

An H1-histamine receptor antagonist decreases serum interleukin-31 levels in patients with atopic dermatitis

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MADAM, Atopic dermatitis (AD) is an intractable inflammatory skin disease characterized by an intensely pruritic skin rash with a typical morphology and distribution in accordance with an impaired skin barrier. Pruritus in AD affects quality of life and is sometimes difficult to control. There is a wide variety of mediators of pruritus, including histamine, neuropeptides, prostaglandins, serotonin and bradykinin.

It has recently been reported that interleukin (IL)-31, a 4-helix-bundle cytokine, is a new candidate of itch mediator, preferentially produced by T cells skewed toward Th2.¹ Transgenic mice overexpressing IL-31 spontaneously developed severe pruritus, resulting in eczematous skin lesions with hyperkeratosis, acanthosis and inflammatory cell infiltration, which closely resembled those of AD.¹ Leucocytes in patients with AD expressed significantly higher IL-31 levels compared with those of control subjects.² In addition, IL-31 levels correlate with disease activity in AD.³

Epinastine is an H1-histamine receptor antagonist that is widely used throughout the world (18 countries). As epinastine is known to inhibit the development of Th2 immune responses,⁴ it is of interest to evaluate the effect of epinastine on IL-31 expression. In this study, we have evaluated the effect of epinastine on serum IL-31 levels in patients with AD in line with pruritus.

After obtaining informed consent and approval by the local ethics committee, peripheral blood was taken from 12 Japanese patients with AD (10 men and two women; mean age 38 years, range 19–66) before and after 1 month of treatment with oral epinastine 20 mg daily. During the study the subjects were not treated with any other oral antihistamine, ciclosporin or corticosteroids except for topical steroid ointment. Severity of

pruritus was assessed by a visual analogue scale (VAS) score (0–100). Serum IL-31 levels were measured with a commercially available enzyme-linked immunosorbent assay kit (PeproTech Inc., Rocky Hill, NJ, U.S.A.). The mean $\pm$ SEM serum IL-31 levels and VAS score were 206.6 ± 79.4 pg mL⁻¹ and 55.8 ± 4.9 in patients with AD before epinastine treatment. Mean $\pm$ SEM serum IL-31 levels and VAS score were significantly decreased (66.9 ± 42.3 pg mL⁻¹ and 50.0 ± 5.9 , respectively) in patients with AD after treatment with epinastine (Fig. 1a, b). No adverse effects of the medication were reported.

While epinastine decreased both serum IL-31 levels and VAS score, there was no association between these two factors (data not shown). This is probably because VAS depends on subjective sensation of the patients and there is no objective measurement for intensity of itch. Although we analysed serum IL-31 levels and VAS score in a relatively small group with AD, our results raise the possibility that serum IL-31 levels may be a candidate to evaluate the extent of pruritus objectively.

A recent study has demonstrated that the H4-histamine receptor in T cells is upregulated under Th2 conditions, and its stimulation leads to induction of IL-31.⁵ It has been reported that epinastine inhibits the development of Th2 immune responses through the modulation of dendritic cell functions.⁴ Although epinastine is an H1-histamine receptor antagonist, it may cross-react with H4-histamine receptor. It is of interest how other antipruritic drugs including antihistamines affect IL-31 production. Although there still remains much to learn, we report here that epinastine, an H1-histamine receptor antagonist, has the potential to decrease serum IL-31 levels in patients with AD.

*Department of Dermatology and

†Center for Innovation in Immunoregulative Technology and Therapeutics, Kyoto University Graduate School of Medicine, 54 Shogoin-Kawara, Sakyo, Kyoto 606-8507, Japan
Correspondence: Kenji Kabashima.
E-mail: kaba@kuhp.kyoto-u.ac.jp

A. OTSUKA*†

T. HONDA*

H. DOI*

Y. MIYACHI*

K. KABASHIMA*

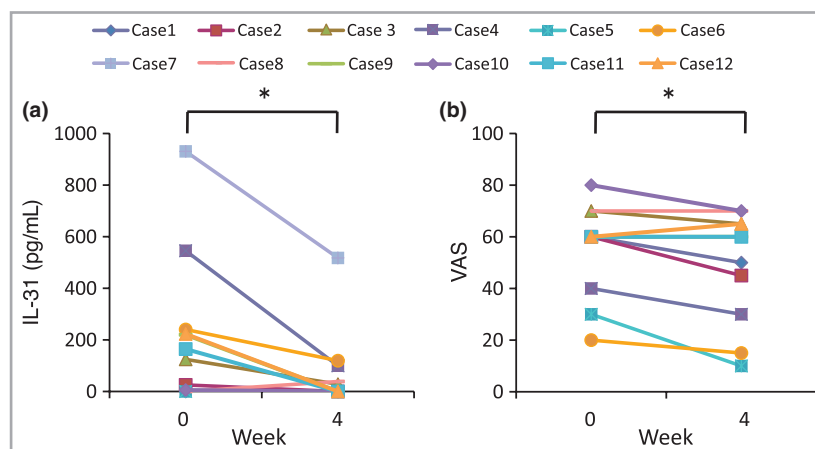


Fig 1. Serum interleukin (IL)-31 levels (a) and visual analogue scale (VAS) scores (b) in patients with atopic dermatitis ($n = 12$) before and after epinastine treatment. Data were analysed with the paired t -test. *Statistically significant at $P < 0.05$.

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Primary cutaneous CD8+ small/medium-sized pleomorphic T-cell lymphoma, ear-type: a unique cutaneous T-cell lymphoma with a favourable prognosis

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MADAM, Compared with CD4+ primary cutaneous T-cell lymphomas (CTCLs), CD8+ CTCLs occur infrequently. Among CD8+ CTCLs, CD8+ variants of CD4+ CTCL predominate; these display clinical features and prognosis similar to their CD4+ counterparts. According to the World Health Organization (WHO)–European Organisation for Research and Treatment of Cancer (EORTC) classification for cutaneous lymphomas, CD8+ variants of CD4+ CTCL occur in mycosis fungoides and its variant pagetoid reticulosis, Sézary syndrome (SS), CD30+ lymphoproliferative disorders, subcutaneous panniculitis-like T-cell lymphoma and nasal-type natural killer/T-cell lymphoma.¹ Among the provisional entities in the WHO–EORTC classification, primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma is defined by CD8 expression and is almost invariably associated with a fatal clinical outcome. In contrast, the provisional entity of small/medium-sized pleomorphic CTCL was defined by the expression of CD4 to exclude the few CD8 cases that could not be lumped together by clinical presentation, histomorphology and course of disease.² Recently, several groups have reported on an indolent CD8+ lymphoid proliferation on the ear with highly characteristic clinical and pathological features in a total of 10 patients.^{3–6} Here we describe another patient with this condition and suggest classifying this novel entity as primary cutaneous CD8+ small/medium-sized pleomorphic T-cell lymphoma, ear-type.

A 61-year-old man presented with a 3-year history of a recurrent erythematous, tender swelling of the left ear

(Fig. 1). Routine laboratory tests were normal, while a total body contrast-enhanced computed tomography scan revealed minor cervical, axillary and paratracheal lymphadenopathy that remained stable 6 months later. Repeated histological examination revealed a dense, diffuse, lymphoid infiltration in the dermis with a clear-cut Grenz zone towards the epidermis that consisted of monoclonal CD3+, CD5+, CD8+, TIA-1+, CD4–, perforin-negative pleomorphic, medium-sized lymphocytes with a low proliferation index (Fig. 1). As this case resembled indolent CD8+ lymphoid proliferation of the ear,⁶ the patient did not receive any further therapeutic interventions and did not show progression over more than 12 months.

Indolent CD8+ lymphoid proliferation of the ear was first described by Petrella et al.⁶ The four reported cases were characterized by an indolent clinical behaviour and a histology suggesting high-grade lymphoma. Immunohistochemistry revealed a CD4–, CD8+, TIA-1+, granzyme B-negative phenotype with a low proliferative index. A monoclonal rearrangement of the T-cell receptor genes was found by polymerase chain reaction in three out of three cases. Beltraminelli et al., Suchak et al. and Li et al. described a total of six additional cases on the ear or nose with similar clinical and histological features.^{3–5} Clinical and histological features of all 11 published cases including our case are summarized in Tables 1 and 2. Analysis revealed a predilection for males (M : F, 9 : 2) and a mean age of 54 years (range 29–69). The preferred site of involvement was the ear (10 of 11). Staging procedures, when done, were normal in all cases and treatment was either surgery, radiation or none. Consistently, a monoclonal infiltration of CD3+, CD8+, TIA-1+, CD4–, CD30–, CD56–, granzyme B-negative, perforin-negative small/medium-sized pleomorphic lymphocytes without epidermotropism was found on histological, immunohistochemical and molecular examination.

Beltraminelli et al. and Suchak et al. both proposed that this entity might be a CD8+ variant of small/medium-sized pleomorphic CTCL.^{3,4} Although small/medium-sized pleomorphic CTCL is defined as CD4+/CD8–,¹ CD8+ variants have been described (three out of 136⁷), but no detailed analysis of these cases exists^{2,7,8} leading to exclusion from the WHO–EORTC classification of small/medium-sized pleomorphic CTCL. In addition, in most series, CD8+ CTCLs are mainly composed of medium-to-large pleomorphic lymphocytes and show an aggressive clinical behaviour suggesting CD8+ primary cutaneous aggressive epidermotropic cytotoxic T-cell lymphoma.^{2,9,10} Thus, CD8+ small/medium and medium/large pleomorphic CTCLs seem to be a heterogeneous group that requires further analysis to minimize confusion.

In contrast, the cases reviewed here are highly homogeneous by clinical appearance and localization as well as by histology, immunohistochemistry and molecular biology, and they are associated with a favourable prognosis. Therefore, we propose that these cases do not merely represent an otherwise indiscernible CD8+ variant of CD4+ small/medium-sized pleomorphic CTCL, but constitute a novel entity that should be referred to as primary cutaneous CD8+ small/medium-sized pleomorphic T-cell lymphoma, ear-type.