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INVESTIGATIVE REPORT

Association of Nerve Growth Factor, Chemokine (C-C motif) Ligands and Immunoglobulin E with Pruritus in Cutaneous T-cell Lymphoma

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Many patients with cutaneous T-cell lymphoma (CTCL) experience severe pruritus. This study evaluated serum levels of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) in patients with CTCL. Although serum NGF and BDNF levels in patients with CTCL were not significantly higher than in healthy controls, serum NGF levels in patients with Sézary syndrome were higher than in those with mycosis fungoides and in healthy controls. Enhanced NGF expression by keratinocytes and increased dermal nerve fibres were detected in lesional skin of subjects with Sézary syndrome. Correlations between pruritus in CTCL and serum levels of NGF, BDNF, chemokine (C-C motif) ligand 1 (CCL1), CCL17, CCL26, CCL27, lactate dehydrogenase (LDH), IgE, and soluble interleukin-2 receptor were analysed. Serum CCL1, CCL26, LDH, and IgE levels correlated with pruritus in patients with CTCL. NGF may be associated with increased dermal nerve fibres and pruritus in Sézary syndrome, and CCL1, CCL26, and IgE may be associated with pruritus in CTCL. ***Key words: nerve growth factor; brain-derived neurotrophic factor; pruritus; mycosis fungoides; Sézary syndrome.***

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Patients with mycosis fungoides (MF) or Sézary syndrome (SS) often have severe pruritus. A 2005 survey by the National Cutaneous Lymphoma Foundation in the USA revealed that 340 (53.9%) of 640 patients with MF were affected by pruritus (1). In a phase II trial of oral vorinostat for 33 patients with refractory cutaneous T-cell lymphoma (CTCL), 93% had symptomatic pruritus (2). Many clinical trials in patients with CTCL include pruritus relief as one of objectives in assessing the efficacy of drugs (3). However, the mechanism of pruritus in patients with CTCL remains unknown.

Nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) are members of the neurotrophin family (4, 5). NGF, mainly produced by keratinocytes stimulates the sprouting of nerve fibres and modulates the synthesis and expression of neuropeptides in the skin (6). The level of NGF is increased in inflamed skin and pretreatment with anti-NGF serum prevents increased neuropeptide expression at a neuronal level (7). BDNF is produced by a number of immune cells, including mast cells, B cells, T-helper (Th) 2 cells and eosinophils (8–10). Studies have suggested that NGF and BDNF play important roles in the pathogenesis of atopic dermatitis (AD). Serum levels of NGF and BDNF are increased, providing a useful indicator of disease activity in patients with AD (5, 11–13).

This study evaluated serum NGF and BDNF levels in patients with CTCL in order to elucidate the factors related to pruritus in CTCL. Immunohistochemical staining for NGF and protein gene product (PGP)9.5, a marker for dermal nerve fibres (14), was performed using lesional skin of patch MF, plaque MF, tumour MF, SS, AD and normal skin as reference. Moreover, the study evaluated the correlation between pruritus and serum levels of NGF, BDNF, chemokine (C-C motif) ligand 1 (CCL1), CCL17, CCL26, CCL27, lactate dehydrogenase (LDH), immunoglobulin E (IgE), and soluble interleukin-2 receptor (sIL-2R), which are reported to be elevated in patients with CTCL (15–22).

MATERIALS AND METHODS

Patients

A total of 44 patients with MF/SS (27 males and 17 females; mean ± standard deviation (SD) age: 58.8 ± 13.6 years, 22 cases of patch MF, 7 of plaque MF, 10 of tumour MF, and 5 of SS; 16 cases of stage IA, 9 of stage IB, 1 of stage IIA, 11 of stage IIB, 5 of stage IVA, 2 of stage IVB) and 32 healthy control subjects (14 males and 18 females; 40.0 ± 15.5 years) were enrolled in this study. The tumour cell load in the peripheral blood for the patients with SS ranged from 1,944 to 39,120 counts/μl (mean: 14,090 counts/μl). The diagnosis and clinical stages of MF and SS were based on WHO classification and the criteria of the International Society of Cutaneous Lymphomas (23, 24). The 32 healthy controls had no history of allergy, CTCL or any skin diseases. All samples were collected after informed consent during daily clinical practice. 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.

Enzyme-linked immunosorbent assay

Serum NGF levels were quantified using Human beta-NGF Duo set (R&D Systems, Minneapolis, USA). Serum BDNF, CCL1, CCL17, CCL26 and CCL27 levels were quantified using human

Quantikine enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems). 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 by a curve-fitting program. The detection limits of NGF and DBNF were 2 pg/ml and 0.4 ng/ml, respectively.

Immunohistochemistry

Immunohistochemical staining for NGF and PGP9.5 was performed on the lesional skin of patch MF ($n=5$), plaque MF ($n=5$), tumour MF ($n=5$), SS ($n=5$), AD ($n=5$, all extrinsic type), and with normal skin ($n=5$). Briefly, 5 µm-thick tissue sections from formaldehyde-fixed and paraffin-embedded samples were de-waxed and rehydrated. These sections were then stained with rabbit anti-human NGF monoclonal antibody (Abcam plc, Cambridge, UK), and rabbit anti-human PGP9.5 polyclonal antibody (Ultraclone, Yarmouth, Isle of Wight, UK), followed by ABC staining (Vector Lab, Burlingame, CA, USA). Diaminobenzidine was used for visualizing the staining, and counterstaining with Mayer haematoxylin was performed, according to the manufacturers' instructions.

Assessment of pruritus in patients with cutaneous T-cell lymphoma

Pruritus in patients with CTCL was evaluated using a visual analogue scale (VAS) ranging from 0 (no itching) to 10 (maximum itching). We examined the prevalence of pruritus in patients with CTCL according to the types of skin lesions and clinical stages of CTCL.

Statistical analysis

Statistical analysis was performed using the Mann–Whitney *U* test for comparison of 2 groups. For testing equality of population means among 3 or more groups, Kruskal–Wallis test and Scheffe's F test were used. *p*-values <0.05 were considered statistically significant.

RESULTS

Serum levels of NGF and BDNF in patients with cutaneous T-cell lymphoma

Serum levels of NGF in patients with CTCL did not differ from those found in healthy controls (34.7 ± 43.5 (mean ± SD) pg/ml vs. 36.1 ± 26.0 pg/ml; Fig. 1a). Serum NGF levels in patients with patch MF, plaque MF, tumour MF and SS were 21.4 ± 22.9, 16.2 ± 22.4, 39.6 ± 48.7 and 109.1 ± 54.3 pg/ml, respectively. There were statistically significant differences between SS and normal controls, patch MF, plaque MF and tumour MF ($p<0.01$, $p<0.01$, $p<0.01$, and $p<0.05$, respectively). Serum NGF levels in stage IA, stage IB, stage II, and stage IV patients were 20.8 ± 21.8, 13.4 ± 16.2, 35.3 ± 47.6 and 85.3 ± 60.4 pg/ml, respectively. There were statistically significant differences between stage IV and normal controls, stage IA, stage IB, and stage II ($p<0.05$, $p<0.01$, $p<0.01$, and $p<0.05$, respectively).

Serum levels of BDNF were similar between patients with CTCL and healthy controls (35.6 ± 19.2 ng/ml vs. 47.0 ± 24.3 ng/ml) (Fig. 1b). Serum BDNF levels in patients with patch MF, plaque MF, tumour MF and SS were 38.4 ± 18.4, 40.8 ± 28.8, 29.2 ± 20.1, and 34.4 ± 15.3 ng/ml, respectively; there were no significant differences between the groups.

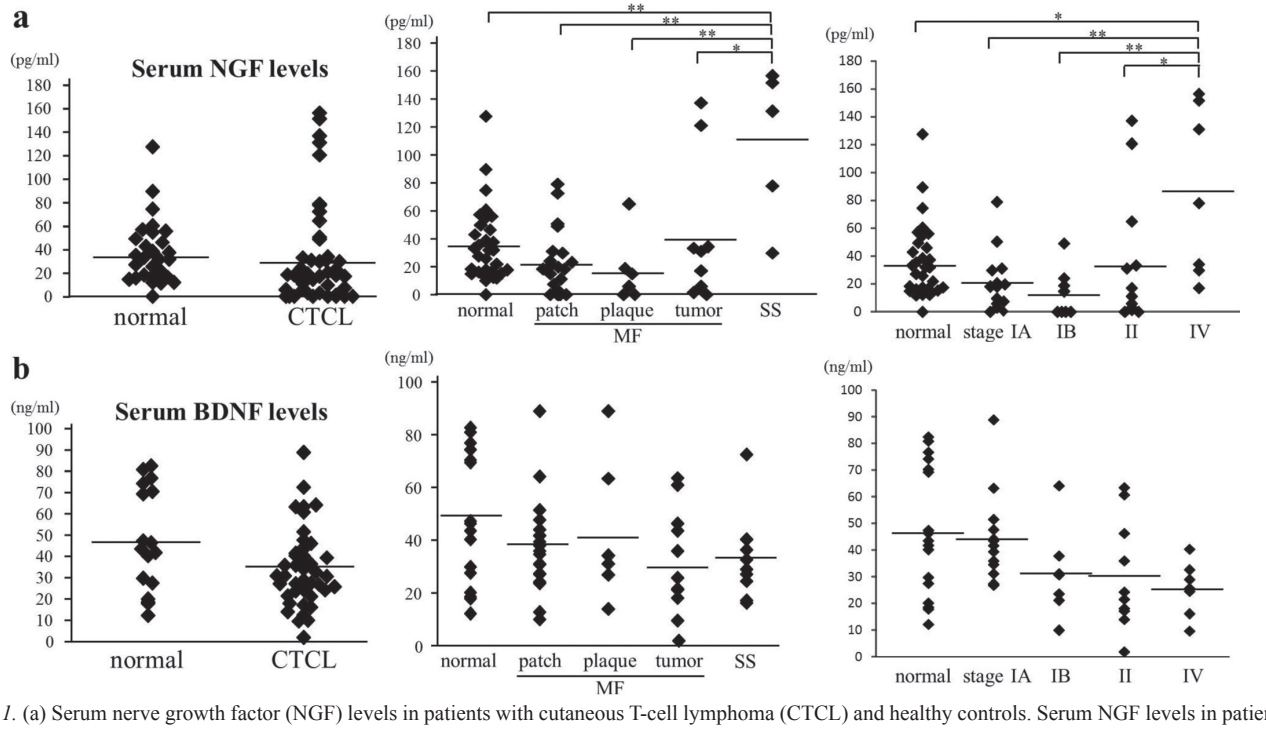

Fig. 1. (a) Serum nerve growth factor (NGF) levels in patients with cutaneous T-cell lymphoma (CTCL) and healthy controls. Serum NGF levels in patients with Sézary syndrome (SS) were significantly higher than patch, plaque, tumour mycosis fungoides (MF), and healthy controls. Serum NGF levels in stage IV patients were significantly higher than normal controls, stage IA, stage IB, and stage II patients. *$p<0.05$ and **$p<0.01$. (b) Serum brain-derived neurotrophic factor (BDNF) levels in patients with CTCL and healthy controls. There was no significant difference between the groups.

NGF expression and number of dermal nerve fibres in lesional vs. normal skin

Immunohistochemical staining for NGF and PGP9.5 was performed in biopsies of patch MF, plaque MF, tumour MF, SS, AD and normal skin (Fig. 2 and Table I). In almost all cases of SS and AD, keratinocytes showed enhanced NGF expression, while it was minimal in most cases of MF and normal skin. Similarly, increased numbers of PGP95-positive dermal nerve fibres were detected in SS and AD cases, while they were sparsely seen in most MF cases and normal skin. Thus, like in AD, enhanced NGF expression and increased numbers of dermal nerve fibres were detected in SS, which may explain the severe pruritus frequently seen in these patients.

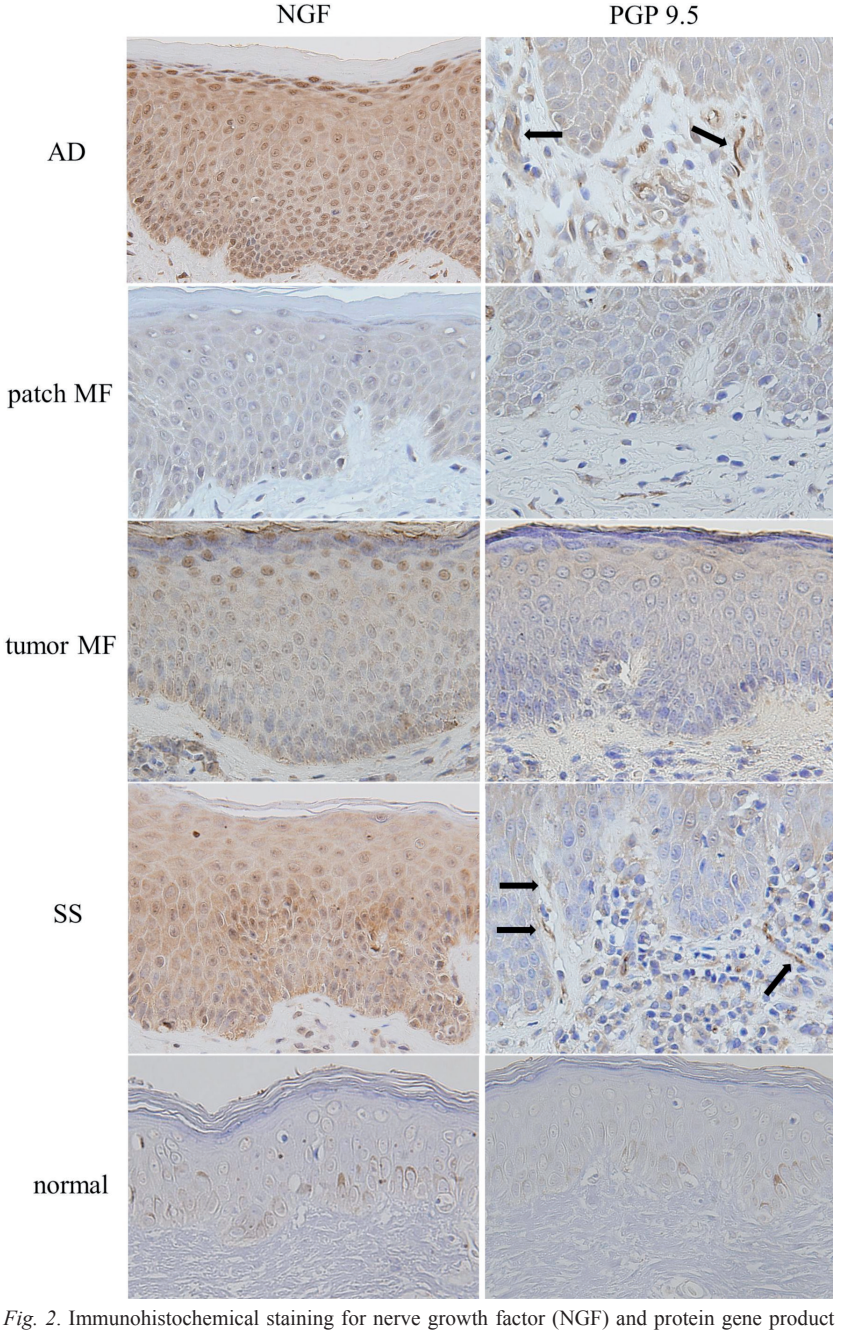

Fig. 2. Immunohistochemical staining for nerve growth factor (NGF) and protein gene product (PGP)9.5 (original magnification ×400). Representative photomicrographs of 5 cases in each group. Epidermis of the lesional skin of atopic dermatitis (AD) and Sézary syndrome (SS) showed enhanced expression of NGF (++). Epidermis of the lesional skin of tumour mycosis fungoides (MF) showed moderate expression of NGF (+) compared with patch MF and normal skins (–). Increased numbers of dermal PGP9.5^{+} nerve fibres (*arrows*) were detected in the lesional skin of AD and SS compared with patch/tumour MF and normal skin.

Assessment of pruritus in patients with CTCL

Pruritus in patients with CTCL was analysed using VAS. Patients with tumour MF or SS showed significantly higher VAS scores than those with patch MF (Fig. 3a). Moreover, stage II and stage IV patients showed significantly higher VAS scores than stage IA patients (Fig. 3b). VAS scores in stage IV patients were also higher than in stage IB patients. Thus, pruritus was more common in patients with advanced stage MF/SS, which was consistent with previous reports (25, 26).

Serum levels of NGF and BDNF, CCL1, CCL17, CCL26, CCL27, LDH, IgE and sIL-2R and their association with pruritus

Correlations between VAS scores and serum levels of NGF, BDNF, CCL1, CCL17, CCL26, CCL27, LDH, IgE and sIL-2R were analysed in patients with CTCL. Serum CCL1, CCL26, LDH and IgE levels correlated significantly with VAS scores (Fig. 4). As some researchers have reported that MF and SS represent malignancies arising from 2 different T-cell subsets (27), serum levels in SS were compared with those in MF. Serum levels of NGF, LDH and sIL-2R were significantly higher in SS than in MF (Fig. 1a and data not shown). Thus, CCL1, CCL26, LDH and IgE are associated with pruritus in patients with CTCL, while NGF is associated with SS. Increased dermal nerve fibres, probably induced by enhanced NGF expression, may explain the severe pruritus frequently seen in patients with SS.

DISCUSSION

This study measured levels of serum NGF and BDNF in patients with

Table I. *Expression of nerve growth factor (NGF) and protein gene product (PGP)9.5 in the lesional skin of patch, plaque, tumour mycosis fungoides (MF), Sézary syndrome (SS), atopic dermatitis (AD) and in normal skin (*n = *5)*

	NGF expression			PGP9.5+ nerve fibres	
Diagnosis	– *n* (%)	+ *n* (%)	++ *n* (%)	– (Not increased) *n* (%)	+ (Increased) *n* (%)
MF (patch)	4/5 (80)	1 (20)	0 (0)	5 (100)	0 (0)
MF (plaque)	4/5 (80)	1 (20)	0 (0)	5 (100)	0 (0)
MF (tumour)	2/5 (40)	2 (40)	1 (20)	4 (80)	1 (20)
SS	0/5 (0)	1 (20)	4 (80)	1 (20)	4 (80)
AD	0/5 (0)	0 (0)	5 (100)	0 (0)	5 (100)
Normal	2/5 (40)	3 (60)	0 (0)	5 (100)	0 (0)

CTCL. Levels of serum NGF in patients with SS were significantly elevated. Enhanced NGF expression by keratinocytes and increased numbers of dermal nerve fibres were detected in lesional skin of SS as well as AD. These results suggest that NGF may be essential for the survival and development of nerve fibres, and is associated with pruritus in SS as well as in AD. Analysis of correlations between pruritus in patients with CTCL and serum protein levels showed that serum CCL1, CCL26, LDH and IgE levels correlated with pruritus.

Some patients with AD present clinically as erythroderma. It can be difficult to distinguish between the erythrodermic form of AD and SS. Clinical and laboratory features, including pruritus and serum levels of sIL-2R, LDH, IgE, and several chemokines, do not differentiate SS from AD (26, 28). Our study suggests that enhanced NGF expression by keratinocytes and increased numbers of dermal nerve fibres detected in lesional skin explain severe pruritus in SS as well as in AD (29). By contrast, NGF expression was not enhanced in the sera and skin lesions of patients with MF. Although the present results support the idea that SS has some unique characteristics different from those of MF, further research is necessary to determine whether MF and SS are distinct diseases (27).

Both SS and AD are characterized by Th2-dominant immune responses (30). Th2 lymphocytes not only express TrkA, a high-affinity tyrosine kinase receptor for NGF, but also release biologically active NGF (31). It has also been shown that NGF accumulates at the sites of inflammatory response, displaying a potent chemoattractant activity for leukocytes, including eosinophils (32). Moreover, it is suggested that NGF stimulates proliferation of T lymphocytes and mast cells (33). Thus, enhanced NGF expression in patients with SS may be associated not only with pruritus, but also with tumour cell proliferation and Th2-dominat inflammatory status.

Regarding pruritus in patients with CTCL, in the present study serum levels of CCL1, CCL26, LDH and IgE correlated significantly with VAS scores. CCL1 is secreted by Langerhans' cells, endothelial cells, mast cells, monocytes, lymphocytes and epithelial cells. CC chemokine receptor (CCR)-8, a sole receptor for CCL1 (34), is expressed preferentially on Th2 cells (35). CCL1 is a potent attractant for Th2 cells, suggesting that it plays a key role in the progression of Th2 type diseases. Indeed, serum CCL1 levels in AD patients were reported to be higher than those in healthy controls (36). Moreover, we showed previously that serum CCL1 levels in patients with CTCL are increased, whereas those in

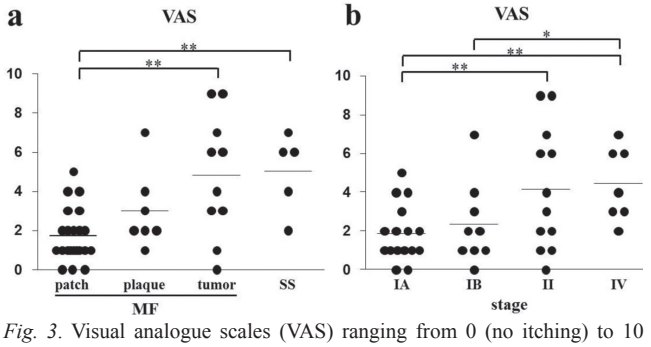

Fig. 3. Visual analogue scales (VAS) ranging from 0 (no itching) to 10 (maximum itching) in patients with cutaneous T-cell lymphoma. MF: mycosis fungoides; SS: Sézary syndrome. (a) Patients with tumour MF or SS showed significantly higher VAS scores than those with patch MF. *$p<0.05$. (b) Stage II and stage IV patients showed significantly higher VAS scores than stage IA patients. *$p<0.05$ and **$p<0.01$.

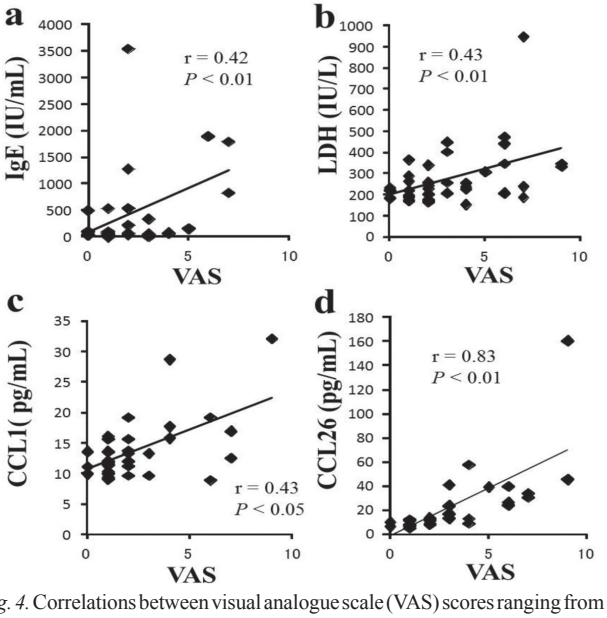

Fig. 4. Correlations between visual analogue scale (VAS) scores ranging from 0 (no itching) to 10 (maximum itching) and serum levels of (a) immunoglobulin E (IgE), (b) lactate dehydrogenase (LDH), (c) chemokine (C-C motif) ligand 1 (CCL1), and (d) CCL26 in patients with cutaneous T-cell lymphoma.

psoriatic patients are decreased compared with healthy controls (15). Taken together, CCL1 seems to be related to both disease activity and pruritus in CTCL through regulation of the Th2-dominant tumour environment.

CCL26 is a ligand for CCR3. CCR3 is preferentially expressed on eosinophils and Th2 cells (37). We have shown that cultured fibroblasts isolated from the lesional skin of CTCL express higher amounts of CCL26 mRNA compared with those from normal skin (16). The lesional skin of advanced-stage CTCL contained significantly higher levels of CCL26 mRNA compared with early-stage CTCL (16). Moreover, serum levels of CCL26 in advanced-stage CTCL were significantly higher than in normal controls (16). Eosinophil counts ranged from 0 to 1,467 counts/μl (mean: 210 counts/μl) in patients with CTCL. Although no correlation was found between serum levels of CCL26 and eosinophil counts in patients with CTCL, association of up-regulation of CCL26 and activated eosinophils has been described in bullous pemphigoid (38, 39). Taken together, CCL26, as well as CCL1, seem to be associated with both the disease activity and pruritus in CTCL.

Pruritus is most common in advanced-stage MF/SS, in which LDH is often elevated (17). Correlation between VAS scores and serum levels of LDH may simply reflect the disease activity. Serum levels of IgE are also reported to be elevated in patients with CTCL (19, 26). IgE binds to Fc receptors expressed on the surface of mast cells, basophils, eosinophils, monocytes and macrophages, releasing chemical mediators such as histamines and various cytokines. IgE production is promoted by IL-4 produced by Th2 cells, and suppressed by interferon-gamma (19). In patients with CTCL, the Th2-dominant environment may promote IgE production, which in turn may induce pruritus.

One limitation of this study is that some patients had already been treated with anti-histamines or oral steroids at the time of blood collection. Another limitation is that there are only 5 patients with SS in this study. There are fewer than 10 new patients with SS in Japan each year. Further research with a larger number of patients is needed.

In summary, expression of NGF is enhanced in the sera and skin lesions of SS, and might be associated with increased dermal nerve fibres and severe pruritus. Serum CCL1, CCL26 and IgE levels were found to correlate with pruritus in patients with CTCL, thus they might be possible novel therapeutic targets for pruritus in CTCL.

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The authors declare no conflicts of interest.

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