

**Successful dupilumab treatment for ichthyotic and atopic  
 features of Netherton syndrome**

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Complete List of Authors:	Murase, Chiaki; Nagoya University Graduate School of Medicine, Dermatology Takeichi, Takuya; Nagoya University Graduate School of Medicine, Dermatology Taki, Tomoki; Nagoya University Graduate School of Medicine, Dermatology Yoshikawa, Takenori; Nagoya University Graduate School of Medicine, Dermatology Suzuki, Akiko; Fujita Health University, Department of Dermatology Ogi, Tomoo; Department of Genetics, Research Institute of Environmental Medicine Suga, Yasushi; Juntendo University Urayasu hospital, Department of Dermatology Akiyama, Masashi; Nagoya University Graduate School of Medicine, Department of Dermatology
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13 *Letters to the Editor*

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17 **Successful dupilumab treatment for ichthyotic**  
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21 **and atopic features of Netherton syndrome**

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27 Chiaki Murase, MD, PhD<sup>a</sup>, Takuya Takeichi, MD, PhD<sup>a</sup>, Tomoki Taki, MD, PhD<sup>a</sup>,  
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29 Takenori Yoshikawa, MD<sup>a</sup>, Akiko Suzuki, MD<sup>b</sup>, Tomoo Ogi, PhD<sup>c</sup>, Yasushi Suga, MD,  
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32 PhD<sup>d</sup>, Masashi Akiyama, MD, PhD<sup>a\*</sup>

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38  
39 <sup>a</sup>Department of Dermatology, Nagoya University Graduate School of Medicine, 65

40  
41 Tsurumai-cho, Showa-ku, Nagoya 466-8560, Japan

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43  
44 <sup>b</sup>Department of Dermatology, Fujita Health University School of Medicine, 1-98

45  
46  
47 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi 470-1192, Japan

48  
49  
50 <sup>c</sup>Department of Genetics, Research Institute of Environmental Medicine, Nagoya

51  
52  
53 University, Furo-cho, Chikusa-ku, Nagoya 464-8601, Japan

54  
55  
56 <sup>d</sup>Department of Dermatology, Juntendo University Urayasu Hospital, 3-1-3 Hongo,

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5  
6 Bunkyo-ku, Tokyo 113-8431, Japan  
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12 **\*Corresponding author:**  
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15 Masashi Akiyama, M.D., Ph.D.  
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17  
18 Department of Dermatology, Nagoya University Graduate School of Medicine  
19

20  
21 65 Tsurumai-cho, Showa-ku, Nagoya 466-8560, Japan  
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24 Phone: +81-52-744-2314  
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27 Fax: +81-52-744-2318  
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30 E-mail: [makiyama@med.nagoya-u.ac.jp](mailto:makiyama@med.nagoya-u.ac.jp)  
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39 dupilumab, Netherton syndrome, atopic dermatitis, hair shaft disorder, ichthyosis  
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10 **Running head:** Netherton syndrome treated with dupilumab  
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**Conflicts of interest:** The authors have no conflict of interest to declare.

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*To the Editor:*

There have been some case reports of Netherton syndrome (NS) successfully treated with dupilumab recently [1-4]. We report the courses of the patients' atopic features including the time course of serum thymus and activation-regulated chemokine (TARC), serum IgE, soluble IL-2 receptor (sIL-2R), and IL-4, and the scalp hair condition before and after dupilumab treatment. We also evaluated Clinical Ichthyosis Score (CIS) [5]. Ethics committee approval was obtained. Written informed consent was obtained from the participants. Two NS patients were enrolled: a 32-year-old female (Case 1) and a 17-year-old female (Case 2).

Case 1 had ichthyosis linearis circumflexa with double-edged scales on the trunk and extremities (Fig. 1a). She had optic nerve inflammation at age 23 years. She had been treated with repetitive pulse prednisolone therapy four times in seven years for the optic nerve inflammation. The patient is clinically allergic to eggs, cucurbitaceous fruits and vegetables, and crustaceans. Blood samples showed a total IgE of 76633 IU/mL and a serum TARC of 2102 pg/mL. Whole-exome sequencing (WES) revealed the patient to have the compound heterozygous mutations c.1621G>T (p.Glu541\*) and c.2245A>T (p.Arg749\*) in *SPINK5*. They were confirmed by Sanger sequencing. The mutations were previously reported in patients with NS [6].

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7 Case 2 showed erythroderma on the face and trunk, and ichthyosis linearis  
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9 circumflexa lesions on the extremities (Fig. 1c). She had received treatment with the  
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11 humanized monoclonal anti-IgE antibody omalizumab at a previous hospital 10 times at  
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13 age 16 years, but the response had been inadequate. She had no notable medical history.  
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18 She is allergic to wheat, buckwheat, eggs, seafood, poultry, and kiwifruit. Blood samples  
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21 showed a total IgE of 5781 IU/mL and a serum TARC of 1858 pg/mL. WES revealed the  
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23 patient to have the previously reported homozygous nonsense mutation c.2368C>T  
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25 (p.Arg790\*) in *SPINK5*, which was confirmed by Sanger sequencing [7].  
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31 Several treatments including oral and topical steroids had been used for many  
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33 years for both patients, with limited effectiveness. Case 1 reported that her skin condition  
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35 had improved temporarily and that her hair had grown longer temporarily after the steroid  
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37 pulse therapy. In Case 2, omalizumab treatment was tried but it did not work much. In  
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41 both patients, the dupilumab treatment was initiated at a dose of 600 mg and was re-  
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43 administered every 2 weeks at a dose of 300 mg. Both patients reported marked  
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45 improvements in the pruritus on the day after the initial injection. After 6 months of  
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49 dupilumab therapy, the CIS, Eczema Area and Severity Index (EASI), Investigator Global  
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51 Assessment (IGA), and visual analogue scale (VAS) values for itching were improved  
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55 (Figs. 1b, d, Fig. 2a-d). Serum IgE and TARC were decreased (Fig. 2e, f). sIL-2R  
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6 decreased moderately, but IL-4 did not change noticeably (Supplementary Fig. 1). No  
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9 adverse events from the dupilumab treatment were detected in either patient.  
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12 The scalp hair of both patients was coarse and brittle before treatment (Case 1,  
13 Fig. 1e; Case 2, Fig. 1g). Trichoscopy showed trichorrhexis invaginata in both patients  
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15 (Case 1, Fig. 1i, Supplementary Fig. 2a, c; Case 2, Supplementary Fig. 2e, g). Light  
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17 microscopic and scanning electron microscopic observations of the hair shafts are  
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19 presented in Supplementary Figure 3. The hair shafts were so easily breakable that Case  
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21 1 had never had a haircut, and Case 2 had not had a haircut in years. At 6 months of  
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23 dupilumab treatment, the scalp hair was noticeably longer (Case 1, Fig. 1f; Case 2, Fig.  
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25 1h). Trichorrhexis invaginata was still seen, but broken hairs were less numerous and the  
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27 average hair length had increased (Case 1, Fig. 1j, Supplementary Fig 2b, d; Case 2,  
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29 Supplementary Fig. 2f, h). We analyzed the hair area percentage (HAP) and hair shaft  
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31 diameter (HSD) as reported previously [8]. The HAP gradually increased for Case 1, but  
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33 did not increase for Case 2 (Supplementary Fig. 4a, b). HSD significantly decreased in  
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35 Case 1 ( $<0.01$ ), although it did not change noticeably in Case 2 (Supplementary Fig. 4c,  
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60 d).

NS patients have a deficiency of serine protease inhibitor LEKTI in the stratum  
corneum. It results in the increased activity of serine proteases, the accelerated

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6 desquamation of corneocytes, the thinning of the stratum corneum and the breakdown of  
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9 the stratum corneum barrier, which accelerates percutaneous allergen sensitization and  
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12 the overproduction of pro-Th2 cytokines [9]. Patients with NS show the highest induction  
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15 of Th17 pathway genes of any ichthyosis subgroup [10]. The significant atopic diathesis  
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18 and Th2 cytokine profile of NS may explain the improvement by the action of dupilumab  
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21 on pro-Th2 cytokines [2].  
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24 Both patients in this study reported that their symptoms were improved in the  
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27 first week after the injection of dupilumab, but that the pruritus recurred gradually in the  
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30 second week. A larger injection dose or a shorter interval might be recommended for NS  
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33 patients. There were discrepancies in the clinical and laboratory responses to dupilumab  
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36 between the two cases (i.e., in IL-4, HAP, and HSD). As can be seen from previous case  
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39 reports of treatment with dupilumab, the efficacy varies from person to person [1-4].  
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42 This is the first report to evaluate and analyze the hair symptoms of NS patients  
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45 during dupilumab therapy. Interestingly, both of NS patients in our study had episodes in  
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48 which their scalp hair grew longer when their skin was in good condition. During our  
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51 observational study, hair length increased with the suppression of Th-2 mediated  
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54 inflammation. Although the hair shaft nodules are not completely eliminated, hair growth  
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57 seems to occur when the allergic inflammation has subsided. Improvement of skin  
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6 inflammation and itching is thought to reduce scratching behaviors, resulting in reduced  
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9 hair breakage at the nodules from physical stress. Scalp hair symptoms are serious  
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12 burdens for NS patients, affecting their quality of life, and dupilumab might be helpful in  
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15 improving the hair symptoms.  
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18 The present study suggests that the blockade of IL-4 and IL-13 signaling by  
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21 dupilumab is a promising treatment for NS, although further studies enrolling a large  
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24 number of NS patients are needed to confirm the efficacy of dupilumab as a treatment for  
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27 NS.  
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**FIGURE LEGENDS**

**Fig. 1.** Clinical features of both patients before and after dupilumab treatment. (a, b) Case

1: The lesions of ichthyosis linearis circumlexa are improved at 6 months of dupilumab treatment (a, before treatment; b, after treatment). (c, d) Case 2: The erythematous lesions

are improved at 10 months of dupilumab treatment (c, before treatment; d, after treatment).

(e-h) Hair volume and length are increased at 6 months of dupilumab treatment (e, f, Case 1; g, h, Case 2; e, g, before treatment; f, h, after treatment).

(i, j) Enlarged trichoscopic images for Case 1 at the early stage of and after treatment.

(See Supplementary Figure 2c, d for the whole image.) Nodules are indicated by arrowheads. At the nodules, the hair shafts fracture easily, leaving cupped (invaginated) distal ends. The hairs are sparse, broken, and short, less than 2 cm long, at the early stage of treatment (i). The hairs are less broken and the average of hair length had increased after treatment (j).

**Fig. 2.** Evaluation scores of the skin lesions and itching, and serum IgE and TARC levels before and after dupilumab.

(a) Clinical Ichthyosis Score (CIS), (b) Eczema Area and Severity Index (EASI), (c) Investigator Global Assessment (IGA) scale, (d) Visual Analogue Scale (VAS) for itching,

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6 (e) serum IgE, (f) serum thymus and activation-regulated chemokine (TARC). CIS (a),  
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9 EASI (b), IGA (c), VAS for itch (d), serum IgE (e) and TARC (f) levels were calculated  
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12 for 6 months from the initial administration of the dupilumab treatment. All CIS, EASI,  
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14 IGA and VAS for itching were improved after the treatment. Serum IgE and TARC levels  
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16 were significantly decreased after the treatment.  
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23 **Supplementary Fig. 1.** Serum sIL-2R and IL-4 levels before and after dupilumab.

24 sIL-2R and IL-4 levels were calculated for 6 months from the initial administration of  
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26 the dupilumab treatment. (a) sIL-2R decreased moderately in both patients. (b) IL-4  
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28 increased slightly in Case 1, but did not change noticeably in Case 2.  
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38 **Supplementary Fig. 2.** Trichoscopy findings of the scalp.

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40 Trichoscopy findings of the scalp reveal trichorrhexis invaginata. (a, c, e, g) The hairs  
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42 are very sparse at the early stage of treatment (Case 1 on Day 71; a, c, Case 2 on Day  
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44 14; e, g). (b, d, f, h) Improved hair growth and increased hair volume are seen (Case 1;  
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46 b, d, Case 2; f, h). Areas of the yellow rectangles in (c) and (d) are enlarged as Figures  
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48 1i and 1j, respectively.  
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7 **Supplementary Fig. 3.** Light microscopic and scanning electron microscopic images of  
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9 the hair shafts.

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12 (a-c) Light microscopic images of the hair shafts reveal trichorrhhexis invaginata (a, b)  
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14 (a-c, Magnification 6.4×). Nodules are indicated by arrowheads (a, Case 1; b, Case 2; c,  
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16 a healthy control). (d-i) Scanning electron microscopic images: A bamboo joint-like  
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18 nodule on a hair (d, g). An asymmetrically swollen bamboo joint-like nodule on a hair  
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20 (e, h). A normal hair shaft of a healthy control (f, i). Scale bars = 100  $\mu\text{m}$  (d-f), and 10  
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28  $\mu\text{m}$  (g-i).

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33 **Supplementary Fig. 4.** Assessment of hair density and hair shaft diameters.

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36 (a, b) Hair area percentage (HAP). HAP was increased after treatment in Case 1 (a), but  
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38 was not improved in Case 2 (b). In Case 1, conditions of the scalp hair were monitored  
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40 from Day 71. In Case 2, conditions of the scalp hair were monitored from Day 14. (c, d)  
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42 Hair shaft diameter (HSD). The HSD in Case 1 (c) significantly decreased ( $p < 0.01$ ),  
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44 although it did not change noticeably in Case 2 (d). HAP increased for Case 1 after the  
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46 dupilumab treatment. The trichoscopic features suggested that hair breakage was reduced  
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48 and thin hairs remained unbroken, resulting in the increased HAP in Case 1. However,  
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60 HSD decreased in Case 1. We speculate that the decrease in HSD was due to an increased

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6 number of thin hairs remaining unbroken. An increase in the number of thin hairs means  
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9 that the newly grown, still thin hairs are multiplying, are not broken off or do not  
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12 disappear. The period of the observational study in this report was 6 months, although it  
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15 is expected that HSD would increase with longer-term observation.  
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18 HAP is the rate of scalp areas appearing black in images. The HAP score was calculated  
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21 by taking the average of the values obtained from the vertex (areavert) and lateral  
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24 (arealat) views, using the following formula:  $HAP = (1 \times \text{areavert} + 2 \times \text{arealat}) / 3$ .  
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27 HSD is the diameter of hair shafts in the temporal and the occipital regions.  
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30 Dermoscopic images were recorded for these two regions. In these images, we  
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33 measured the diameter of 30 randomly selected hair shafts by using ImageJ.  
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Fig. 1. Clinical features of both patients before and after dupilumab treatment. (a, b) Case 1: The lesions of ichthyosis linearis circumlexa are improved at 6 months of dupilumab treatment (a, before treatment; b, after treatment). (c, d) Case 2: The erythematous lesions are improved at 10 months of dupilumab treatment (c, before treatment; d, after treatment). (e-h) Hair volume and length are increased at 6 months of dupilumab treatment (e, f, Case 1; g, h, Case 2; e, g, before treatment; f, h, after treatment). (i, j) Enlarged trichoscopic images for Case 1 at the early stage of and after treatment. (See Supplementary Figure 2c, d for the whole image.) Nodules are indicated by arrowheads. At the nodules, the hair shafts fracture easily, leaving cupped (invaginated) distal ends. The hairs are sparse, broken, and short, less than 2 cm long, at the early stage of treatment (i). The hairs are less broken and the average of hair length had increased after treatment (j).

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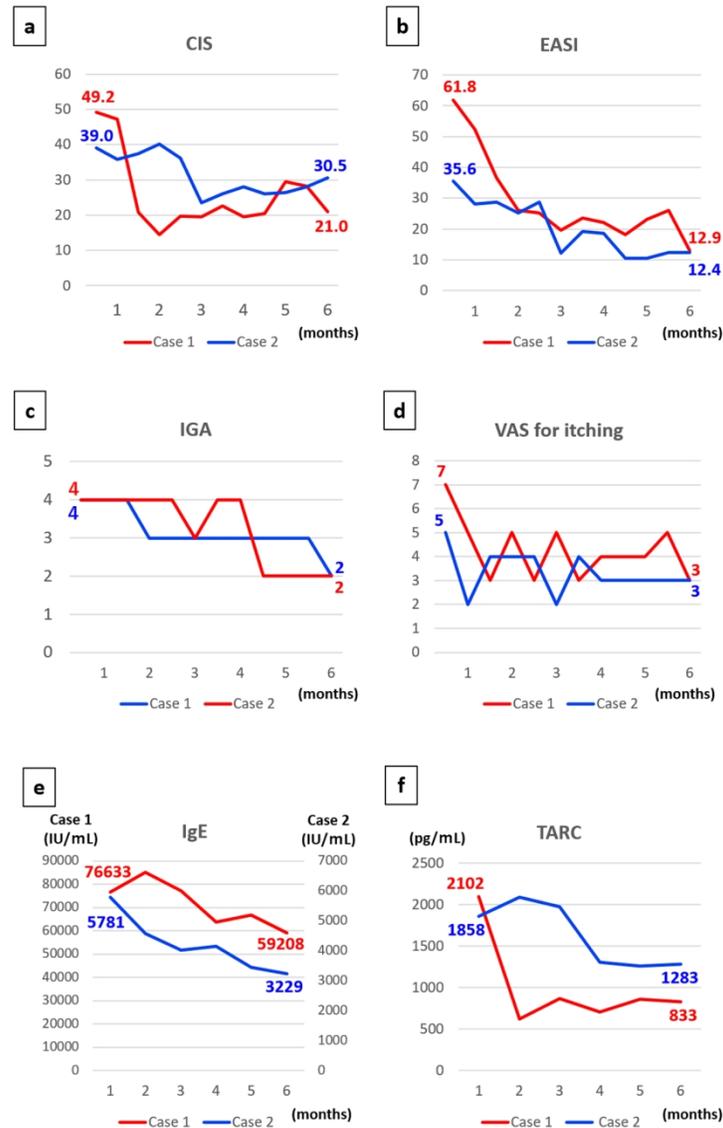
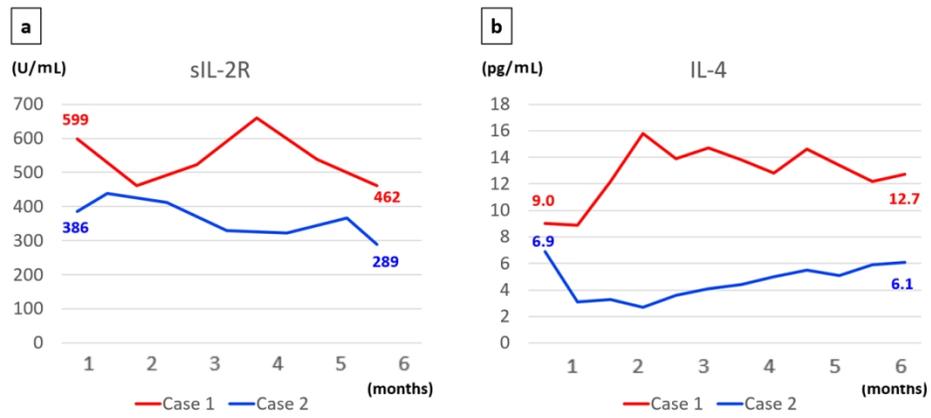


Fig. 2. Evaluation scores of the skin lesions and itching, and serum IgE and TARC levels before and after dupilumab.

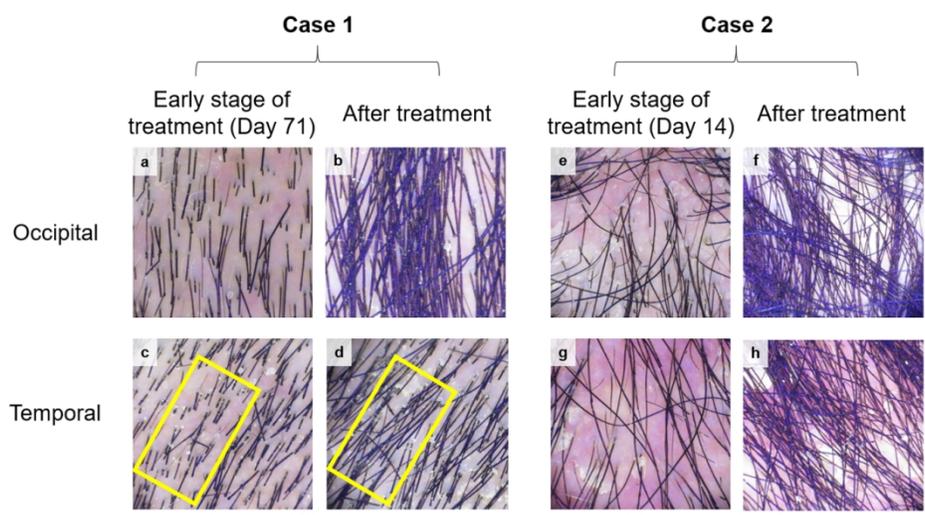
(a) Clinical Ichthyosis Score (CIS), (b) Eczema Area and Severity Index (EASI), (c) Investigator Global Assessment (IGA) scale, (d) Visual Analogue Scale (VAS) for itching, (e) serum IgE, (f) serum thymus and activation-regulated chemokine (TARC). CIS (a), EASI (b), IGA (c), VAS for itch (d), serum IgE (e) and TARC (f) levels were calculated for 6 months from the initial administration of the dupilumab treatment. All CIS, EASI, IGA and VAS for itching were improved after the treatment. Serum IgE and TARC levels were significantly decreased after the treatment.

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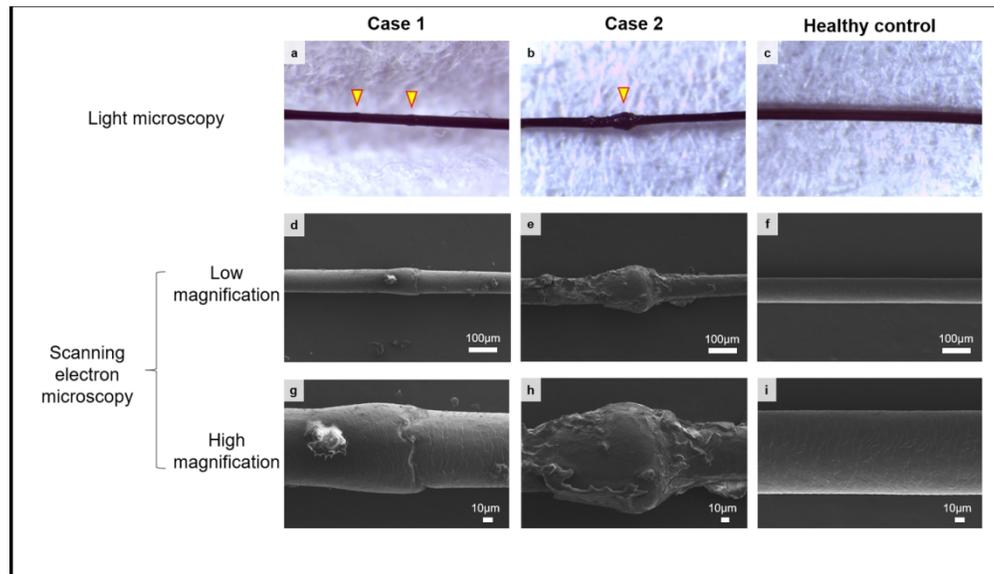


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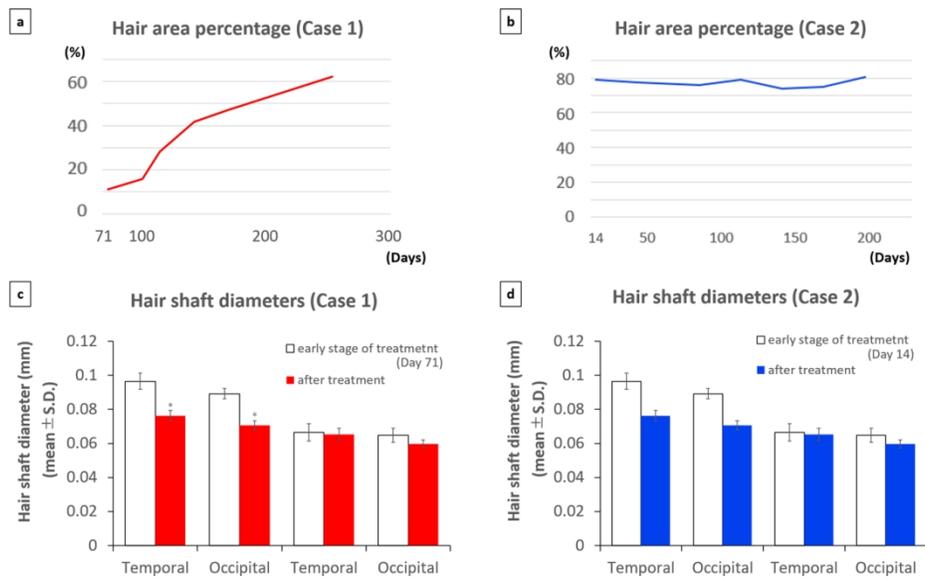


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