

Serum IL-31 Levels are Increased in Patients with Cutaneous T-cell Lymphoma

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Interleukin-31 (IL-31) is expressed by activated Th2 cells, signalling through a receptor complex composed of IL-31RA and oncostatin M receptor β (OSMR β) (1). Atopic dermatitis (AD) is an inflammatory skin disease with intense pruritus. The mechanisms underlying dermatitis and pruritus are not fully understood, but there is emerging evidence that IL-31 may play an important role. Transgenic mice over-expressing IL-31 developed dermatitis mimicking AD with severe pruritus (1). In an AD-like murine model (NC/Nga mice), high IL-31 mRNA expression is associated with scratching behaviours (2). Previous studies have reported that plasma or serum IL-31 levels were elevated in AD patients (3), and positively correlated with disease severity (4).

Mycosis fungoides (MF) and Sézary syndrome (SS) are the most common types of cutaneous T-cell lymphoma (CTCL). MF is a malignant proliferation of neoplastic T cells that preferentially traffic to the skin. SS is characterized by erythroderma, lymphadenopathy and leukaemic involvement. Laboratory findings in CTCL are similar to AD, such as eosinophilia, high serum levels of immunoglobulin E and Th2-associated chemokines (5, 6). Thus, we decided to investigate IL-31 involvement in CTCL.

MATERIALS AND METHODS

Forty patients with AD (mean \pm standard deviation (SD) age: 33.9 \pm 11.1 years), 38 patients with CTCL (34 MF cases and 4 SS cases; 58.8 \pm 13.9 years), and 23 healthy control subjects (39.4 \pm 15.2 years) were enrolled in this study. Patients with CTCL were subgrouped into patch and plaque ($n=22$), tumour ($n=11$), and erythroderma ($n=5$) according to their types of skin lesions defined by International Society of Cutaneous Lymphoma (ISCL) and the European Organization of Research and Treatment of Cancer (EORTC) (7). They were also subgrouped into stage I (21 cases), stage II ($n=7$), stage III ($n=2$) and stage IV ($n=8$) according to the staging system proposed by the ISCL/EORTC (7). The healthy controls had no history of allergy, AD, CTCL or other immune diseases. Serum samples were stored at -20°C until use. 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. Informed consent was obtained to use sera. IL-31 was quantified by an IL-31 (Human) enzyme-linked immunosorbent assay kit (Avnova, Taipei City, Taiwan). The measured values from individual patients were plotted using dots. Statistical analysis between multiple groups was performed using the one-way analysis of variance (ANOVA) (Kruskal-Wallis test) followed by Dunn's Multiple Comparison test. Correlation coefficients were determined by using the Spearman's rank correlation test. p -values <0.05 were considered statistically significant.

RESULTS

As previously reported (4), serum IL-31 levels were significantly higher in patients with AD (2.13 ± 0.26 pg/ml) than those of healthy controls (0.94 ± 0.28 pg/ml; $p < 0.01$; Fig. 1a). In addition, serum IL-31 levels were significantly higher in patients with CTCL (3.19 ± 0.74 pg/ml) than those of healthy controls ($p < 0.05$; Fig. 1a). We subsequently examined serum IL-31 levels in CTCL patients with different types of skin lesions. Serum IL-31 levels in patients with patch and plaque, tumour and erythroderma were 1.05 ± 0.30 pg/ml, 6.25 ± 2.11 pg/ml and 5.00 ± 1.46 pg/ml, respectively (Fig. 1b). Serum IL-31 levels in patients with tumour were extremely high, which were significantly higher than those with healthy controls ($p < 0.01$) and patients with patch and plaque ($p < 0.05$). Serum IL-31 levels in patients with erythroderma were also significantly higher than those in healthy controls ($p < 0.01$). Serum IL-31 levels in patients with stage I, stage II, stage III and stage IV were 0.95 ± 0.29 pg/ml, 3.97 ± 1.43 pg/ml, 2.07 ± 0.00 pg/ml and 7.98 ± 2.56 pg/ml, respectively (Fig. 1c). Serum IL-31 levels in patients with stage IV were significantly higher than those with healthy controls and patients with stage I ($p < 0.05$). Serum IL-31 levels in patients with stage II were significantly higher than those with healthy controls ($p < 0.05$). We also found that serum IL-31 levels correlated significantly with serum sIL-2R and LDH levels ($r=0.43$, $p < 0.05$ and $r=0.34$, $p < 0.05$, respectively; Fig. 1d, e), which have been reported to reflect disease activity of CTCL (8, 9). Thus, serum IL-31 levels correlate with disease activity of CTCL.

DISCUSSION

IL-31 as well as IL-31RA and OSMR β , receptors for IL-31, is expressed in varieties of tissues other than skin, such as thymus, testis, and trachea (1), suggesting that this cytokine may have potential multiple, pleiotropic physiological functions. Moreover, IL-31 stimulates secretion of proinflammatory cytokines, chemokines, and matrix metalloproteinases from human colonic subepithelial myofibroblasts (10). In this study, patients with CTCL exhibited elevated levels of serum IL-31 compared with healthy controls. A variety of cytokines and chemokines are reported to be involved in the development of CTCL (11), some of which may be regulated by IL-31.

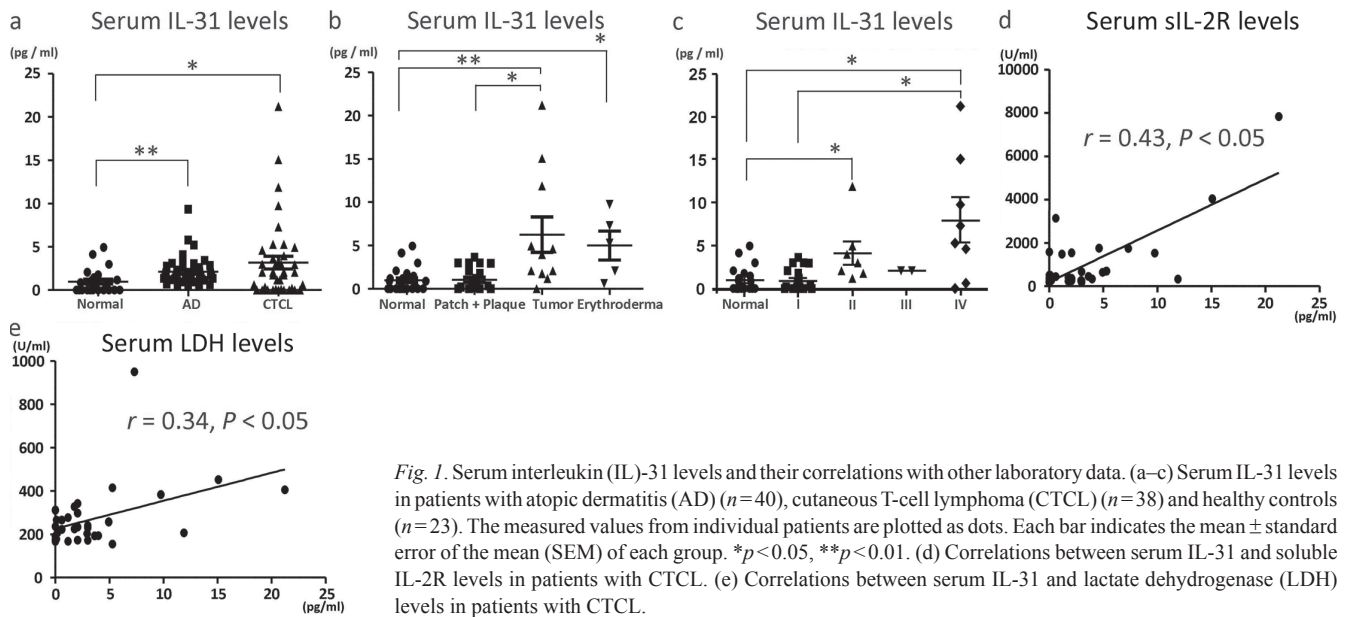


Fig. 1. Serum interleukin (IL)-31 levels and their correlations with other laboratory data. (a–c) Serum IL-31 levels in patients with atopic dermatitis (AD) ($n=40$), cutaneous T-cell lymphoma (CTCL) ($n=38$) and healthy controls ($n=23$). The measured values from individual patients are plotted as dots. Each bar indicates the mean \pm standard error of the mean (SEM) of each group. * $p < 0.05$, ** $p < 0.01$. (d) Correlations between serum IL-31 and soluble IL-2R levels in patients with CTCL. (e) Correlations between serum IL-31 and lactate dehydrogenase (LDH) levels in patients with CTCL.

Serum IL-31 levels reflected the severity of CTCL and had correlations with serum sIL-2R and LDH levels. Serological immunomarkers might be useful for disease monitoring during treatment (9). IL-31, as well as other immunomarkers, may have prognostic value for predicting the clinical course. In addition, a 2005 National Cutaneous Lymphoma Foundation survey revealed that 340 (53.9%) of 640 MF patients are affected by pruritus (12). IL-31 may play a role in causing pruritus in CTCL patients, as has been reported in AD patients (1–4).

In conclusion, serum IL-31 levels are significantly elevated and associated with disease severity in CTCL. IL-31 may play an important role in inflammatory conditions and pruritus in CTCL.

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The authors declare no conflicts of interest.

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