

ORIGINAL ARTICLE

Increased serum levels of interleukin 33 in patients with atopic dermatitis

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Background: Interleukin (IL)-33 is a new member of the IL-1 cytokine family and a promoter of T helper type 2 (Th2) inflammation. IL-33 may be involved in the pathogenesis of atopic dermatitis (AD), but its relationship with disease severity, laboratory markers, and eruption types in patients with AD are unclear.

Objective: The aim of this study was to quantify serum IL-33 levels in patients with AD and to examine relationships with disease severity, laboratory markers, and eruption types.

Methods: Serum IL-33 was measured by enzyme-linked immunosorbent assay in patients with AD, chronic idiopathic urticaria, and psoriasis and in healthy control subjects.

Results: Serum levels of IL-33 were significantly higher in patients with AD compared with those in patients with urticaria and psoriasis and in healthy control subjects, and were correlated with the disease severity of AD. IL-33 levels were also significantly correlated with excoriation and xerosis scores, but not with blood eosinophilia, serum IgE, serum thymus and activation-related chemokine, and serum lactate dehydrogenase. Elevated IL-33 levels were significantly reduced after improvement of skin lesions by drug treatment.

Limitation: A limitation in the study was the small number of subjects.

Conclusion: Our results suggest that IL-33 released from mechanically injured or barrier-disrupted skin may increase inflammation in AD. (J Am Acad Dermatol <http://dx.doi.org/10.1016/j.jaad.2014.01.867>.)

Key words: atopic dermatitis; excoriation; inflammation; interleukin 33; psoriasis; urticaria; xerosis.

Interleukin (IL)-33 is a new member of the IL-1 family of cytokines, which also includes IL-1 β and IL-18.¹ IL-33 binds to its receptors ST2 and IL-1RAcP.^{1,2} ST2, which is also known as T1, IL-1RL1, and DER4, is strongly expressed on Th2 cells, mast cells, and eosinophils,¹⁻⁴ and IL-33 activates these cells and promotes Th2-type immune responses.¹ Recent data suggest that IL-33 is involved in the pathogenesis of various allergic diseases, and associations between genetic polymorphism of IL-33 and asthma⁵ and allergic rhinitis⁶ have been described. Significantly higher serum IL-33 levels have also been

Abbreviations used:

AD: atopic dermatitis
EASI: Eczema Area and Severity Index
IL: interleukin

found in patients with Japanese cedar pollinosis compared with healthy control subjects.⁶ IL-33 has also been suggested to be involved in the pathogenesis of animal models of asthma,⁷ allergic rhinitis,⁸ and allergic conjunctivitis.⁹

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Atopic dermatitis (AD) is a chronic eczematous skin disease characterized by increased levels of Th2 cytokines such as IL-4 and IL-5, high serum IgE levels, positive immediate hypersensitivity to food or environmental allergens, and peripheral blood eosinophilia.¹⁰ Recent reports have described involvement of IL-33 in the pathogenesis of AD.¹¹⁻¹⁵ Expression of IL-33 is increased in keratinocytes, endothelial cells, and fibroblasts of lesional skin in patients with AD^{11,12} and injection of recombinant IL-33 into mouse skin elicits production of Th2 cytokines¹³ and accumulation of eosinophils, T cells, and macrophages.¹⁴ Imai et al¹⁵ have also shown development of spontaneous itchy dermatitis resembling features of AD, such as eosinophil infiltration in inflamed skin and high serum IgE levels, in transgenic mice expressing the IL-33 gene. Genetic polymorphisms in the ST2 gene region also have a strong association with AD¹⁶ and ST2 is found mainly in dermal infiltrating cells in patients with AD.¹¹

These findings suggest that IL-33 may be important in the pathomechanism of AD. However, the relationships between serum IL-33 levels and disease severity, laboratory markers, and eruption types in patients with AD are unknown. In the current study, we evaluated serum levels of IL-33 in patients with AD, urticaria, and psoriasis, and in healthy control subjects, and examined whether these levels correlated with disease severity, laboratory markers, and eruption types in patients with AD. We also examined changes in the marker levels in association with improvement of eruption in AD.

METHODS

Subjects

A total of 62 adult patients (43 men, 19 women; median age: 31 years old; range: 16-55 years old) with AD were randomly selected and enrolled in the study. Diagnosis of AD was based on the criteria of Hanifin and Rajka¹⁷ and clinical severity was determined using the Eczema Area and Severity Index (EASI) score¹⁸ (median score: 27.0; range: 5.8-58.4). Based on the EASI score, patients with AD were divided into 3 groups: mild (score <10), moderate (score 10-20), and severe (score >20). Skin lesion severity (erythema score, edema/papule score, oozing/crust score, excoriation score, lichenification score, and xerosis score) and itch severity were

evaluated in areas of most affected skin, as previously described.¹⁹ Peripheral blood was obtained when the eruptions in patients with AD were exacerbated. The peripheral eosinophil count (median: 597 μ L; range: 10-3220/ μ L; reference range: 50-590/ μ L), serum IgE (median: 4855 IU/mL; range: 125-54,500 IU/mL; reference range: 0-380 IU/mL),

serum lactate dehydrogenase (median: 255 IU/L; range: 114-762 IU/L; reference range: 120-240 IU/L), and serum thymus and activation-regulated chemokine (TARC/CCL17) (median: 1807 IU/L; range: 152-30,623 IU/L; reference range: 0-449 pg/mL) were also examined. Each patient had a history of AD for more than 3 years. Patients were treated with conventional therapy, including systemic antihista-

mine and topical steroids and calcineurin inhibitors. Patients were not treated with systemic steroids or immune suppressive agents.

Thirty-five patients with chronic idiopathic urticaria (18 men, 17 women; median age: 30 years old; range: 22-50 years old) were also included in the study. All these patients had experienced occurrence of urticaria several times a week for at least 6 weeks. Eighteen patients with psoriasis (16 men, 2 women; median age: 48 years old; range: 28-78 years old) were also included in the study. Severity of psoriasis was assessed using the Psoriasis Area and Severity Index score²⁰ (median score 15.2; range 12.2-18.7). The control group consisted of 22 healthy subjects (12 men, 10 women; median age: 28 years old; range: 24-43 years old) who had not taken any medication for at least 2 weeks preceding the study. All subjects gave written consent and the study was approved by the university ethics committee and conducted in accordance with the Declaration of Helsinki.

Measurement of IL-33 in blood samples

Serum levels of IL-33 were measured by enzyme-linked immunosorbent assay kits for quantitative detection of IL-33 (BioLegend, San Diego, CA). The reference range for the enzyme-linked immunosorbent assay kit was 0 to 1000 pg/mL. When a sample's value fell outside the reference range for the enzyme-linked immunosorbent assay kit, the sample was reanalyzed at a higher dilution. All measurements were made in triplicate and mean values were obtained.

CAPSULE SUMMARY

- Interleukin (IL)-33 is a Th2 cytokine involved in the pathogenesis of atopic dermatitis (AD).
- IL-33 levels are correlated with severity of AD and IL-33 released from damaged skin may increase inflammation in AD.
- IL-33 may be a useful marker for monitoring the outcome of drug therapy for AD.

Statistical analysis

Data are expressed as means $\pm$ SD unless otherwise indicated. A Mann-Whitney U test was used to compare variables between 2 groups because most data were not normally distributed. Spearman rank correlation analysis was used to examine the relationship between 2 continuous variables. Multiple regression analysis was performed to assess the relationships between serum IL-33 levels and age, gender, disease severity, and history of other atopic diseases. The receiver operating characteristic curve was prepared and analyzed using data from patients with AD. Paired samples were analyzed by Wilcoxon signed ranks test. Differences with P less than .05 were considered to be statistically significant.

RESULTS

Serum levels of IL-33 in patients with AD and urticaria

Serum levels of IL-33 in patients with AD (median 71.0; range 34–4296 U/mL) were significantly higher than those in control subjects (median 5.9; range 0–75 U/mL) ($P < .01$), patients with urticaria (median 32.0; range 22–233 U/mL) ($P < .01$), and psoriatic patients (median 37.1; range 0–176 U/mL) ($P < .01$) (Fig 1). There was no significant difference in serum IL-33 levels between patients with urticaria or psoriasis and control subjects. The average coefficient of variation for the 3 measurements in all tests was 5.9%.

Relationship of IL-33 with disease severity in patients with AD

Serum levels of IL-33 were significantly correlated with EASI scores in patients with AD ($r = 0.331$, $P < .001$) (Fig 2). The receiver operating characteristic curve establishing cut-off levels between patients with moderate and severe AD for serum IL-33 levels is shown in Fig 2. The area under the receiver operating characteristic curve was determined to be 0.890. This procedure was used to obtain a cut-off value, 68.18 pg/mL, giving the maximum efficiency in prediction of moderate to severe AD with a sensitivity of 82% and a specificity of 91%.

Relationship of IL-33 with eruption type in patients with AD

Correlations between serum IL-33 and skin lesion severity (erythema score, edema/papule score, oozing/crust score, excoriation score, lichenification score, and xerosis score) were evaluated in the areas of most affected skin in the patients with AD. Among the 6 types of eruptions, erythema, edema/papule, oozing/crust, excoriation, lichenification, and xerosis, serum IL-33 levels were significantly correlated with the excoriation score ($r = 0.299$, $P = .018$) and

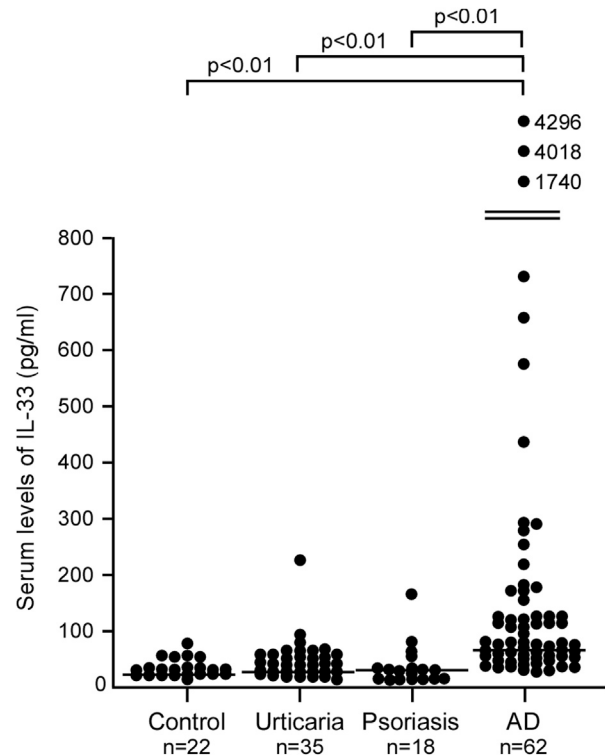


Fig 1. Serum levels of interleukin (IL)-33 in patients with atopic dermatitis (AD) ($n = 62$), patients with chronic idiopathic urticaria ($n = 35$), patients with psoriasis ($n = 18$), and healthy control subjects ($n = 22$). IL-33 levels were measured by enzyme-linked immunosorbent assay.

the xerosis score ($r = 0.287$, $P = .024$), but not with the erythema score ($r = 0.060$, $P = .644$), edema/papule score ($r = 0.039$, $P = .764$), oozing/crust score ($r = -0.039$, $P = .763$), or lichenification score ($r = -0.168$, $P = .192$) (Fig 3). The itching score was also not correlated with the serum IL-33 level ($r = -0.209$, $P = .103$) (Fig 3).

Relationship of IL-33 with laboratory markers in patients with AD

Relationships were examined between serum levels of IL-33 and laboratory markers known to be elevated in AD. Serum levels of IL-33 were not significantly correlated with serum IgE levels ($n = 59$; $r = -0.138$, $P = .298$), peripheral eosinophil count ($n = 61$; $r = -0.114$, $P = .381$), serum lactate dehydrogenase ($n = 60$; $r = 0.058$, $P = .657$), or TARC ($n = 54$; $r = -0.099$, $P = .473$) (Table I).

Relationship of IL-33 with age, gender, the EASI score, and history of asthma and rhinoconjunctivitis in patients with AD

To analyze which factor among age, gender, the EASI score, and history of asthma and rhinoconjunctivitis related to elevation of serum IL-33 levels,

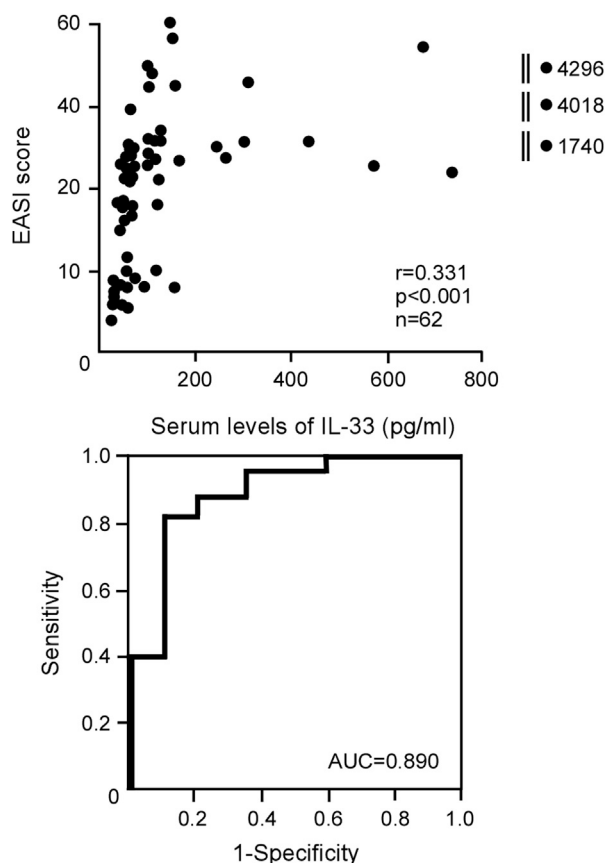


Fig 2. Relationship between serum levels of interleukin (IL)-33 and Eczema Area and Severity Index (EASI) scores in patients with atopic dermatitis (AD) ($n = 62$), and the receiver operating characteristic curve establishing cut-off levels between patients with moderate and severe AD for serum IL-33 levels ($n = 50$). AUC, Area under curve.

multiple regression analysis was performed. The multiple regression analysis showed that the EASI score accounted for elevation of serum IL-33 levels among these factors (Table II).

Changes in serum IL-33 levels before and after treatment

A comparison of serum levels of IL-33 was performed before and after treatment in 10 patients with AD who received conventional therapy with topical steroids and calcineurin inhibitors. Serum samples were collected after 4 to 8 weeks of therapy when skin lesions had improved. At this time, the mean EASI score of the 10 patients had decreased from 28.3 to 6.6 ($P < .01$), with corresponding decreases in the mean serum levels of IL-33 from 595.5 to 73.0 pg/mL ($P < .05$) (Fig 4).

DISCUSSION

The results of the study show that serum levels of IL-33 are significantly elevated in patients with AD

compared with healthy control subjects. Serum IL-33 level was significantly associated with the EASI score and the elevated IL-33 levels were significantly reduced after clinical improvement of skin lesions. These findings suggest that IL-33 plays an important role in the pathomechanism of AD.

The serum levels of IL-33 were also correlated with the xerosis score among the 6 types of eruptions, erythema, edema/papule, oozing/crust, excoriation, lichenification, and xerosis. Dickel et al²¹ have shown up-regulation of IL-33 messenger RNA in human skin after tape stripping and expression of IL-33 is spontaneously up-regulated in the skin of filaggrin-deficient mice, which have defects in skin barrier function.¹¹ These findings suggest that skin barrier dysfunction is sufficient to elicit expression of IL-33. Epicutaneous sensitization with protein antigen after tape stripping has been shown to induce Th2-dominated immune responses.^{22,23} Our previous study showed that expression of thymic stromal lymphopoietin, which is also an epithelial cell-derived cytokine, similarly to IL-33, is elevated and correlated with the xerosis score in the stratum corneum of patients with AD.¹⁹ Thymic stromal lymphopoietin is also increased in skin tissue by tape stripping and induces Th2 polarization of cutaneous dendritic cells.^{24,25} These findings suggest that skin barrier dysfunction may elicit expression of tissue-derived cytokines such as IL-33 and thymic stromal lymphopoietin, leading to development of Th2-type immune responses in patients with AD.

Serum levels of IL-33 were also correlated with the excoriation score among the 6 types of eruptions, erythema, edema/papule, oozing/crust, excoriation, lichenification, and xerosis. Patients with AD often scratch their skin because of itch, resulting in excoriation, and the itch-scratch cycle further promotes skin inflammatory reactions. Whereas other members of the IL-1 family, IL-1 and IL-18, require maturation by caspase-1 for biological activity, IL-33 is produced in an active full-length form and is stored in the nucleus. Damage to cells induces necrosis and release of full-length IL-33. During apoptosis, IL-33 is cleaved by caspase-3/7, leading to its inactivation.²⁶ Therefore, it has been hypothesized that IL-33 acts as an endogenous “danger signal” or “alarmin” that may alert the immune system in response to tissue damage.²⁷ Our results imply that tissue injury caused by scratching of the skin may result in increased release of IL-33 from damaged cells in patients with AD.

IL-33 is released from skin structural cells by trigger factors such as mechanical injury, allergens, and bacteria,^{11,28} and acts on various ST2-expressing cells, such as Th2 cells, mast cells, and eosinophils. IL-33 induces increased release of Th2 cytokines

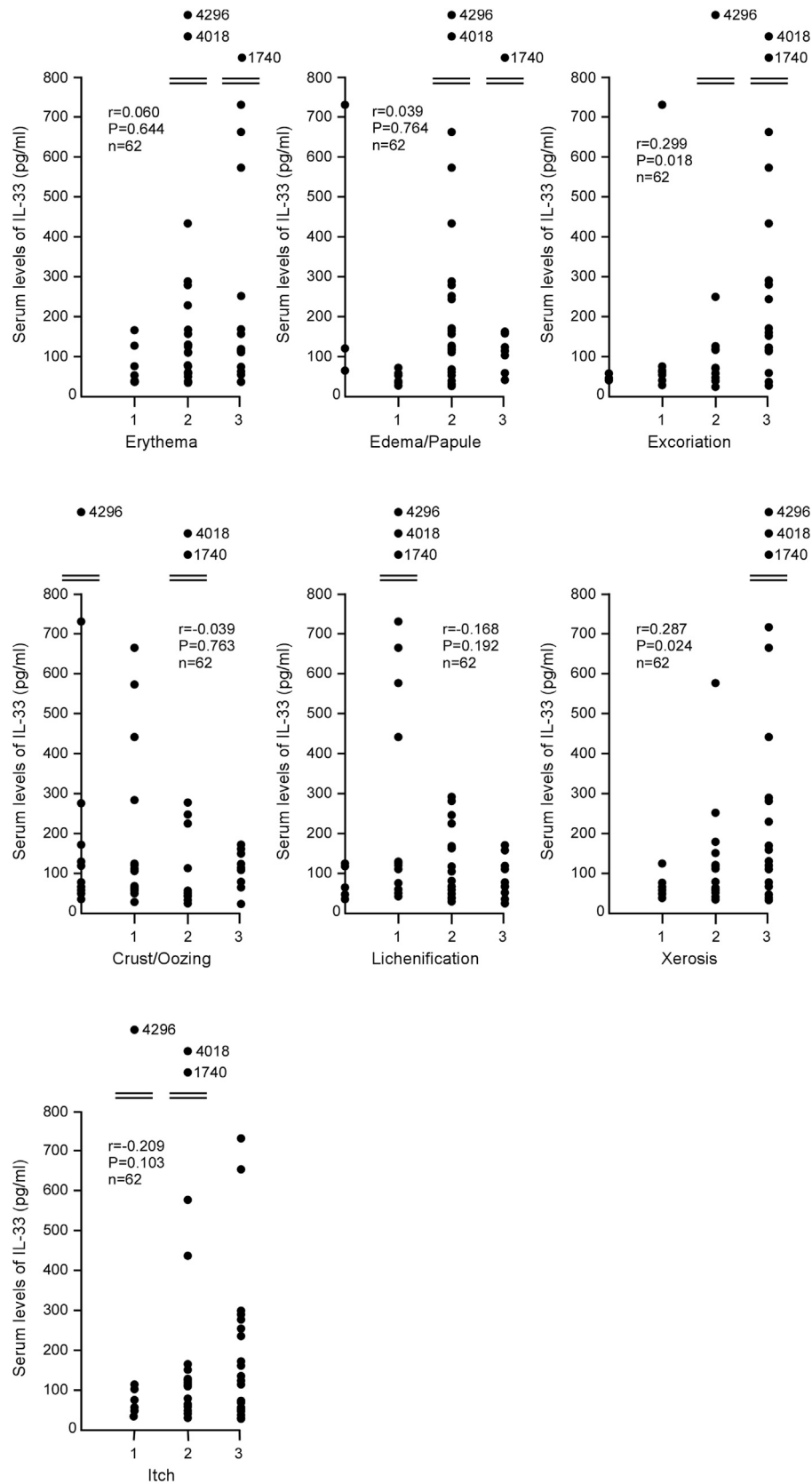


Fig 3. Relationship between serum levels of interleukin (IL)-33 and skin symptom severity scores for the most affected skin in patients with atopic dermatitis (n = 62).

Table I. Correlation between serum interleukin 33 levels and laboratory markers

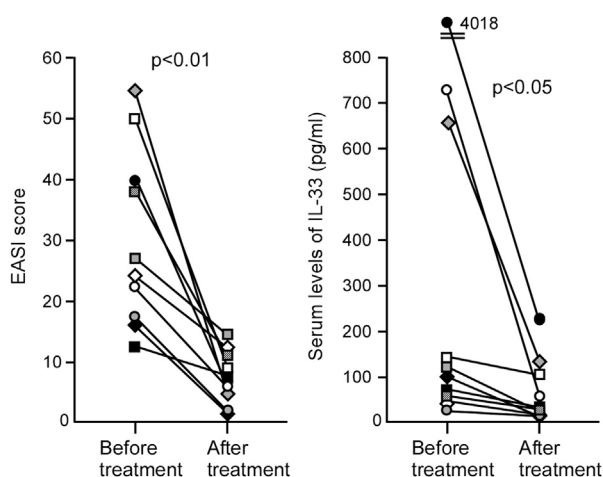
	<i>r</i>	<i>P</i>
Serum IgE levels (n = 59)	−0.138	.298
Peripheral eosinophil count (n = 61)	−0.114	.381
Serum LDH (n = 60)	0.058	.657
Serum TARC (n = 54)	−0.099	.473

LDH, Lactate dehydrogenase; TARC, thymus and activation-related chemokine.

Table II. Multiple regression analysis to evaluate which factors account for elevation of serum interleukin 33 levels

	Standard partial regression coefficient	<i>P</i>
Age	0.059	.654
Gender (female = 0; male = 1)	−0.226	.076
EASI score	0.386	.005
History of asthma (no = 0; yes = 1)	−0.067	.589
History of rhinoconjunctivitis (no = 0; yes = 1)	−0.190	.153

EASI, Eczema Area and Severity Index.

**Fig 4.** Changes in Eczema Area and Severity Index (EASI) scores and serum levels of interleukin (IL)-33 before and after treatment in paired samples obtained from 10 patients with atopic dermatitis.

such as IL-5 and IL-13 from Th2 cells in vitro and elevated levels of serum IgE and blood eosinophils in vivo.¹ IL-33 also causes activation, maturation, and Th2 cytokine production in mast cells^{12,29} and induces eosinophil-dependent cutaneous fibrosis.¹⁴ Thus, IL-33 may play a pivotal role in the development of inflammatory reactions and fibrotic remodeling in AD.

Our study showed that serum levels of IL-33 were not increased in patients with chronic idiopathic

urticaria compared with healthy control subjects. Urticaria occurs as a clinical manifestation of immunologic mechanisms, or may be idiopathic.³⁰ Urticarial reactions may develop after IgE- or IgE receptor-dependent reactions or after direct mast cell degranulation. Levels of IL-33 are markedly elevated in serum and tissue from patients with AD during anaphylactic reactions that are systemic immediate-type hypersensitivity reactions involving IgE antibodies.¹² IL-33 also causes antigen-independent passive cutaneous and systemic anaphylaxis in a mast cell-dependent manner in a murine model of AD.¹² Therefore, IL-33 may be involved in the mechanisms of urticarial reactions in patients with AD, but may not be closely associated with the pathogenesis of nonatopic chronic urticaria.

Furthermore, serum levels of IL-33 were not elevated in patients with psoriasis compared with healthy control subjects. Psoriasis is a chronic inflammatory disorder of the skin. Psoriatic plaque is characterized by the infiltration of leukocytes, such as T cells, and excessive keratinocyte proliferation. It is thought that the pathogenesis of psoriasis is associated with several pathways such as the IL-17 pathway.³¹ Our results suggest that IL-33 may not be deeply involved in the pathomechanism of psoriasis.

In conclusion, our results indicate that serum levels of IL-33 are elevated in patients with AD and are closely related to the EASI score in these patients. The elevated levels of IL-33 were significantly reduced after improvement of skin lesions, and serum IL-33 levels were also significantly correlated with excoriation and xerosis scores. These findings suggest that IL-33 is heavily involved in the pathomechanism of AD, and that mechanical injury and barrier disruption can lead to IL-33 release from skin tissue. Serum IL-33 levels may be a useful indicator of the disease severity of AD.

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