Rosacea-like eruptions associated with upadacitinib in atopic dermatitis: two case reports and management strategies

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Abstract

Atopic dermatitis (AD) is a chronic inflammatory skin disease often requiring systemic therapies for moderate-to-severe cases. Janus kinase (JAK) inhibitors, including upadacitinib, have emerged as effective options, targeting pro-inflammatory cytokines involved in AD pathogenesis. However, adverse dermatologic reactions, such as rosacea-like eruptions, have been observed, potentially linked to immune pathway modulation. This report describes two patients with severe AD who achieved complete disease clearance with upadacitinib but developed rosacea-like eruptions. Both cases required discontinuation of the drug and treatment with antibiotics, which resolved the symptoms. However, withdrawal led to AD flares in one patient, necessitating the reintroduction of upadacitinib at a reduced dose combined with prophylactic antibiotics. These cases underscore the efficacy of JAK inhibitors while highlighting the challenge of managing adverse effects. Individualized treatment approaches, including dose adjustments and adjunctive therapies, are essential for balancing AD control and tolerability. Further research is needed to optimize the management of these reactions.

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Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by intense pruritus, skin inflammation, and barrier dysfunction. The therapeutic landscape for AD includes both topical and systemic agents, with more severe cases often requiring advanced treatment options.[1] Recently, Janus kinase (JAK) inhibitors, such as upadacitinib, have emerged as promising alternatives for managing moderate-to-severe AD, particularly in patients unresponsive to conventional therapies. Upadacitinib is a selective JAK1 inhibitor approved for the treatment of moderate-to-severe AD in adults and adolescents, acting to reduce inflammation by modulating pro-inflammatory cytokine signaling pathways involved in AD pathogenesis.[2] While generally effective, upadacitinib, like other JAK inhibitors, is associated with a range of adverse events, including acneiform eruptions, a side effect that can significantly impact patient quality of life and may necessitate therapeutic adjustments. Acneiform eruptions have been previously observed in patients on JAK inhibitors across various indications, yet this adverse reaction remains underreported in the context of AD therapy.[3] Recent reports highlight that upadacitinib-related acneiform eruptions may be linked to the drug's mechanism of action, specifically through modulation of immune pathways. However, the role of JAK proteins in the pathogenesis of acne has not been previously elucidated.[4] Understanding the onset and management of these dermatologic adverse effects is crucial for optimizing AD treatment with JAK inhibitors. In this case report, we present two patients with moderate-to-severe AD who developed rosacea-like eruptions while receiving upadacitinib at daily doses of 15 and 30 mg. This report aims to contribute to the growing body of evidence on JAK inhibitor-associated dermatologic adverse events, with a particular focus on the management strategies necessary to balance treatment efficacy and patient tolerability.

Case Report

Case 1

Patient 1 is a 52-year-old male with a history of severe AD since the age of 15. The patient presented with a head-and-neck phenotype and had previously been treated with dupilumab for one year, which was discontinued due to secondary inefficacy and recurrent conjunctivitis. In June 2024, the patient was initiated on upadacitinib 15 mg daily. Baseline disease parameters included an Eczema Area and Severity Index (EASI) score of 16, a pruritus numeric rating scale (NRS) score of 7, a sleep NRS score of 5, and a Dermatology Life Quality Index (DLQI) score of 10. At the first follow-up, 8 weeks after initiating treatment, the patient achieved complete disease clearance, with an EASI score of 0 (EASI-100), resolution of lesions, and an absence of pruritus. Hematological parameters remained within normal limits. However, at week 12, the patient experienced a sudden onset of papular-pustular lesions localized to the face, primarily on the cheeks and forehead. Notably, comedones were absent (Figure 1a). Based on the clinical presentation and the acute nature of the dermatosis, we classified the reaction as a rosacea-like eruption rather than an acneiform reaction. Upadacitinib was immediately discontinued, and the patient was started on oral doxycycline 100 mg twice daily for 7 days, oral metronidazole 250 mg twice daily for 14 days, and topical metronidazole for 20 days. After one week of treatment, most of the lesions had already resolved. Complete resolution of the eruption was achieved within 30 days (Figure 1b). The patient is currently undergoing treatment with slow-release doxycycline at a dosage of 40 mg per day and is being closely monitored in our department. Further therapeutic options for the underlying AD are currently under evaluation.

Case 2

Patient 2 is a 42-year-old male with a history of severe AD since the age of 19. The patient exhibited a head-and-neck phenotype and had been previously treated with dupilumab for two years, which was discontinued due to secondary inefficacy and recurrent

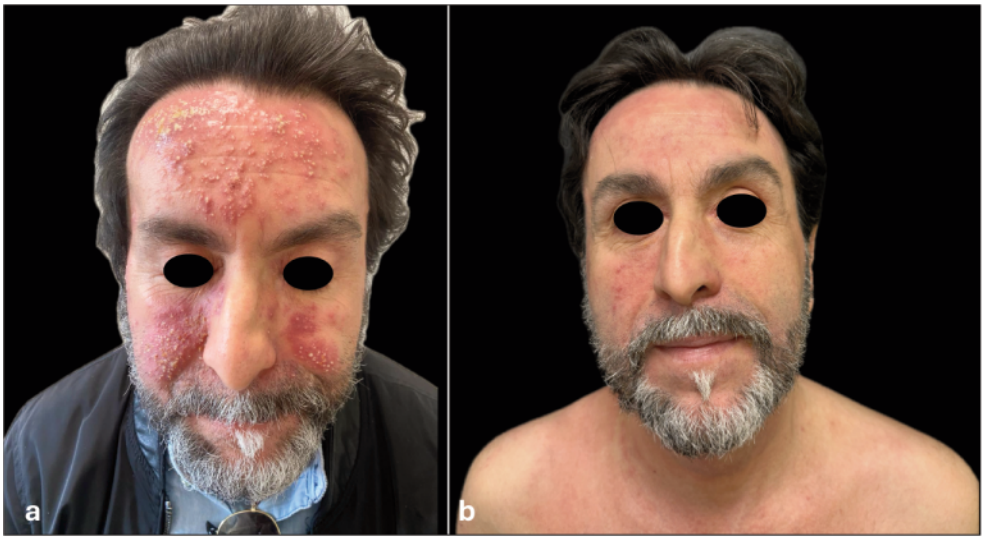

Figure 1. a) Rosacea-like eruption at week 12 of upadacitinib therapy in patient 1. Papulopustular lesions predominantly on the cheeks and forehead, with no comedones present. **b**) Resolution of lesions 30 days after initiating antibiotic treatment and discontinuation of upadacitinib.

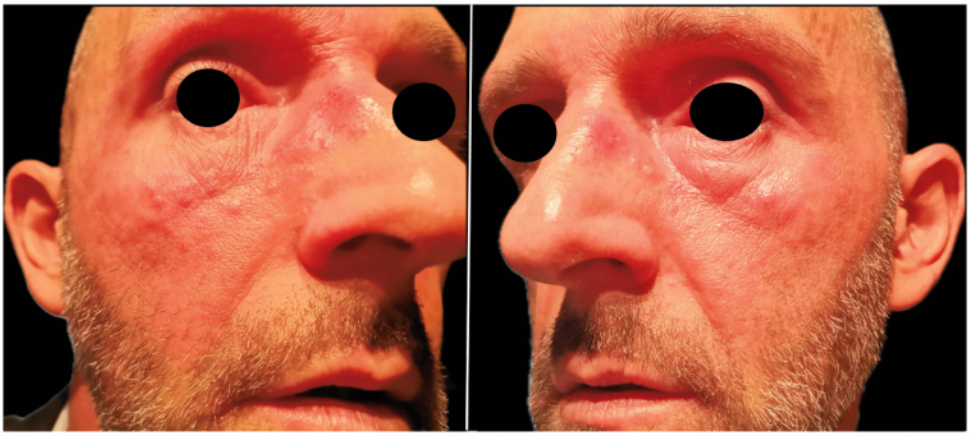

Figure 2. Rosacea-like eruption with erythematous papules and pustules localized to the nasogenian area observed after 43 months of upadacitinib 30 mg daily in patient 2.

episodes of conjunctivitis. In July 2021, the patient was initiated on upadacitinib 30 mg daily. Baseline disease parameters included an EASI score of 30, a pruritus NRS score of 8, a sleep NRS score of 7, and a DLQI score of 19. At the first follow-up, 8 weeks after treatment initiation, the patient achieved complete disease clearance, with an EASI score of 0 (EASI-100), resolution of lesions, and complete absence of pruritus. Hematological and biochemical parameters were within normal limits. The therapeutic benefit persisted for approximately three years, during which the patient maintained good disease control. During this period, there were occasional transient elevations in serum cholesterol levels, which were managed conservatively. In October 2024, the patient developed a rosacea-like reaction, initially characterized by erythematous papules and a few pustules on the nasogenian area, which later extended to the cheeks and forehead (Figure 2). Upadacitinib 30 mg was immediately discontinued, and the patient was treated with oral doxycycline 100 mg twice daily for 7 days. The antibiotic regimen resulted in significant improvement of the rosacea-like lesions (Figure 3). However, following the discontinuation of upadacitinib, the patient experienced a flare of atopic dermatitis, with new eczematous lesions primarily affecting the trunk and face. At this time, disease parameters included an EASI score of 8, a pruritus NRS score of 8, a sleep NRS score of 3, and a DLQI score of 10. To manage the AD flare while mitigating the risk of recurrence of rosacea-like reactions, upadacitinib was reintroduced at a reduced dose of 15 mg daily, combined with a low-dose regimen of doxycycline (40 mg daily) for two months. This approach resulted in the gradual improvement of both AD and rosacea-like symptoms. The patient continues this modified regimen with ongoing monitoring of disease activity and adverse effects.

Discussion

In the presented cases, both patients achieved complete disease clearance (EASI-100) within eight weeks of initiating upadacitinib, demonstrating the efficacy of this therapy for refractory AD. However, both developed rosacea-like eruptions during treatment. Acneiform adverse reactions are reported in the literature, with a *post hoc* analysis of phase 3 trials indicating acne incidences of 9.8% to 15.2% in patients treated with upadacitinib, compared to 2.2% in placebo groups.[5] These eruptions, often mild to moderate, are thought to result from immune pathway modulation.[4] However, while acneiform eruptions during upadacitinib therapy are well documented, a recent group of authors described a clinical case of rosacea occurring during therapy, suggesting a potential correlation with the drug.[6] According to the authors, rosacea could be explained by upadacitinib-induced inhibition of type 2 innate lymphoid cells (ILC2), leading to dysregulation of *Demodex* levels. In our cases, the acute evolution of the dermatosis, the absence of comedones, and the typical localization suggest a diagnosis of rosacea rather than acneiform dermatitis, supporting the evidence proposed in the previous paper. In both cases, this reaction required discontinuation of upadacitinib and antibiotic therapy, which resolved the symptoms. However, discontinuation led to AD flares, particularly in patient 2, underscoring the challenge of balancing effective disease control with the management of adverse events. Literature supports the reintroduction of upadacitinib at a lower dose, as in patient 2, as a viable strategy for maintaining AD control while reducing the risk of recurrence of adverse effects.[5] The combination of a reduced-dose JAK inhibitor with prophylactic antibiotics, as implemented here, aligns with existing evidence and provides a practical approach for clinicians managing similar scenarios.

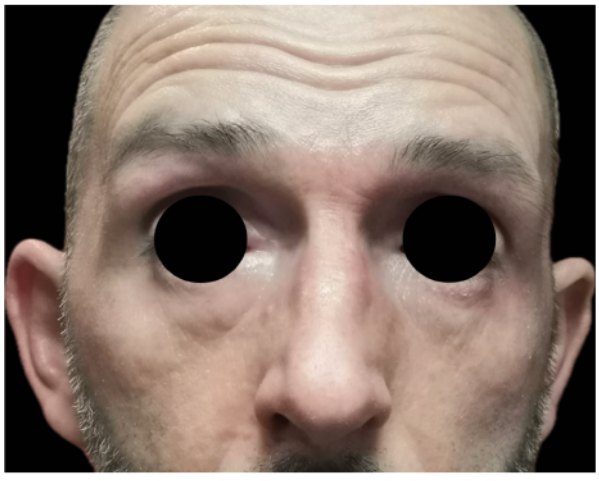

Figure 3. Resolution of rosacea-like lesions following discontinuation of upadacitinib and initiation of oral doxycycline 100 mg twice daily for 7 days. Residual erythema is minimal.

Conclusions

These cases highlight the importance of monitoring for dermatologic and metabolic side effects during JAK inhibitor therapy. Individualized management, including dose adjustments and adjunctive treatments, is crucial to optimize outcomes. Further research is needed to elucidate the mechanisms of rosacea-like reactions and refine strategies for their prevention and management.

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