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Letter to the Editor

Dupilumab-resistant facial erythema - Dermoscopic, histological and clinical findings of three patients

Dear Editor,

Some atopic dermatitis (AD) patients have facial redness that is resistant to dupilumab,¹ even though the lesions on other parts of their body are responsive to treatment. The reason for this phenomenon is unclear. We report the dermoscopic, histological, and clinical findings of dupilumab-resistant facial erythema (DRFE).

Case 1: A 49-year-old female patient had suffered from AD and used topical corticosteroids on her face, trunk, and extremities from childhood. Before she was treated with dupilumab, her face exhibited erythema and lichenification with mild itching (Fig. 1A). We performed a pretreatment biopsy of her cheek erythema, which showed epidermal acanthosis with spongiosis, perifollicular inflammatory infiltrates, composed of histiocytes and lymphocytes, and dilated superficial vessels (Fig. 2A, D). After 52 weeks of dupilumab treatment, the lichenification lesions had gradually improved; however, the facial erythema remained; i.e., she had DRFE (Fig. 1D). Dermoscopy of her facial erythema showed many linear vessels (Fig. 1G). Serum levels of specific IgE antibody to *Malassezia* species were 57.50 UA/mL before dupilumab therapy and 28.8 UA/mL at one year and a half after the initiation. She had no adverse effects including conjunctivitis and continued dupilumab treatment.

Case 2: A 33-year-old male with AD had used topical tacrolimus and topical corticosteroids on his face, trunk, and extremities for a long time. Prior to being treated with dupilumab, his face exhibited lichenification and papules with persistent erythema with flushing symptom and a little itch (Fig. 1B). Eight weeks of dupilumab treatment improved the patient's lichenification and papules, including on his face, but facial erythema with flushing symptom remained on his nose, cheeks, and forehead (Fig. 1E). Phototesting and patch testing of the ointments used on his face and the Japanese Standard Series produced negative results. Dermoscopy of his DRFE showed many linear and polygonal vessels (Fig. 1H). Serum level of specific IgE antibody to *Malassezia* species was 0.49 UA/mL at one year and a half after the initiation. Based on a biopsy of his forehead ery-

thema performed after 8 weeks of dupilumab treatment, which showed perifollicular granulomas with dilated vessels (Fig. 2B, E), we replaced topical tacrolimus and corticosteroids with moisturizer alone. However, his DRFE remained. He had no adverse effects including conjunctivitis and continued dupilumab treatment.

Case 3: A 39-year-old male with AD had used topical corticosteroids on his face for several decades. He had developed facial erythema with papules and lichenification with severe itch and stinging symptoms before the initiation of dupilumab treatment (Fig. 1C). After 6 weeks of dupilumab treatment, only facial erythema with strong itch and stinging symptoms remained on his cheeks and nose (Fig. 1F). Dermoscopy showed many dilated polygonal vessels on his face (Fig. 1I). Serum level of specific IgE antibody to *Malassezia* species was 17.00 UA/mL at one year after the initiation. Based on a biopsy of his cheek erythema performed after 6 weeks' treatment, which showed some dilated blood vessels in superficial dermis and inflammatory infiltrates around follicles in superficial dermis (Fig. 2C, F), we replaced the topical corticosteroids with moisturizer and topical tacrolimus. However, his DRFE with stinging symptom remains. Moreover, he suffered from conjunctivitis but could continue dupilumab treatment.

Some patients have DRFE¹ despite clinical trials showing that there are no significant differences in the extent to which dupilumab ameliorates skin eruptions between anatomical regions.² Several cases of new-onset dupilumab-induced facial eruptions have been reported previously, including cases of contact dermatitis^{3,4} and *Malassezia* hypersensitivity.⁵ It has been reported that AD patients treated with dupilumab developed a paradoxical, mainly asymptomatic erythema in a head and neck distribution.⁶ In the study, histological examination showed a psoriasiform reaction pattern suggestive of a drug-induced skin reaction.⁶ However, there have been few reports describing persistent DRFE that have included dermoscopic or histological information.

We present the dermoscopic, histological, and clinical findings of three patients with DRFE (Fig. 1, 2, Supplementary Table 1). Post-pubertal AD patients have a tendency to suffer from dermatitis of

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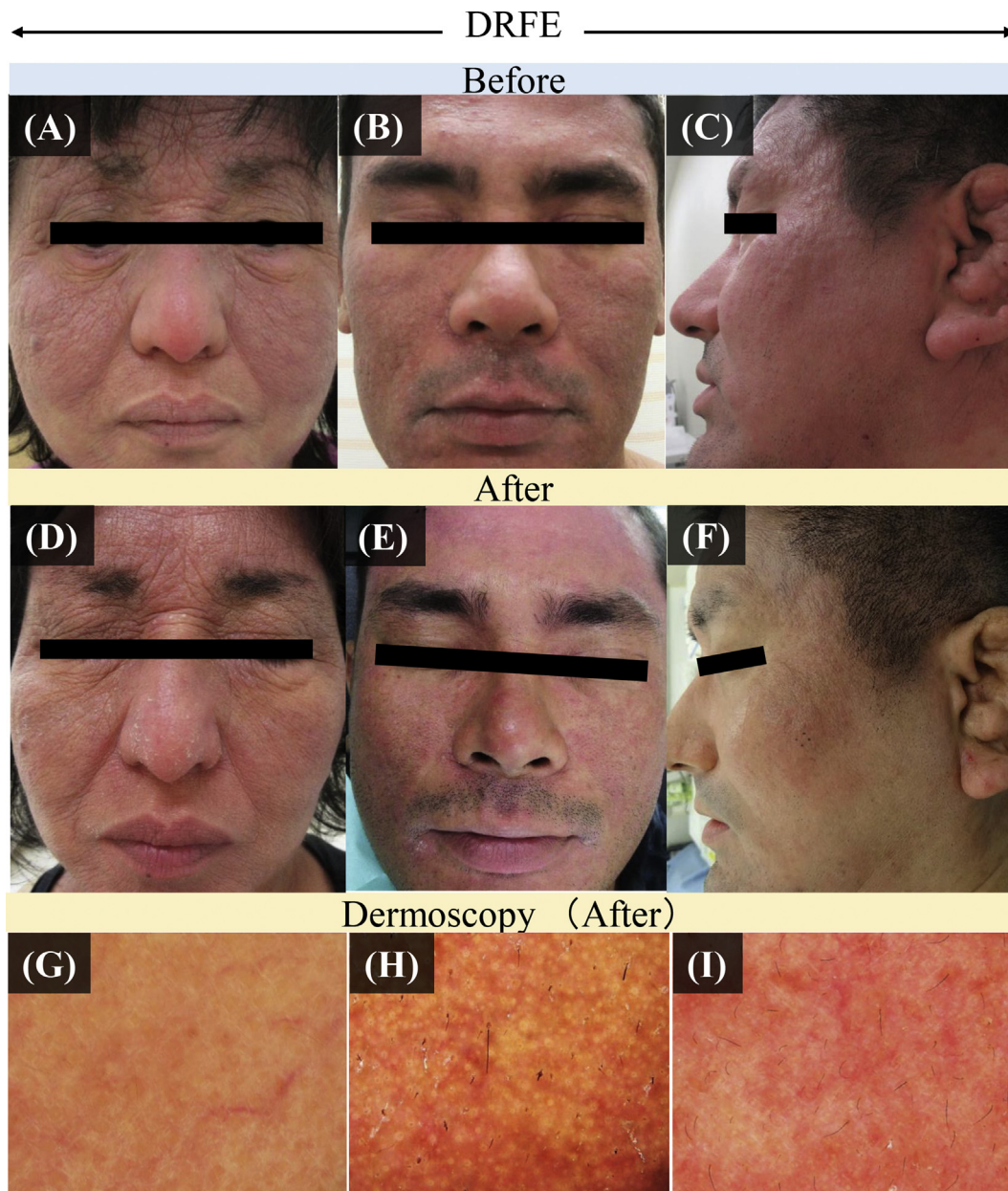


Fig. 1. Clinical and dermoscopic findings of facial eruptions before and after dupilumab treatment. Clinical findings of their faces before (A, B, C) and after (D, E, F) dupilumab treatment are shown. Dermoscopic findings of their faces after the initiation of dupilumab treatment are shown (G, H, I). A permission from the patients has been obtained for the use of their images.

their head and neck, in which there are features of eczematous scaly, papular or lichenified patches, of rosacea-like diffuse erythema or flushing with telangiectasia, and of both eczematous and rosacea-like eruption.⁷ Kim *et al.* have reported that many patients with the head and neck distribution had anti-*Malassezia furfur*-specific IgE antibodies.⁷ Our patients had serum high or low levels of specific IgE antibody to *Malassezia* species, suggesting that *Malassezia* species might not be associated with the

pathomechanisms of DRFE. Biopsies of their faces performed before (Case 1) and after (Cases 2 and 3) the initiation of dupilumab treatment showed many dilated blood vessels in superficial dermis. We also could detect their vessel dilation via dermoscopy. Therefore, some dupilumab-treated AD patients with telangiectasia might have DRFE. Interestingly, in our cases of DRFE, the erythema tended to be located on the nose, cheeks, and forehead. This might have been due to the density of follicles and sebaceous glands in these

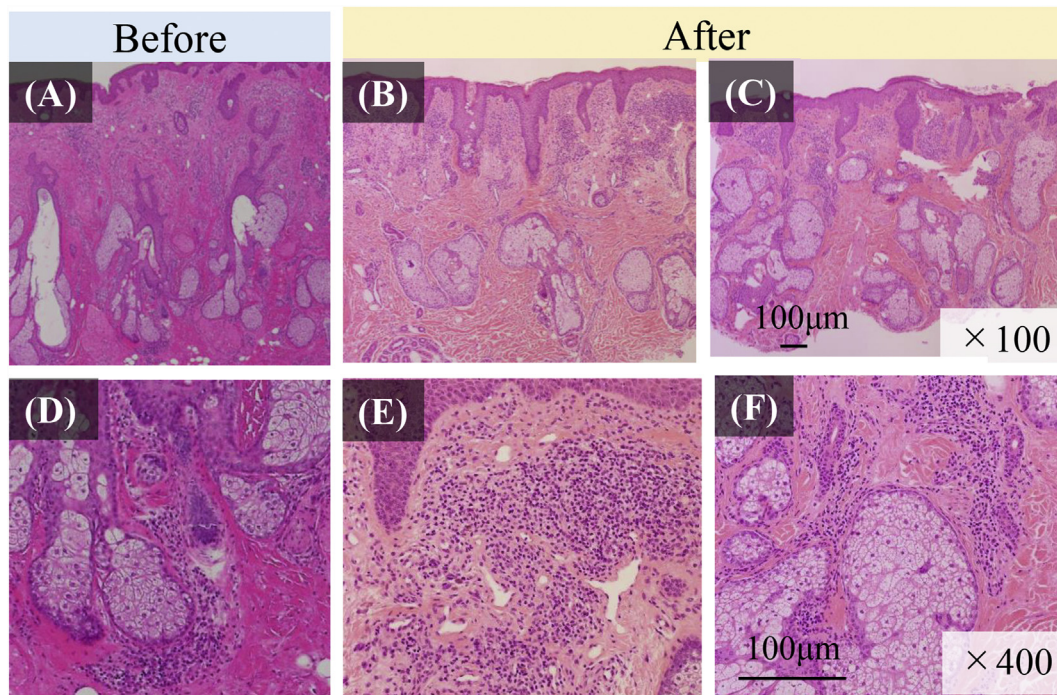


Fig. 2. Histological findings of facial eruptions before and after dupilumab treatment. Biopsies of their faces were performed before (Case 1) and after (Cases 2 and 3) the initiation of dupilumab treatment. Hematoxylin and eosin staining. Original magnification: $\times 40$ (A, B, C), $\times 100$ (D, E, F), scale bar = 100 μm .

areas, and these areas are frequent sites of rosacea. Their DRFE was not typical of rosacea but might possibly be the pre-existing rosacea like dermatosis. The degree of subjective symptoms including itch and flash was different among the patients. The mechanisms underlying of DRFE need to be clarified by further research.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2020.07.001>.

Conflict of interest

KM has received honoraria from Sanofi. NK has received honoraria and research grants (to the Department of Dermatology, Kyoto Prefectural University of Medicine) from Regeneron and Sanofi. The rest of the authors have no conflict of interest.

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Supplementary Table 1. Patients' characteristics and dermoscopic/histological findings

Case	Age/ Sex	Topical therapy before dupilumab therapy	Biopsy timing	Histological findings and diagnosis	Dermoscopic findings	Serum levels of specific IgE antibody to <i>Malassezia</i> species (ImmunoCAP®)
1	49/F	Topical corticosteroids	Before dupilumab therapy	Perifollicular inflammatory infiltrates with superficial dilated vessels and epidermal spongiosis; RD with AD	Linear and polygonal vessels	57.50 UA/mL (Before dupilumab therapy), 28.8 UA/mL (One year and a half after the initiation)
2	33/ M	Topical tacrolimus and corticosteroids	On 8 weeks after the initiation of dupilumab therapy	Perifollicular granulomas with many dilated vessels; RD	Linear and polygonal vessels	0.49 UA/mL (One year and a half after the initiation)
3	39/ M	Topical corticosteroids	On 6 weeks after the initiation of dupilumab therapy	Perifollicular granulomas with many dilated vessels; RD	Linear and polygonal vessels	17.00 UA/mL (One year after the initiation)