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CASE REPORT

A Case of Upadacitinib-Associated Ileus Secondary to Psoriasis Induced by Treatment of Atopic Dermatitis with Dupilumab

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Abstract: A 69-year-old man with severe atopic dermatitis (AD) received a single 600 mg subcutaneous injection of dupilumab, which resulted in a psoriatic rash on day 10. He was then given 30 mg of oral upadacitinib daily, and after 10 weeks of treatment, both the AD and the psoriasis had significantly improved. However, at week 16, the patient had no bowel movement for a week, and paralytic ileus was suspected based on the patient's symptoms and laboratory findings. Without surgery or other treatment, one week after stopping upadacitinib, the patient resumed bowel movements and the ileus improved, suggesting a possible link between the drug and the ileus, which was considered to be possibly due to the off-target effect of Janus kinase inhibitor (JAKi). This case illustrates the complexity of the immunomodulatory effects of targeted therapies and the need for long-term observation of their mechanisms of action and side effects.

Keywords: upadacitinib, paralytic ileus, atopic dermatitis, psoriasis

Introduction

Upadacitinib is a highly selective Janus kinase1 (JAK1) inhibitor approved for the treatment of rheumatoid arthritis, psoriatic arthritis (PsA), ulcerative colitis, atopic dermatitis (AD) and others. While inhibition of the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway can reduce certain symptoms of inflammation, it is also likely to interfere with the normal transmission of essential cytokines in the body. The serious adverse events reported for upadacitinib in the randomized controlled trial (RCT) and real-world evidence (RWE) were mainly related to infections, such as urinary tract infections, herpes zoster, diverticulitis, and others,[1] but not ileus. We presented a patient with concomitant AD and psoriasis who was treated with upadacitinib and subsequently developed paralytic ileus.

Case Report

A 69-year-old man presented to our outpatient clinic with a generalized pruritic rash. He had a 20-year history of AD with concomitant hyperlipidemia and no personal history or family history of psoriasis. Physical examination revealed generalized erythema and papules with scaling and lichenification on the trunk and extremities. His Eczema Area and Severity Index (EASI, range: 0–72) score was 33.2 and his Pruritus-Numerical Rating Scale (P-NRS, range: 0–10) itch score was 8. He had an elevated blood eosinophil count (0.82×10^9/L; normal range, 0.02–0.52×10^9/L) and immunoglobulin E level (1598 IU/mL; normal, <60 IU/mL). A diagnosis of severe AD was made. Dupilumab was started with a subcutaneous injection at a loading dose of 600 mg.

However, he developed a new rash 10 days after a single treatment. Physical examination revealed well-defined red plaques with scaling on the upper and lower extremities (Figure 1A–C), and dermoscopy revealed a coexisting psoriasiform rash (Figure 1D) and AD rash (Figure 1E) with a Psoriasis Area Severity Index (PASI) score of 4.8 (range: 0–72), body surface area (BSA) involvement of 6%, static Physicians Global Assessment (sPGA) score of 2 (range: 0–4).

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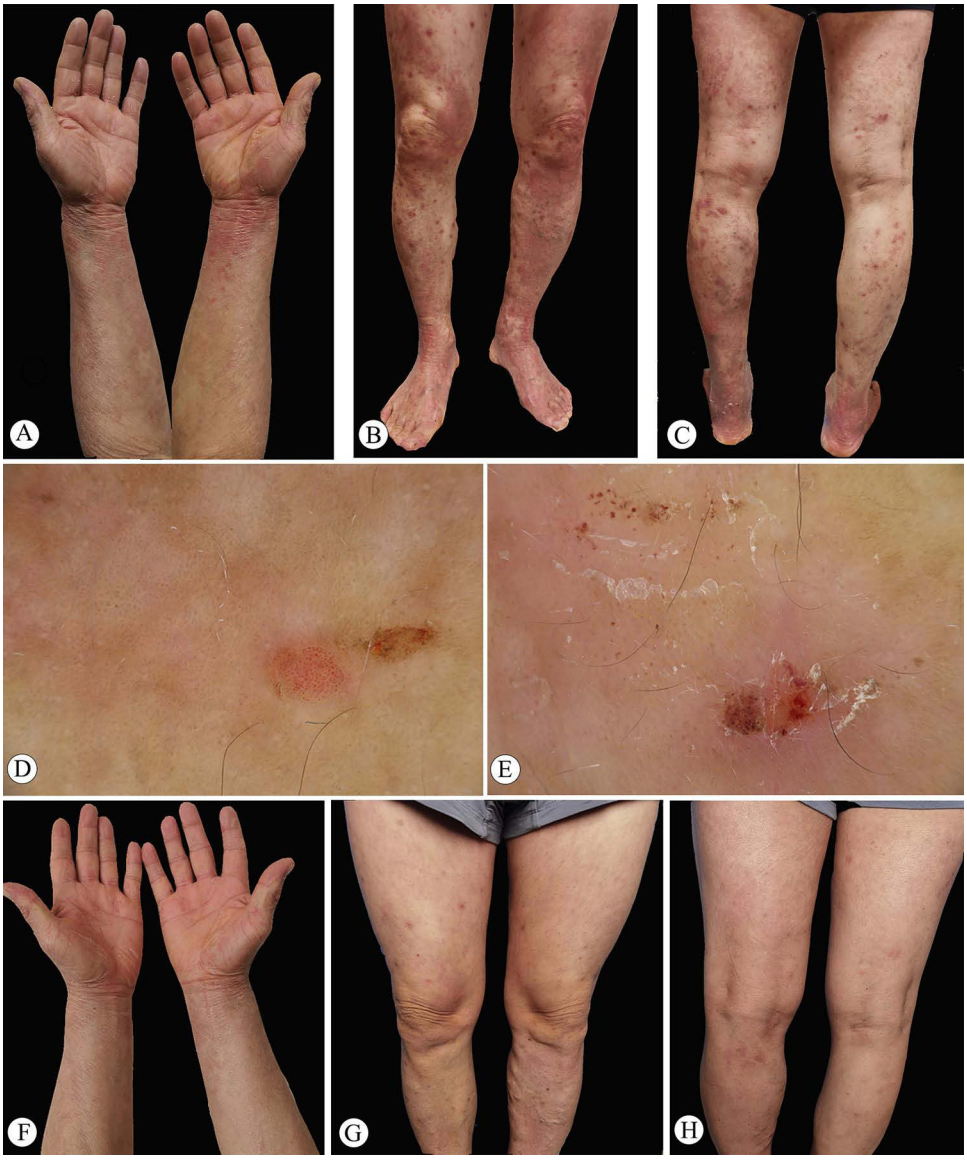

Figure 1 Skin lesions before upadacitinib treatment (**A-C**). On the palmar and plantar, some lesions showed a light red background with regularly distributed dotted vessels (20×) (**D**), and some lesions showed a yellow-red background with focal dotted vessels, focal yellow-white scales and serocrusts (20×) (**E**). Remission after upadacitinib treatment in 1 week (**F**) and 10 week (**G** and **H**).

The patient's blood showed elevated levels of interleukin-17 (IL-17) (2.25%; normal range: 0. 58–1.8%) and interferon-γ (31.91%; normal range: 6.8–18.0%) by flow cytometry, and a diagnosis of coexisting AD and psoriasis was made. He was then treated with oral upadacitinib 30 mg once daily. After two weeks, his pruritus was significantly reduced (P-NRS: 4), the eosinophil count was significantly reduced to 0.02 ×10^9, and IL-17 was normal, but interferon γ remained high (29.8%). The patient experienced a significant remission of both AD and psoriasis after 10 weeks (Figure 1F–H).

At week 16, the patient's skin rash disappeared, but he developed severe constipation, characterized by a complete absence of bowel movements for a week, accompanied by abdominal distension and pain. There were no significant reasons that could have contributed to the onset of the ileus. He was then admitted to the gastroenterology department, where examination revealed mild distension and tenderness in the right abdomen and peri-umbilical region, with sluggish bowel sounds. Notably, he had no history of constipation. Laboratory parameters showed a mild leukocyte elevation of 10.25×10^9/L (normal range, 3.5–9.5×10^9/L), but a normal of D-dimer. Gastroscopy and colonoscopy revealed that

chronic superficial gastritis with erosion, multiple polyps of the colon, and a possible lipoma in the proximal ascending colon. Both thrombosis and mechanical obstruction were ruled out, a paralytic ileus suspected to be related to the use of upadacitinib was diagnosed, and the clinical symptoms of the ileus improved steadily without surgery or other treatment one week after stopping upadacitinib, and the patient was discharged from the hospital.

However, one week after discontinuing the drug, the palmar, plantar and extremity rash recurred with erythema and desquamation, NRS score was 4. He then intensified topical treatment with halometasone and emollient cream, applied twice daily, and took oral cetirizine, 10mg daily, for one month, but the therapeutic effect was unsatisfactory. He then resumed oral upadacitinib, taken once every 5–7 days, 15mg each time. The skin lesions were well controlled and there were no adverse events after 12 months of treatment.

Discussion

Dupilumab, a monoclonal antibody against the IL-4 receptor α, inhibits IL-4 and IL-13 signalling. It is approved for treatment of moderate-to-severe AD, asthma, chronic rhinosinusitis with nasal polyps, and recently prurigo nodularis. Rare adverse events have been reported that may lead to other skin conditions have been reported, including psoriasiform eruptions,[2] cutaneous T-cell lymphoma[3] and vitiligo.[4] The occurrence of psoriasiform eruptions may be associated with T helper 2 (Th2) inhibition, which could shift the immune response towards IL-23/Th17 and Th1 pathways.[2]

Blocking the JAK/STAT pathway suppresses cytokine production, reduces inflammation and modulating immune responses in the Th1, Th2, Th17, and Th22 pathways. Upadacitinib, a JAK1 inhibitor, has shown efficacy in patients with AD and PsA, and the patient who had AD and developed psoriasis following dupilumab treatment, experienced significant improvement in the skin manifestations of both conditions after initiation of upadacitinib therapy; this is consistent with the findings reported by Cataldo Patruno et al.[2] However, our patient developed symptoms of paralytic ileus at week 16. To our knowledge, intestinal adverse events caused by JAK inhibitors (JAKi) are rare; intestinal perforations have been observed with JAKi (baricitinib) therapy, but ileus has not been reported.[5] Due to the increased risk of venous thrombosis, our patient underwent a coagulation testing to rule out thromboembolism.

The pathogenesis of JAK in ileus seems to be controversial. Sun et al[6] found that JAK1 activation mediates intestinal manipulation-induced resident macrophage activation after intestinal manipulation, and subsequent complex inflammatory cascade and intestinal dysmotility. JAK1 inhibition appears to be a prospective and convenient approach for the prevention of postoperative ileus. However, Yang et al[7] found that electroacupuncture ameliorated intestinal inflammation by activating the α7 nicotinic acetylcholine receptor-mediated JAK2/STAT3 signaling pathway in postoperative ileus. This demonstrated that inhibition of JAK2/STAT3 may be associated with ileus.

At the cellular level, upadacitinib is 60 and 100 times more selective for JAK1 than for JAK2 and JAK3, respectively, but as the intracellular concentration of the drug increases, it is likely to affect the binding of adenosine triphosphate to these other JAK family members, with loss of selectivity (off-target effect). The intracellular concentration depends not only on the dose, but also on patient-specific factors, such as age, weight, liver and kidney function, other medications, etc.[8] Therefore, inhibition of JAK2 by upadacitinib may be a possible mechanism of paralytic ileus in patients taking JAK inhibitors.

Patient Consent Statement

The authors certify that they have obtained all appropriate patient consent forms for use of patient photographs and data obtained.

Ethics Statement

The Hospital Ethics Committees of the Peking University People's Hospital approved to publish the case details.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Wu Y, Wei M, Zhang J. A real-world pharmacovigilance analysis of FDA adverse event reporting system database for upadacitinib. *Front Pharmacol*. 2023;14:1200254. doi:10.3389/fphar.2023.1200254
2. Patruno C, Fabbrocini G, De Lucia M, Picone V, Genco L, Napolitano M. Psoriasiform dermatitis induced by dupilumab successfully treated with upadacitinib. *Dermatol Ther*. 2022;35(11):e15788. doi:10.1111/dth.15788
3. Hasan I, Parsons L, Duran S, Zinn Z. Dupilumab therapy for atopic dermatitis is associated with increased risk of cutaneous T cell lymphoma: a retrospective cohort study. *J Am Acad Dermatol*. 2024;91(2):255–258. doi:10.1016/j.jaad.2024.03.039
4. Picone V, Napolitano M, Torta G, Fabbrocini G, Patruno C. Vitiligo during dupilumab therapy. *JAAD Case Rep*. 2023;36:51–53. doi:10.1016/j.jdcr.2023.03.025
5. Klein B, Treudler R, Simon JC. JAK-inhibitors in dermatology – small molecules, big impact? Overview of the mechanism of action, previous study results and potential adverse effects. *J Dtsch Dermatol Ges*. 2021;20(1):19–24. doi:10.1111/ddg.14668
6. Sun Y, Shi H, Hong Z, Chi P. Inhibition of JAK1 mitigates postoperative ileus in mice. *Surgery*. 2019;166(6):1048–1054. doi:10.1016/j.surg.2019.07.016
7. Yang -N-N, Yang J-W, Ye Y, et al. Electroacupuncture ameliorates intestinal inflammation by activating α7nAChR-mediated JAK2/STAT3 signaling pathway in postoperative ileus. *Theranostics*. 2021;11(9):4078–4089. doi:10.7150/thno.52574
8. Isaacs JD, Cooles FAH, Lin CMA. Basic mechanisms of JAK inhibition. *Mediterranean J Rheumatol*. 2020;31(Suppl 1):100–104. doi:10.31138/mjr.31.1.100

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