Generalized Eczema as a Transient Paradoxical Adverse Effect of Dupilumab

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Dupilumab is a monoclonal antibody that inhibits the signaling of the interleukins IL-4 and IL-13, both of which are key cytokines in the pathogenesis of type 2 inflammation. Approved by the United States Food and Drug Administration in 2017 for moderate-to-severe atopic dermatitis and in 2018 for uncontrolled severe eosinophilic and/or allergic asthma [1], this biologic has proven effective for the treatment of other type 2 inflammatory skin conditions, such as nummular eczema, allergic contact dermatitis, chronic hand eczema, spontaneous chronic urticaria, and prurigo nodularis [2]. Despite a favorable safety profile, various skin-related adverse events have been documented, including injection site reaction [3], allergic contact dermatitis, psoriasis, and other hypersensitivity responses [4-6]. The most common reaction involves erythema of the face and neck [7].

We report the case of a 52-year-old woman with a history of uncontrolled eosinophilic severe asthma, nonsteroidal anti-inflammatory drug hypersensitivity, and chronic rhinosinusitis with nasal polyps (CRSwNP) previously treated with endoscopic sinus surgery. Notably, she had no history of skin disease. Her baseline blood eosinophil count averaged 200-300 cells/μL. The patient's poorly controlled asthma (Asthma Control Test score of 15) and treatment-resistant CRSwNP (Sinonasal Outcome Test score of 83 with persistent anosmia) led us to initiate dupilumab (600 mg subcutaneously on day 0, followed by 300 mg every 2 weeks).

Within 24 hours of the initial dose, the patient developed pruritic, erythematous, infiltrated, and scaly plaques on her back, hips, and legs, as well as a rounded, indurated wheal at the injection site. Treatment with methylprednisolone aceponate cream rapidly relieved the itching and resolved the lesions within 2-3 days. Dupilumab was continued, yielding a substantial improvement in the symptoms of asthma and CRSwNP. However, similar skin reactions recurred following each injection, with progressively reduced intensity and resolution within 2-3 days after treatment with methylprednisolone cream. The skin lesions following the second and third injections are shown in the Figure and in Supplementary Figure 1. A peak eosinophil count of 2200 cells/μL was recorded with the third dupilumab injection, subsequently falling to 1300 cells/μL after 1 month. Biopsy of a back lesion revealed parakeratosis, spongiosis, and lymphocytic exocytosis without eosinophils, consistent with eczema. Periodic acid–Schiff (PAS) staining excluded fungal infection. The frequency and intensity of skin lesions diminished over 7 months (14 injections). These eventually resolved. The patient gave her informed consent for the publication of her clinical case, although she refused to undergo another skin biopsy to amplify the immunohistochemical analysis.

Dupilumab is highly effective for treating atopic dermatitis and other type 2 inflammatory skin diseases [1,2]. While cutaneous adverse effects are typically associated with a history of atopic dermatitis and primarily affect the face and neck [3,5,7,8], the present case was remarkable for a novel and paradoxical reaction in the form of generalized eczema in a patient with no prior history of skin involvement.

The skin reactions were successfully managed using topical corticosteroids, enabling continued administration of dupilumab. This approach is consistent with those used in previously published cases, although not with others, which required the biologic to be suspended [8,9]. The rapid onset of the reaction, appearing within 24 hours after treatment, contrasts with reported cases, where reactions typically arise 1-6 months after initiation of therapy [7,8].

Studies indicate that conventional atopic dermatitis and dupilumab-induced dermatitis have distinct inflammatory profiles [9]. Whereas classic atopic dermatitis is driven by IL-4/13 signaling, dupilumab-associated dermatitis appears to upregulate IL-22 [9]. Although no immunohistochemical analysis was performed in the present case owing to the absence of a control biopsy, the lack of eosinophils (a marker of type 2 inflammation) in the eczematous skin biopsy makes IL-4/13 signaling unlikely. This is consistent with histopathologic findings in similar cases involving face and neck dermatitis, where IL-4 was not detected in response to increased levels of IL-22 on the skin [9]. To date, it has not been possible to explain this IL-driven switch according to the known mechanism of action [10].

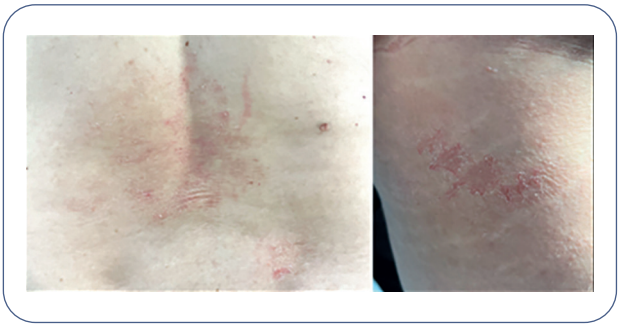

Figure. Skin reactions 24 hours after the second dupilumab injection: erythematous, infiltrated, and scaly plaques on the back, hips, and legs.

The pathophysiological mechanism of dupilumab-induced dermatitis remains unclear [6-8]. Theories such as involvement of *Malassezia furfur* and preexisting skin lesions in the affected area (eg, rosacea, psoriasis, atopic dermatitis) have been proposed as an underlying mechanism. However, both mechanisms were excluded in the case we report based on the clinical history, disease course, and biopsy findings.

We present the first documented case of generalized eczema following administration of dupilumab in a patient with no prior skin disease who achieved tolerance after 7 months of therapy. Further research is needed to elucidate the mechanisms underlying these adverse dermatologic responses to dupilumab.

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Conflicts of Interest

Dr Betancor was supported by a Rio Hortega Research Grant funded by the ISCIII. Dr Valverde has received fees for a lecture from GSK and participates on advisory boards for Organon outside the submitted work. Dr Sastre reports grants and personal fees from Sanofi, GSK, Novartis, AstraZeneca, Mundipharma, and FaesFarma outside the submitted work. The remaining authors declare that they have no conflicts of interest.

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