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Successful treatment of dupilumab-induced rosacea with upadacitinib in a patient with atopic dermatitis

Selami Aykut Temiz[1], Ayman Abdelmaksoud[2,3], Hasan Emre İlgenli[1], Recep Dursun[1], Uwe Wollina[4,5,6] ✉

[1]Department of Dermatology, Meram Medical Faculty, Necmettin Erbakan University, Meram, Konya, Turkey. [2]Mansoura Dermatology, Venerology, and Leprology Hospital, Mansoura, Egypt. [3]Department of Dermatology, Guglielmo Marconi University, Rome, Italy. [4]Department of Dermatology and Allergology, Dresden Municipal Hospital, Dresden, Germany. [5]Academic Teaching Hospital, Dresden, Germany. [6]Department of Dermatology, Venerology, and Leprosy, Adjuvant International Faculty, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education & Research – Premier Deemed to be University, Wardha, Maharashtra, India.

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Dear Editor,

Atopic dermatitis is a chronic inflammatory disease caused by environmental and genetic factors. The leading symptom is pruritus. Rosacea is also accompanied by disturbed epidermal barrier function and dry skin (1).

Dupilumab has been used in the treatment of moderate to severe atopic dermatitis since 2017. The drug blocks the interleukin (IL) 4/13 pathway, which is a major pathway in atopic dermatitis. The IL-4 receptor, of which there are two known types, is found on the surface of various cells, including eosinophils and macrophages. It plays a key role in the pathogenesis of type 2 allergic responses. Binding of cytokines to these receptors leads to immunoglobulin (Ig) E class switching, Th2 differentiation, and M2 macrophage differentiation. In the pathogenesis of atopic dermatitis, IL-4 and IL-13 play important roles in modulating the epidermal barrier and in the development of dermal inflammation and remodeling. Blockade of this pathway might prevent the onset and progression of allergic diseases (2).

Exacerbation of rosacea has been observed in patients treated with dupilumab for atopic dermatitis. This needs to be differentiated from dupilumab-associated facial erythema and rosacea-like reactions. Rosacea, according to the Global ROSacea COnsensus (ROSCO) criteria, is characterized by persistent facial erythema, redness, telangiectasias, and central facial papulopustules, and has a complex and multifactorial etiology, including the possible role of certain microorganisms, dermal matrix degeneration, neurovascular dysregulation, pilosebaceous unit abnormalities, and immune and environmental factors. Dupilumab-mediated Th2 blockade followed by Th1/Th17 conversion can trigger rapid proliferation of demodex mites in the follicular epithelium, as demonstrated in Th2-deficient mouse models. This Th1-dominant response, combined with demodex overgrowth, can provide a favorable inflammatory environment for the development of rosacea. Similarly, it has been suggested that dupilumab-associated conjunctivitis is a variant of ocular rosacea. Consequently, disruption of the Th1/Th2 balance through Th2 blockade may predispose these patients to Th1-mediated diseases such as rosacea. Dupilumab-associated facial dermatitis is also a common side effect, characterized by fine scaling and edematous pinkish-red plaques affecting the face, neck, and forearms. Similarly, head and neck dermatitis may also be observed. In fact, in some patients with atopic dermatitis that present with severe disease in the head and neck region at the time of presentation, Janus kinase (JAK) inhibitor therapy is primarily recommended, and dupilumab should be considered secondarily. Rosacea-like reactions are also observed after dupilumab and should be differentiated from rosacea. Only a few case reports of paradoxical rosacea-like symptoms occurring under dupilumab treatment are known to exist in the literature, and in all cases previous systemic treatment was completely discontinued (3–5). It is thought that rosacea-like side effects are more likely to be a result of IL-4Rα blockade. In the case reported by Grote et al., switching from dupilumab to anti-IL-13 antibody was associated with a better response than standard rosacea treatment (5). In our case, similar to Grote et al., we wanted to emphasize that the change in therapeutic agent in the primary disease compared to standard rosacea treatment was also therapeutic and related to the secondary condition.

A 53-year-old woman with a 15-year history of atopic dermatitis had an initial Eczema Area and Severity Index (EASI) score of 22. At her initial diagnosis, dermatologic examination revealed similar hyperpigmented plaques around the eyes and neck, and excoriated papules on the antecubital area of the arms, trunk, and legs. There was mild erythema and telangiectasias but no pustules on her face (Fig. 1a). The patient had been followed up at our clinic for more than 2 years. She had been treated with topical and systemic corticosteroids intermittently for 2 years, depending on the severity of her symptoms, and, after an insufficient response to corticosteroids, she was treated with cyclosporine for 6 months. However, due to the lack of response to these treatments, dupilumab treatment was initiated. She had been receiving dupilumab for 3 months.

The patient presented to our clinic complaining of facial redness and itching for the previous 2 weeks, accompanied by a strong feeling of heat. She had telangiectasias on an erythematous base in her malar region, and she reported that these symptoms waxed and waned periodically (Fig. 1b). Dermatoscopic examination of the patient's malar region revealed polygonal vascular structures composed of linear blood vessels, superficial crusting and follicle openings, and the tails of demodex parasites (Fig. 2a). Our patient had numerous demodex parasites in her standardized skin surface biopsy (Fig. 2b). The patient was diagnosed with erythematotelangiectatic rosacea. During this eruption, total IgE levels were 75 and the eosinophil count in peripheral blood was 200 µl.

✉ Corresponding author: uwollina@gmail.com

The patient was initially treated with a course of systemic azithromycin 250 mg three times a week and topical metronidazole plus urea. When the patient's symptoms did not improve after 2 months, the treatment for atopic dermatitis with dupilumab was switched to upadacitinib, a selective JAK inhibitor. This change was made considering a rosacea flare-up that occurred after the patient's initial treatment for atopic dermatitis and recommendations based on literature data. The patient did not subsequently develop any contraindications to dupilumab and had no concomitant secondary conditions. Concomitant treatment for rosacea was continued. Consequently, after 2 months of treatment, azithromycin treatment was discontinued, and topical treatments were continued. At the patient's request, topical treatments were also discontinued after 1 month. After this, both skin conditions improved. Treatment with upadacitinib 15 mg once daily was initiated. After 1 month of follow-up, facial redness and itching had almost completely resolved (Fig. 1c), and the atopic dermatitis EASI score had dropped to 3.6. After 3 months, facial redness and itching had completely subsided, and the EASI score had dropped to 2.2. After 6 months, rosacea-related symptoms had completely disappeared, and the patient's EASI score had dropped to 1.2. The patient benefited clinically from this treatment in terms of both rosacea and atopic dermatitis.

Rosacea is a chronic inflammatory skin disease. Key molecules involved in its pathogenesis include toll-like receptor 2, the antimicrobial LL37, mammalian rapamycin target (mTOR), and IL-17. The JAK/STAT pathway plays a significant role in the pathogenesis of this disease by regulating inflammatory responses and increasing the expression of pro-inflammatory cytokines. These cytokines can cause facial flushing, erythema, and pruritus (6, 7). Furthermore, rosacea triggered by demodex mite infestation can exacerbate inflammation through activation of the JAK/STAT signaling pathway. Given its role in the pathogenesis of rosacea, inhibition of the JAK/STAT pathway is thought to have a therapeutic effect. Possible mechanisms of JAK inhibitors in rosacea treatment may include inhibition of the inflammatory response, modulation of vascular permeability, inhibition of angiogenesis, and improvement of skin barrier function. Suppression of immunological pathways via JAK 1 inhibitors inhibits cytokines that play a role in the pathogenesis of both atopic dermatitis and rosacea (8, 9). A review of the literature reveals that Liane et al. treated rosacea that developed in an atopic dermatitis patient receiving dupilumab therapy with oral ivermectin (10). Because rosacea and similar eruptions have been reported in the literature after dupilumab administration, clinicians should consider this in patients. The mechanisms by which dupilumab causes these effects have been reported above. In patients receiving a biological agent for the first time to treat atopic dermatitis, some accompanying conditions should be considered in the selection of the molecule. Although JAK inhibitors may be preferred as a first-line option in patients with rosacea, in patients receiving dupilumab treatment for other reasons, JAK inhibitors can be considered as a suitable alternative for long-term treatment in cases such as facial erythema and rosacea caused by the drug. Although dupilumab is used by many branches of medicine for many indications due to its mechanism of action and patient compliance, different agent

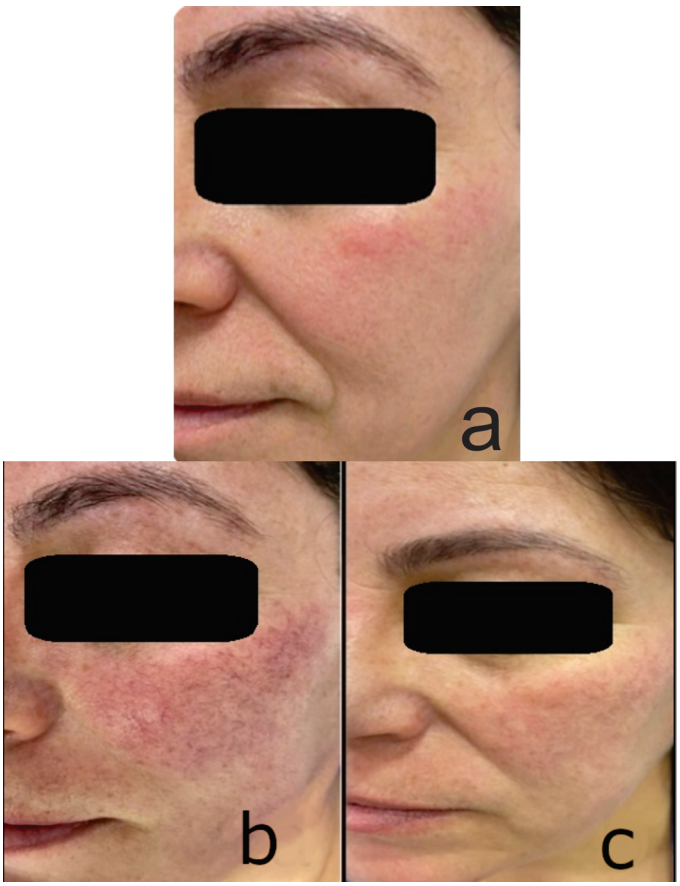

Figure 1 | The patient showed (a) mild erythema and telangiectasias but no pustules on her face before dupilumab initiation; (b) rosacea during dupilumab therapy; and (c) improvement of rosacea symptoms after switching to upadacitinib.

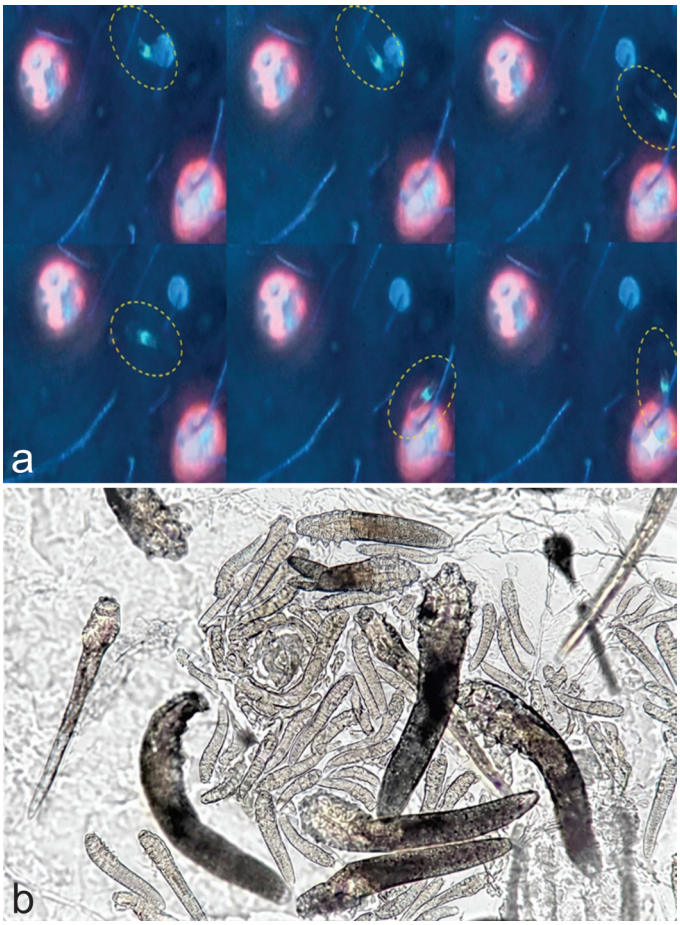

Figure 2 | (a) Dermoscopic examination of the patient's malar region revealed polygonal vascular structures composed of linear blood vessels, superficial crusting and follicle openings, and the tails of demodex parasites; (b) standardized skin surface biopsy revealed numerous demodex parasites.

alternatives should be considered in the maintenance treatment of atopic dermatitis due to other conditions, primarily dermatological, that may arise. In our case, considering both the patient's compliance (oral use) and the literature data, JAK inhibitors were preferred as an alternative to this condition caused by dupilumab. It has been associated with better responses compared to standard rosacea treatment. In conclusion, we wish to emphasize that upadacitinib can be an alternative treatment option for both atopic dermatitis accompanying rosacea that develops as a side effect after dupilumab and for patients with atopic dermatitis that also have rosacea at the primary presentation. This yielded very good results for our patient.

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