated memory T cells, CD26 enhances antigen-specific T cell proliferation by engaging signalling pathways in the antigen presenting cells, in particular, the up-regulation of CD86.¹⁴

There are many studies reported on CD26 involvement in skin diseases. Expression of CD26 on CD8⁺ T cells is decreased in patients with psoriasis.¹⁵ CD26⁺ cells are also increased in peripheral blood in patients with cutaneous T cell lymphoma (CTCL).^{16–18} On the other hand, increased expression of CD26 on keratinocytes is observed both in CTCL and inflammatory skin diseases including psoriasis, lichen planus and spongiotic dermatitis.^{19–21}

CD26 also exists as a secreted isoform, soluble CD26 (sCD26), which lacks the cytoplasmic tail and transmembrane region. It is reported to have the same function or enzymatic activity as the membrane form of CD26.^{22,23} Concentration of sCD26 in plasma or sera has been measured in various diseases. It is increased in patients with infection such as human immunodeficiency virus-1 and leishmaniasis.^{24–26} On the other hand, it is decreased in patients with autoimmune and inflammatory diseases such as rheumatoid arthritis, lupus erythematosus, Sjögren syndrome, anti-neutrophil cytoplasmic autoantibody-associated vasculitis and systemic sclerosis.^{23,27–30} It remains to be determined whether sCD26 can be used as a marker of skin diseases or not.

In this study, we measured serum sCD26 levels in patients with atopic dermatitis (AD), CTCL and psoriasis. We also measured serum levels of thymus and activation-regulated chemokine (TARC), which we and others reported to be a good disease marker for AD and CTCL,^{31,32} to examine whether combination of serum sCD26 and TARC levels is helpful in diagnosis of these diseases.

Materials and methods

Patients

Thirty-two patients with AD (mean $\pm$ standard deviation age: 36.0 ± 10.2 years, 21 men and 11 women), 26 patients with psoriasis (58.7 ± 14.5 years, 20 men and six women), 45 patients with CTCL (39 mycosis fungoides cases and six Sezary syndrome cases; 59.3 ± 13.5 years, 26 men and 19 women), and 27 healthy control subjects (38.3 ± 15.5 years, 12 men and 15 women) were enrolled in this study. The medical ethical committee of the University of Tokyo approved all described studies, and the study was conducted according to the Declaration of Helsinki Principles. Informed consent was obtained to use blood samples from patients and healthy controls. All patients with AD fulfilled the criteria for AD proposed by Hanifin and Rajka.³³ The clinical severity of AD was evaluated using the scoring system proposed by Rajka and Langeland.³⁴ All patients with psoriasis were diagnosed according to the clinical and histopathological findings. The disease activity of psoriasis was assessed using psoriasis area and severity index (PASI) scores.³⁵ All patients with CTCL were given diagnoses according to the current WHO classification.³⁶ Patients were subgrouped into early stage (patch) and advanced stage (plaque, tumour and erythroderma) according to their types of skin lesions. The 27 healthy controls had no history of allergy,

CTCL, psoriasis or any skin diseases. All serum samples were stored at -20°C until use.

Enzyme-linked immunosorbent assay

Immunoreactive sCD26 in sera were quantified using Human DPPIV/CD26 Quantikine ELISA kit (R&D systems, Minneapolis, MN, USA). These assays employ the quantitative sandwich enzyme immunoassay technique. Optical densities were measured at 450 nm using a Bio-Rad Model 550 microplate reader (Bio-Rad Laboratories, Hercules, CA, USA). The concentrations were calculated from the standard curve generated using a curve-fitting programme. The measured values from individual patients were plotted by dots.

Statistical analysis

Statistical analysis was performed using the Mann–Whitney's *U*-test for comparison of values and Steel–Dwass test for multiple comparisons. Correlation coefficients were determined using the Spearman's rank correlation test. *P*-values of <0.05 were considered statistically significant.

Results

Serum sCD26 levels

Serum sCD26 levels in patients with AD, CTCL, psoriasis and healthy controls are shown in Fig. 1. Serum sCD26 levels in patients with AD were 366.0 ± 184.5 ng/mL, which were not statistically different from those of healthy controls (392.6 ± 198.7 ng/mL). Serum sCD26 levels of patients with CTCL were 162.1 ± 80.2 ng/mL, which were significantly lower than those of healthy controls and patients with AD ($P < 0.01$ and 0.01 respectively). Serum sCD26 levels of patients with psoriasis were 125.4 ± 82.1 ng/mL, which were significantly lower than those of healthy controls and patients with AD ($P < 0.01$ and 0.01 respectively).

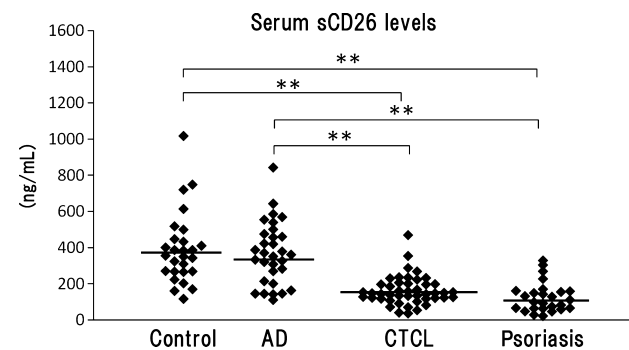


Figure 1 Serum soluble CD26 (sCD26) levels (ng/mL) in patients with atopic dermatitis (AD), cutaneous T cell lymphoma (CTCL), psoriasis and healthy controls. The measured values from individual patients are plotted by dots. Bar represent average. ** $P < 0.01$.

Correlation between serum sCD26 levels and disease severity and laboratory data

We next compared serum sCD26 levels with disease severity and other clinical and laboratory data: age, gender, serum levels of lactate dehydrogenase, immunoglobulin E (IgE), soluble interleukin-2 receptor and numbers of eosinophils in peripheral blood. We also compared serum sCD26 levels in CTCL patients with serum eotaxin, eotaxin-3 and cutaneous T-cell attracting chemokine (CTACK) levels that we previously reported to be disease markers of CTCL.^{37,38} We also compared serum sCD26 levels with the amount of Sézary cells in peripheral blood. In patients with AD, serum sCD26 levels did not correlate with any clinical and laboratory data including serum IgE levels and number of eosinophils in peripheral blood (data not shown). In addition, there was no tendency for sCD26 levels to increase or decrease with the clinical severity of AD (data not shown). In patients with CTCL, serum sCD26 levels of patients with advanced stage were 135.0 ± 51.5 ng/mL, and they were significantly lower than those with

early stage (193.1 ± 96.0 ng/mL; Fig. 2a). Moreover, serum sCD26 levels of patients with CTCL were inversely correlated with serum eotaxin, eotaxin-3 and CTACK levels ($r = -0.46$, $P < 0.05$, $r = -0.50$, $P < 0.05$, and $r = -0.59$, $P < 0.01$ respectively; Fig. 2b–d). We did not find any significant correlation between serum sCD26 levels with the amount of Sézary cells in peripheral blood in six Sézary patients (data not shown). Serum sCD26 levels of patients with psoriasis did not correlate with PASI scores (data not shown).

Serum TARC levels

We next measured serum TARC levels in patients with AD ($n = 24$), CTCL ($n = 23$; six cases with patch, four plaque, eight tumour and five erythroderma) and psoriasis ($n = 19$). We previously reported that patients with AD and CTCL showed increased serum TARC levels, but that those with psoriasis did not.^{31,32} Serum TARC levels of patients with AD and CTCL were $8207.8 \pm 14\,154.6$ pg/mL and $5289.0 \pm 10\,880.3$ pg/mL respectively. They were

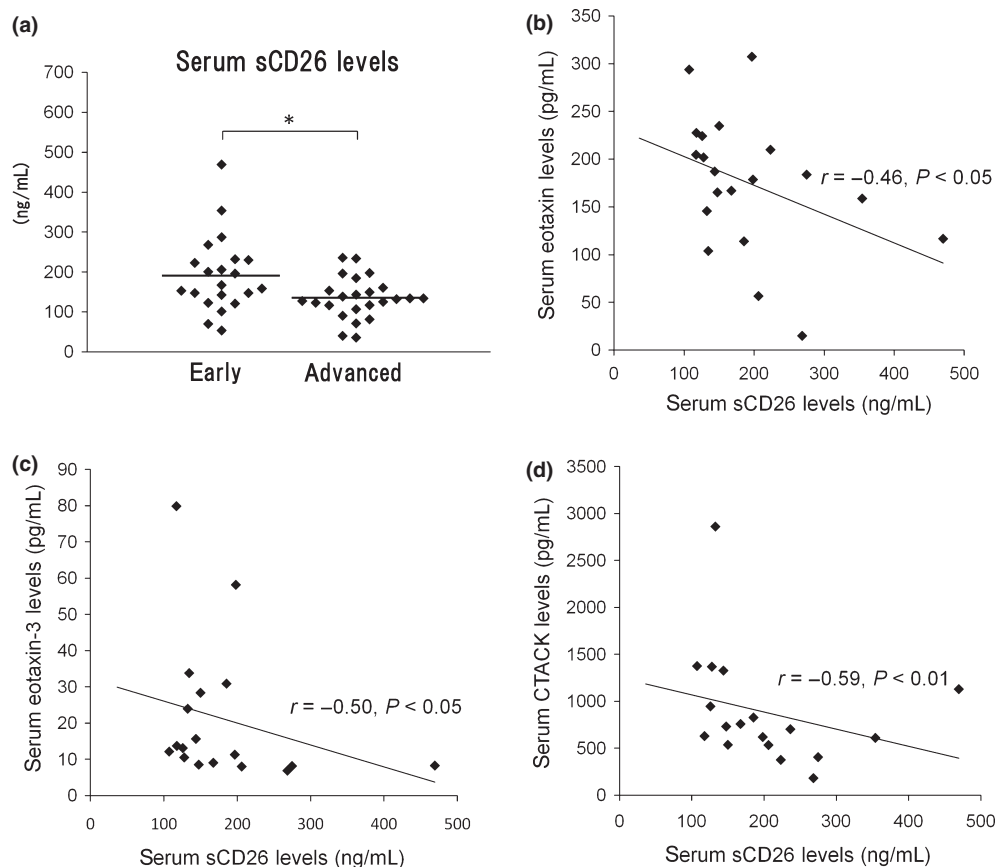


Figure 2 Correlations between serum soluble CD26 (sCD26) levels (ng/mL) and clinical and laboratory data in patients with cutaneous T cell lymphoma (CTCL). (a) Serum sCD26 levels in patients with early CTCL and advanced CTCL. The measured values from individual patients are plotted by dots. Bar represent average. * $P < 0.05$. (b) Correlations between serum sCD26 levels and serum eotaxin levels (pg/mL). (c) Correlations between serum sCD26 levels and serum eotaxin-3 levels (pg/mL). (d) Correlations between serum sCD26 levels and serum cutaneous T-cell attracting chemokine levels (pg/mL).

significantly higher than those with psoriasis (270.4 ± 163.5 pg/mL), which was consistent with our previous reports.^{31,32}

Different serum profiles of sCD26 and TARC levels for different skin diseases

Based on our previous reports and the results above, AD, CTCL and psoriasis have different serum profiles of sCD26 and TARC.^{31,32} In patients with AD, serum sCD26 levels were not changed, whereas serum TARC levels were increased. In patients with CTCL, serum sCD26 levels were decreased and serum TARC levels were increased. In patients with psoriasis, serum sCD26 levels were decreased, whereas serum TARC levels were not changed. The distribution of serum sCD26 and TARC levels in patients with AD, CTCL and psoriasis are shown in Fig. 3. We set the cut-off value of serum sCD26 level at 250 ng/mL and that of TARC level at 450 pg/mL, respectively, and examined whether the diagnostic criteria was useful. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) are listed in Table 1. Sensitivity, specificity, PPV and NPV for AD were 70.8, 97.6, 94.4 and 85.4% respectively. Sensitivity, specificity, PPV and NPV for CTCL were 65.2, 81.4, 65.2 and 81.4% respectively. Sensitivity, specificity, PPV and NPV for psoriasis were 73.7, 85.1, 66.7 and 88.9% respectively.

Discussion

In this report, we measured serum sCD26 and TARC levels of patients with skin diseases. We first showed decreased serum sCD26 levels of patients with CTCL and psoriasis compared with healthy controls, but not in patients with AD. Serum TARC levels of patients with AD and CTCL were increased, and those with psoriasis were not increased. On the basis of these data, we used serum sCD26 and TARC levels for diagnostic criteria for AD, CTCL and psoriasis, which turned out to be helpful for making the diagnosis.

Serum sCD26 is thought to be shed from plasma membrane on CD26-expressing cells that are in contact with blood, such as circulating lymphocytes and vascular endothelial cells.^{39,40} In healthy individuals, the electrophoretic mobility of normal serum sCD26 coincides with that of membranous CD26 on lymphocyte, but not with CD26 purified from liver or kidney, abundant with vascular endothelial cells.⁴¹ Furthermore, plasma sCD26 in HIV-1-infected individuals is predominantly present in a sialylated state, corresponding to the form found on T lymphocyte.⁴² Moreover, immune reconstitution after anti-retroviral therapy not only increases serum sCD26 activity but also the number of CD26⁺ T lymphocytes.^{43,44} Based on these reports, the main source of serum sCD26 should be circulating CD26⁺ lymphocytes. In patients with CTCL, peripheral blood CD26⁺ T cells are extremely increased.^{16–18} CD26 expression on peripheral blood T cells is also reduced in patients with psoriasis.¹⁵ They may explain decreased serum sCD26 levels in patients with CTCL and psoriasis in this study. We also show that serum sCD26 levels are more decreased in

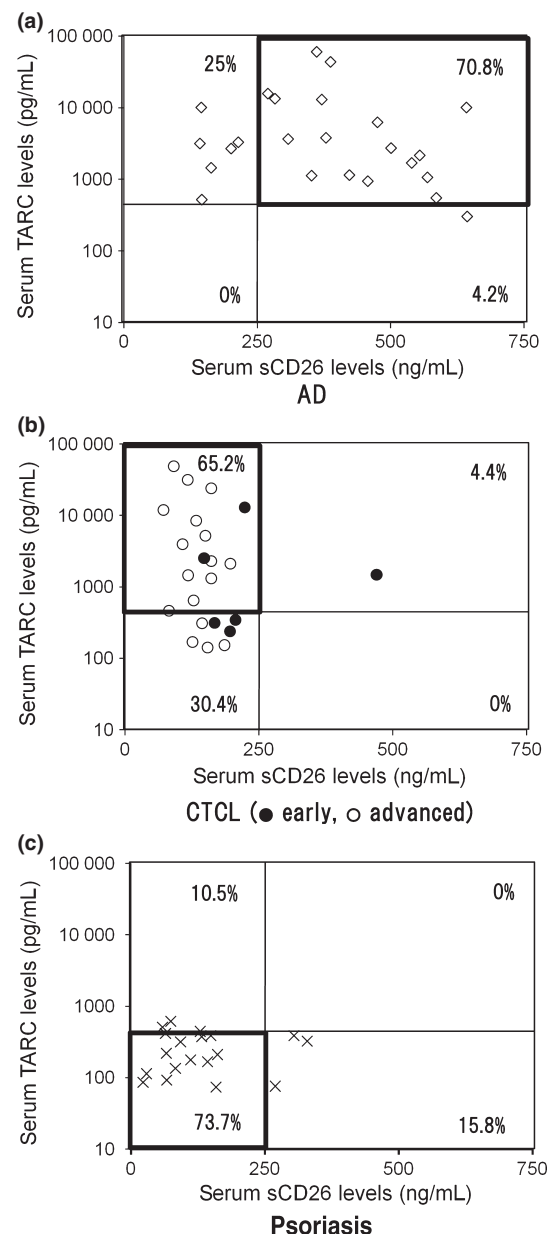


Figure 3 Distribution of serum soluble CD26 (sCD26) levels (ng/mL) and serum thymus and activation-regulated chemokine (TARC) levels (pg/mL) in patients with atopic dermatitis (AD; (a), cutaneous T-cell lymphoma (CTCL); (b) and psoriasis (c). The measured values from individual patients are plotted by dots. The lines represent cut-off value. The numbers are percentages of each quadrant.

patients with advanced CTCL than in patients with early CTCL. This is consistent with previous reports describing that the number of peripheral blood CD26⁺ T cells increased in patients with CTCL as the disease progressed.^{16,17} Moreover, in patients with CTCL, there were significant inverse correlations between serum sCD26 levels and serum eotaxin, eotaxin-3 and CTACK

Table 1 Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of serum sCD26 levels combined with serum TARC levels

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
AD vs. CTCL and psoriasis	70.8	97.6	94.4	85.4
CTCL vs. AD and psoriasis	65.2	81.4	65.2	81.4
Psoriasis vs. AD and CTCL	73.7	85.1	66.7	88.9

AD, atopic dermatitis; CTCL, cutaneous T-cell lymphoma; TARC, thymus and activation-regulated chemokine.

levels, which all correlated with disease severity of CTCL.^{37,38} Among these chemokines, eotaxin have been demonstrated to be cleaved and inactivated by CD26.^{45,46} Low sCD26 levels may explain higher serum levels of eotaxin in CTCL.

What is most important in this study is that serum sCD26 levels are decreased in patients with CTCL, but not in those with AD. CTCL often presents as randomly distributed patches and plaques, and it is often difficult to distinguish clinically from various common and benign diseases including AD and psoriasis. Other than clinical manifestations, diagnosis of CTCL can also be difficult due to the sometimes nonspecific nature of histological findings. Differentiation of CTCL from dermatological conditions mimicking CTCL is important to ensure proper management of the patient's symptoms and treatment, and to provide accurate prognostic information. For example, there is a case report describing psoriasiform mycosis fungoides with fatal outcome after treatment with cyclosporine.⁴⁷ We have previously reported that serum TARC levels are elevated in AD and CTCL, but not in psoriasis,^{31,32} suggesting that TARC is a good marker to distinguish psoriasis from AD and CTCL. It is, however, more important to differentiate CTCL from AD because they have the similar laboratory features, such as high serum IgE levels and high numbers of eosinophils in peripheral blood. Our criteria using combination of serum sCD26 and TARC levels proved to be helpful in the diagnosis of AD, CTCL and psoriasis (Fig. 3, Table 1). It is important that our test have a high NPV (81.4%) to rule out CTCL because immunosuppressive drugs, which are effective for AD and psoriasis, could negatively affect CTCL. In 25% of AD patients, however, the profile was indistinguishable from that of CTCL patients (Fig. 3). Thus, we have to be aware that our test can not completely rule out AD. In addition, we measured serum TARC levels in only a small number of patients with early CTCL in this report. As serum TARC levels correlate with disease severity,³² more early CTCL patients with low serum TARC levels might make it difficult to differentiate CTCL from psoriasis. Therefore, we have to be aware that our test can not completely differentiate early CTCL from psoriasis (Fig. 3). In some cases with CTCL, serum sCD26 levels increased, and in other cases, they decreased after treatment. In most cases, however, serum sCD26 levels remained under 250 ng/mL after treatment (data not shown), suggesting that sCD26 was a useful diagnostic maker even for patients after treatment at other hospitals.

In summary, serum sCD26 levels are significantly lower in patients with CTCL and psoriasis. On the other hand, serum TARC levels are significantly higher in patients AD and CTCL. Serum sCD26 levels, combined with serum TARC level, are helpful in diagnosis of AD, CTCL and psoriasis.

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