

Serum-soluble Herpes Virus Entry Mediator Levels Reflect Disease Severity and Th2 Environment in Cutaneous T-cell Lymphoma

Tomomitsu Miyagaki, Makoto Sugaya*, Hiraku Suga, Hanako Ohmatsu, Hideki Fujita, Yoshihide Asano, Yayoi Tada, Takafumi Kadono and Shinichi Sato

Department of Dermatology, Faculty of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. *E-mail: sugayam-der@h.u-tokyo.ac.jp
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Activated T cells express LIGHT, an acronym for lymphotoxin-like, exhibits inducible expression, and competes with HSV glycoprotein D for herpesvirus entry mediator (HVEM) a receptor expressed by T lymphocytes (1). LIGHT binds to 3 distinct receptors: HVEM, lymphotoxin β receptor, and decoy receptor 3 (2). Of these, HVEM is expressed by many cell types (1). LIGHT-HVEM interactions activate T cells and natural killer (NK) cells to produce T helper type (Th) 1 cytokines (3–7).

Many patients with cutaneous T-cell lymphoma (CTCL) in the advanced stages have eosinophilia and high levels of immunoglobulin E, suggesting that Th2 is dominant in these patients (8, 9).

We reported recently that low HVEM expression on dermal fibroblasts in lesional skin of advanced CTCL attenuates the expression of Th1 chemokines, which may contribute to a shift to a Th2-dominant microenvironment (10). However, little is known about the soluble form of HVEM (sHVEM) and its ligand, LIGHT, in CTCL. The aim of this study was to measure sHVEM and LIGHT levels in the sera of patients with CTCL.

MATERIALS AND METHODS

A total of 38 patients with CTCL (34 cases of mycosis fungoides and 4 cases of Sézary syndrome, mean \pm standard deviation age: 57.4 \pm 13.6 years, 23 men and 15 women), and 19 healthy control subjects (41.6 \pm 15.3 years, 11 men and 8 women) were enrolled in this study. All patients with CTCL were diagnosed according to the World Health Organization–European Organisation for Research and Treatment of Cancer (WHO-EORTC) classification for cutaneous lymphomas. Patients were classified by type of skin lesions (patch 18, plaque 6, tumour 9, and erythroderma 5 cases). The 19 healthy controls had no history of allergy or any skin diseases. Serum samples were obtained with informed consent. The medical ethics committee of the University of Tokyo approved all described studies and the study was conducted according to the principles of the Declaration of Helsinki. Immunoreactive sHVEM and LIGHT in sera were quantified by a human HVEM/TNFRSF14 DuoSet and a human LIGHT/TNFSF14 Quantikine ELISA Kit (R&D systems, Minneapolis, MN, USA), respectively. Statistical analysis between the 2 groups was made with a Mann–Whitney *U* test. Correlation coefficients were determined using Spearman's rank correlation test. *p*-values less than 0.05 were considered statistically significant.

RESULTS

Serum sHVEM levels in patients with CTCL were 2,961.1 \pm 658.0 pg/ml (mean \pm SD), which was compa-

table to levels in healthy controls (2,727.4 \pm 430.9 pg/ml). When classified by type of skin lesions, serum sHVEM levels in patients with CTCL with early skin lesions (patch and plaque), tumours, and erythroderma were 2,708.0 \pm 609.7 pg/ml, 3,307.3 \pm 580.1 pg/ml, and 3,323.2 \pm 535.2 pg/ml, respectively. The levels in patients with tumours and those with erythroderma were significantly higher than those in healthy controls (Fig. 1a). Serum LIGHT levels in patients with CTCL (134.6 \pm 165.0 pg/ml) were significantly higher than those in healthy controls (61.2 \pm 28.7 pg/ml; *p* < 0.05). In patients with early skin lesions, tumours, and erythroderma, serum LIGHT levels were 87.2 \pm 96.1 pg/ml, 146.5 \pm 121.9 pg/ml, and 313.8 \pm 340.3 pg/ml, respectively. The levels in patients with tumours and those with erythroderma were significantly higher than those in healthy controls (Fig. 1b). Serum sHVEM levels correlated significantly with serum LIGHT levels (Fig. 1c), serum sIL-2R levels (Fig. 1d), the percentages and numbers of eosinophils (Fig. 1e, f), and serum IL-4 and IL-10 levels (Fig. 1g, h). Serum sHVEM levels did not show significant correlations with age, sex, or serum LDH and IgE levels. Serum LIGHT levels did not correlate significantly with laboratory data described above except serum sHVEM levels.

DISCUSSION

This study showed elevated serum sHVEM and LIGHT levels in patients with advanced CTCL. Given that LIGHT expression is up-regulated on T cells upon activation (1), elevated serum LIGHT levels in patients with advanced CTCL may reflect systemic activation of T cells, which is also shown in patients with atopic dermatitis and psoriasis (11, 12). A soluble form of HVEM can act as a decoy to block LIGHT-HVEM interactions, preventing too much activation of various immune cells, including T cells. We recently reported that serum sHVEM levels correlated with serum LIGHT levels in normal controls (11). In this study, we also showed significant correlation between serum sHVEM and LIGHT levels in CTCL patients, suggesting that sHVEM functions as a negative feedback regulator.

Although both serum sHVEM and LIGHT levels were elevated in patients with advanced CTCL, our study suggested that the former was a better disease marker, as was previously reported in patients with gastric cancer (13). As LIGHT-HVEM interactions promote Th1 immune responses through T cells and NK cells

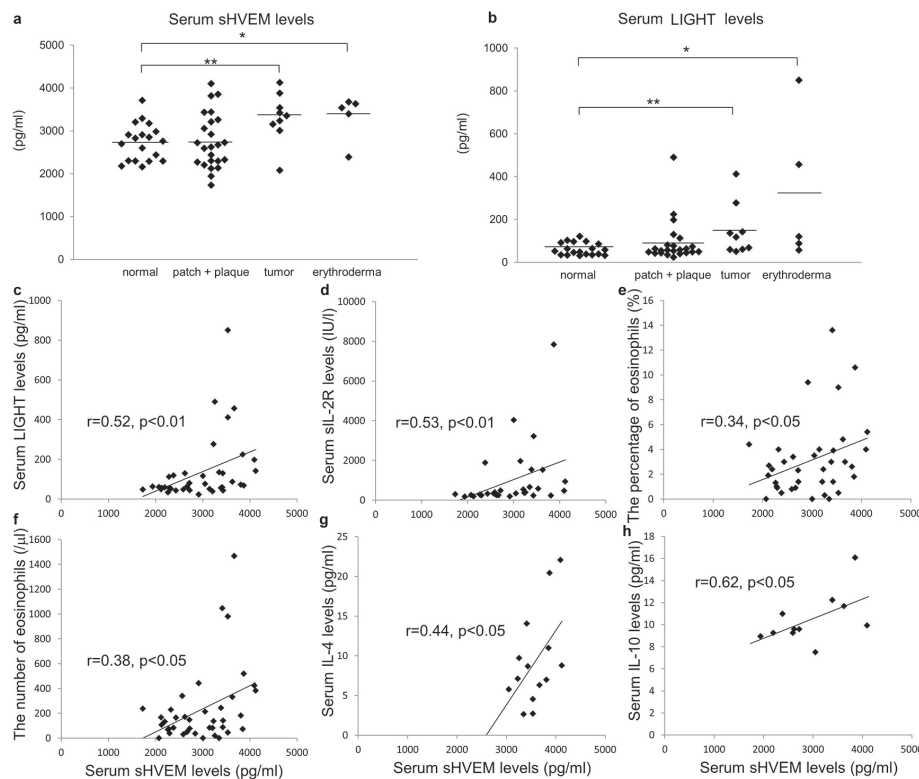


Fig. 1. Serum levels of soluble herpesvirus entry mediator (sHVEM) and LIGHT (lymphotoxin-like, exhibits inducible expression, and competes with HSV glycoprotein D for herpesvirus entry mediator (HVEM) a receptor expressed by T lymphocytes) (a, b) and how they correlate with other laboratory data (c–h) in patients with cutaneous T-cell lymphoma classified by type of skin lesions and in healthy controls. Horizontal bars indicate mean; oblique lines depict regressions. * $p < 0.05$, ** $p < 0.01$ by Mann–Whitney *U* test.

(3–5), increase in sHVEM, in sera may contribute to a shift from Th1- to Th2-dominant immune responses in patients with CTCL. Serum sHVEM levels are consistently increased in allergic diseases, but not in psoriasis (14). Our results, showing correlations between serum sHVEM levels and markers of systemic Th2 environment, also supported this hypothesis. Moreover, significant correlations between the serum sHVEM level and serum sIL-2R, IL-4, and IL-10 levels suggest a possible contribution to development of CTCL because IL-10 functions as a immune regulator. Elevated levels of sHVEM may contribute to enhanced IL-10 production because blocking of the interaction between HVEM and B- and T-lymphocyte attenuator, another ligand of HVEM, decreases IL-10 production (15). Serum sHVEM levels can be a good marker of disease severity and Th2 environment in CTCL.

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