

## Case Report



# Acral erythema arising in patients with atopic dermatitis after dupilumab therapy: A case report of 3 patients

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### Conflict of Interest

The authors have no financial conflicts of interest.

### Author Contributions

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## ABSTRACT

Dupilumab, a monoclonal antibody approved by the U.S. Food and Drug Administration for the treatment of adult patients with moderate-to-severe atopic dermatitis, inhibits interleukins 4 and 13. It is an effective treatment option for atopic dermatitis, but facial redness has been reported as an unexpected adverse effect. Although several theories have been proposed to explain the facial redness caused by dupilumab, the underlying mechanism is yet to be verified. To the best of our knowledge, to date, only few reports have described erythema appearance on nonfacial areas after dupilumab treatment. Herein, we report the cases of 3 patients who presented with erythema on their hands and feet after dupilumab injections. The erythema persisted, even when the atopic dermatitis lesions improved. Additional reports are needed to demonstrate the clinical characteristics of postdupilumab acral erythema.

**Keywords:** Dupilumab; Dermatitis, atopic; Erythema

## INTRODUCTION

Dupilumab, a human monoclonal antibody that inhibits interleukin (IL)-4 and IL-13 as well as downregulates T helper type 2 (Th2)-mediated inflammatory response, is the first biological treatment approved for moderate-to-severe atopic dermatitis (AD). Cutaneous adverse events of dupilumab have been reported, including alcohol-induced facial flushing, lichenoid drug eruption, new-onset psoriasis, rosacea, or seborrheic dermatitis-like lesions [1-8]. Dupilumab facial redness (DFR)—the facial redness occurring after dupilumab use—is known to affect approximately 10% of patients treated with dupilumab [9]. Although there have been several reports on DFR, only few cases have been reported on postdupilumab erythema on the neck and nonhead locations. Herein, we describe 3 cases of patients presenting with acral erythema on their hands and feet following treatments with dupilumab.

We used dupilumab (Dupixent, Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA) to treat AD in 3 adult patients. All 3 patients received dupilumab at a loading dose of 600 mg subcutaneously (SC) on the first day of treatment, followed by 300 mg SC administration every 14 days.

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## CASE REPORTS

### Case 1

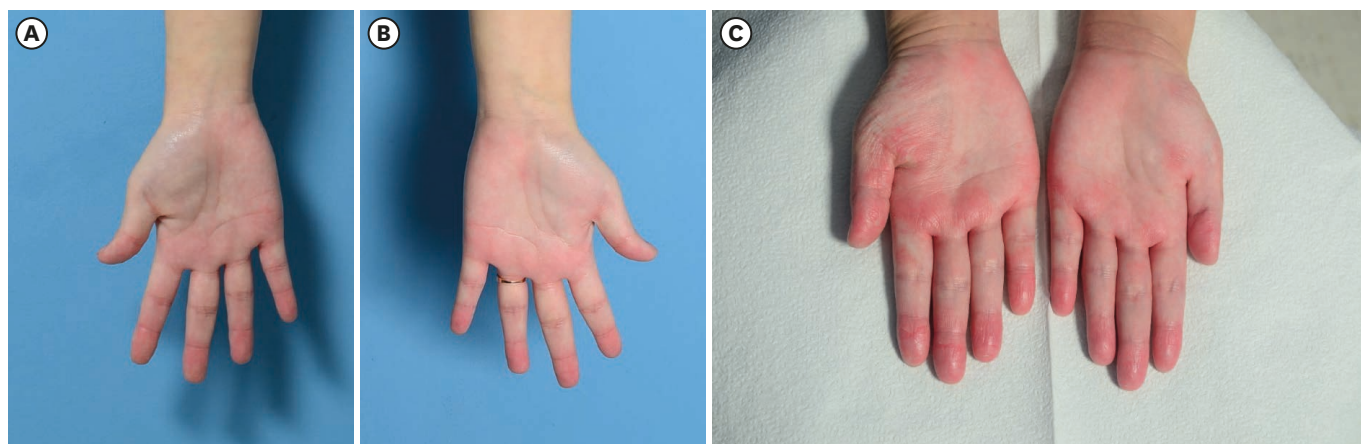
A 21-year-old woman presented with itchy erythematous patches on the flexor areas of both arms and systemic pruritus. Her initial Eczema Area and Severity Index (EASI) score was 9.6. She was started on cyclosporine (150 mg, once a day) for 2 months, but her skin lesions worsened, reaching an EASI score of 25. She continued to take cyclosporine (75–150 mg per day) for another 8 months along with wax and wane course. Since she showed no improvement after taking cyclosporine (150–175 mg per day) for 3 months, with an EASI score of 26.8, she was started on dupilumab. She presented with scaly erythematous patches on the periocular area and both hands one week after the first dupilumab injection (**Fig. 1**). The erythema reappeared after every dupilumab injection for 3 months. At the time of writing this manuscript, the patient has been applying dexamethasone ointment and olopatadine on the periocular area, and taking oral cyclosporine and antihistamines along with dupilumab.

### Case 2

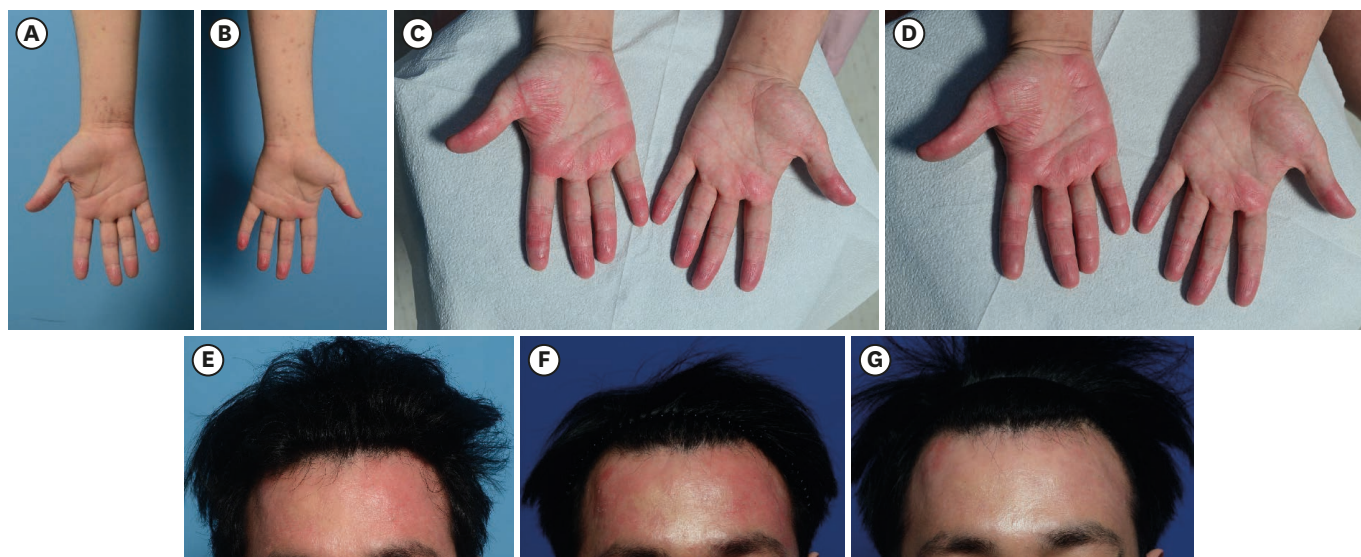
A 23-year-old man presented with a history of AD since infancy. The initial EASI score was 22.5, and he was treated with cyclosporine (150–225 mg per day) for 4 months. Despite the treatment, his skin lesions worsened and his EASI score increased to 26.4. He was therefore started on dupilumab. After 2 months of treatment with dupilumab, the skin lesions cleared up substantially, with the EASI score decreasing to 6.6, but erythema started to develop on his face and hands. He was started on oral itraconazole; the patient showed decreased facial and acral erythema, especially on his forehead, after 2 weeks of itraconazole therapy (100 mg once daily) and an additional pulse of 200 mg twice daily for 1 week (**Fig. 2**). However, the erythema persisted on his hands. Thus, skin biopsy was performed on his right hand. Histopathological examination results were consistent with eczema, showing features of subacute spongiotic dermatitis with irregular acanthosis. The acral erythema steadily improved with the regular application of emollients and topical tacrolimus (0.1% ointment) twice a day for 3 weeks.

### Case 3

A 35-year-old woman consulted us about using dupilumab for her known AD. She was started on dupilumab 1 month after the first visit, and the treatment was well tolerated. However, after 1 year and 9 months of treatment with dupilumab, acral erythema developed on both



**Fig. 1.** The palms of the patient before dupilumab treatment (A, B) and after dupilumab treatment (C).



**Fig. 2.** The patient's palms after 4 dupilumab injections (A, B), after 10 dupilumab injections (C), and after treatment with oral itraconazole (D). The patient's forehead after 4 dupilumab injections (E), 10 dupilumab injections (F), and after treatment with oral itraconazole (G).

hands and feet (Fig. 3). She was treated with oral antihistamine and plasma treatment for the acral erythema, and some improvement was observed.

The patients' characteristics and medical history are summarized in Table 1.

This case study was approved by the Institutional Review Board (IRB) of the Asan Medical Center (IRB No. 2021-1536). An informed consent was obtained from all patients before their participation in the study.



**Fig. 3.** The patient's hands before dupilumab injection (A) and after multiple dupilumab injection (B). The patient's foot before dupilumab injection (C) and after multiple dupilumab injection (D).



**Table 1.** Patient characteristics and medical history related to atopic dermatitis and dupilumab-induced erythema

Patient No.	Sex/age (yr)	EASI (before/after dupilumab)	Eosinophil count (%) (before/after dupilumab)	Time from dupilumab injection to appearance of erythema (mo)	No. of dupilumab injections before the onset of acral erythema	Treatment for dupilumab-induced erythema	Response to treatment for dupilumab-induced erythema
1	F/22	26.8/-	9.4/41.8	0.25	1	Topical corticosteroid and antihistamine, cyclosporine	Partial response, recurred within 1 month
2	M/24	26.4/6.6	9.4/-	4	8	Itraconazole, emollient, topical tacrolimus	Good response on forehead, less response on hands
3	F/37	-/-	7.4/-	21	42	Cold atmospheric plasma treatment, antihistamine	Partial response, sustained for 1 month

EASI, Eczema Area and Severity Index.

None of the patients discontinued dupilumab after experiencing dupilumab-induced acral erythema.

## DISCUSSION

The acral erythematous lesions described in our cases are expected to be caused by a similar mechanism to DFR. A number of possible mechanisms have been suggested: a hypersensitivity reaction, partially untreated AD, seborrheic dermatitis-like response, hypersensitivity to *Malassezia*, or triggered allergic contact dermatitis [9, 10]. First, DFR may arise as a hypersensitivity reaction to dupilumab. Hypersensitivity is defined, by World Allergy Organization, as conditions clinically resembling allergy that cause objectively reproducible symptoms or signs, initiated by exposure to a defined stimulus at a dose tolerated by normal subjects. In this context, DFR could be considered as a kind of hypersensitivity. The newly appeared acral lesions are less likely to be untreated AD lesions; this is because the lesions on their hands or feet were absent or mild before dupilumab treatment. A seborrheic dermatitis-like reaction or hypersensitivity to facial *Malassezia* species has also been suggested to cause DFR since it occurs in seborrheic areas of the face, and occasionally resolves after using topical antifungal agents [10]. The facial and acral erythema of the patient in case 2 improved, especially on his face, after 2 months of oral itraconazole therapy. However, since the hand is not a common location for *M. furfur* colonization, it is questionable whether acral erythema can also be explained as a seborrheic dermatitis-like reaction.

The most compelling explanation for the acral erythema is that it is a sign of unmasked allergic contact dermatitis. As dupilumab suppresses the Th2 response, it can amplify the Th1 response and lead to Th1 dermatoses, such as seborrheic dermatitis, rosacea, and allergic contact dermatitis [4, 9]. A skin biopsy from the patient in case 2 showed characteristics of subacute spongiotic dermatitis with irregular acanthosis, consistent with the diagnosis of allergic contact dermatitis. Further examinations, including patch tests, should be considered [11]. The hands and feet easily come into contact with foreign materials, making them susceptible to allergen exposures and resultant contact dermatitis. The hands were involved in 19.2% of individuals with contact dermatitis [12]. Of note, all of the patients in this report presented with erythema on their hands.

In conclusion, although facial redness is a typical, more frequently reported adverse event of dupilumab therapy, physicians should be aware of the possibility of acral erythema developing on the hands and feet. Additional reports are needed to elucidate this first reported cutaneous event after dupilumab treatment.

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