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Letter to the Editor

Facial Redness in Atopic Dermatitis Patients Treated With Dupilumab: A Case Series

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Dupilumab, a fully humanized antibody, which inhibits IL-4 and IL-13 by blocking the IL-4 receptor α, is approved for the treatment of atopic dermatitis (AD) and some adverse effects were reported.[1,2] Dupilumab facial redness (DFR) is a development of an eczematous facial rash after initiation of dupilumab and is an adverse event not described in the clinical trials. We herein report a case series of DFR to improve clinical knowledge of this possible new adverse event.

We reviewed 4 cases of DFR from November 2018 to September 2019 at the Department of Dermatology, CHA Bundang Medical Center. (**Tables 1** and **2**) Concomitant treatment during the dupilumab treatment included antihistamines, topical corticosteroids and topical calcineurin inhibitors (TCI). Patients did not receive any other systemic drugs.

The mean onset of facial redness was 22.25 weeks after initiation of dupilumab treatment. Most patients presented erythematous and scaly patches on the whole face including the

Table 1. Patient characteristics (n = 4)

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4
Sex	F	F	M	F
Age (yr)	43	22	37	18
Asthma/allergic rhinitis/allergic conjunctivitis	+/+/+	+/+/+	+/+/+	+/+/+
Previous treatments	CsA, prednisone, antihistamine, TCS, TCI	CsA, prednisone, antihistamine, TCS, TCI	CsA, AZA, MTX, prednisone, antihistamine, TCS, TCI	Prednisone, antihistamine, TCS, TCI

CsA, Cyclosporine A; TCS, topical corticosteroids; TCI, topical calcineurin inhibitors; AZA, azathioprine; MTX, methotrexate.

Table 2. Clinical characteristics (n = 4)

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4
Onset of DFR (treatment duration of dupilumab, wk)	27	25	20	17
Signs and symptom of facial redness (+/−) erythema/scale/itching/pain	+/+/−/−	+/+/−/−	+/+/−/−	+/−/−/−
Skin biopsy (+/−)	−	−	+	−
Patch test (+/−)	+	−	−	−
Concomitant treatment	Emollients, TCS, TCI, antihistamine	Emollients, TCS, TCI, prednisone, antihistamine	Emollients, TCS, TCI	Emollients, TCS, TCI, antihistamine
Prescriptions for DFR	Minocycline, TCI, brimonidine tartrate 0.33% topical gel	Minocycline, TCI, TCS	Minocycline, TCI, TCS, brimonidine tartrate 0.33% topical gel	Minocycline, TCI, TCS
Duration of treatment for DFR (wk)	28	10	22	32

DFR, dupilumab facial redness; TCS, topical corticosteroids; TCI, topical calcineurin inhibitors.

Respiratory Disease

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periocular area (**Fig. 1**). In all patients, there were no other side effects other than facial redness. In one patient, histopathology showed mild dermal edema and perifollicular chronic inflammation (**Fig. 2**); in another patient, the patch test was positive for nickel.

DFR was exacerbated by continued administration of dupilumab, but due to improvements in other skin lesions, patients did not want to stop dupilumab. Facial redness was considerably improved with minocycline, TCI and brimonidine tartrate 0.33% topical gel on the average within 23 weeks (range, 10 to 32 weeks) of treatment.

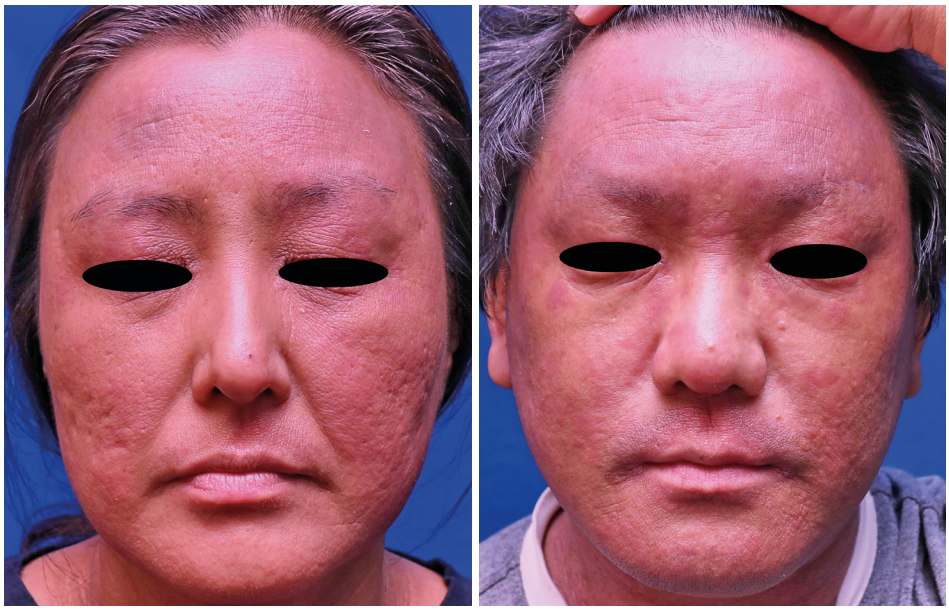

Fig. 1. Clinical pictures of dupilumab-induced facial redness.

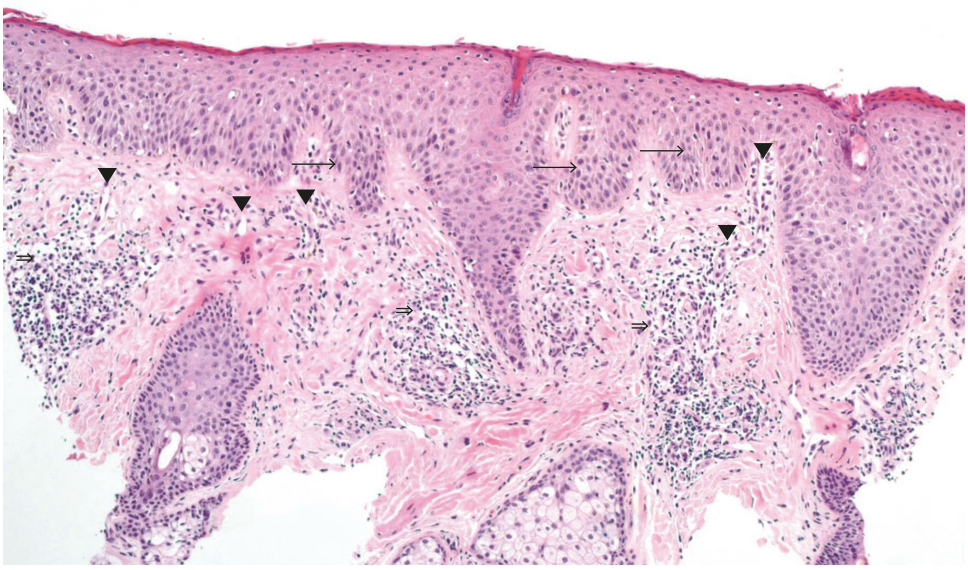

Fig. 2. Histopathology of a left lower lid skin punch biopsy specimen shows irregular epidermal hyperplasia with bulbous elongated rete ridges (→), increased number of ectatic capillaries in the papillary dermis (▼) and a perivascular and perifollicular lymphocytic infiltration (⇒) (hematoxylin and eosin, × 100).

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There are several case reports of DFR, but the cause of this new side effect is not clear. Many hypotheses have been proposed to explain the development of DFR, including 1) allergic contact dermatitis (ACD), 2) hypersensitivity/photosensitivity reactions to dupilumab, 3) *Malassezia furfur* associated seborrheic dermatitis-like reactions and 4) *Demodex* associated rosacea like dermatosis.[3,4]

Patch testing for ACD was performed in 1 patient, which showed positivity to nickel. However, avoidance of the allergens did not improve erythema. The distribution of the lesions was also suggestive of photosensitivity reactions. None of the patients were using any photosensitive drug or had any history of overexposure to ultraviolet light.[5] It has been suggested that *M. furfur,* a normal skin flora, probably plays a role in the pathophysiology. However, in the mouse models, *Malassezia* causes massive infiltration of neutrophils and monocytes into the skin, but we could not find this in the skin biopsy specimens of our patients.[6] Dupilumab inhibits T-helper cell 2 signaling, which may include immune responses against helminth infections. In theory, the treatment of dupilumab could promote Demodex proliferation in follicles and increase IL-17-mediated inflammation involved in the pathophysiology of rosacea.[7] The clinical presentation in our patients was not typical for rosacea and none of them had a history of rosacea before. However, the histologic findings of 1 patient was considered to be rosacea.

In our experience, DFR is an underappreciated adverse event of dupilumab. We reported a case series of facial redness in 4 patients treated with dupilumab for AD to improve clinical knowledge of this new adverse event.

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