Review

Paradoxical Psoriasis Associated With JAK Inhibitors: Current Evidence, Proposed Mechanisms, and Clinical Management

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Abstract

The use of Janus kinase (JAK) inhibitors has been rapidly increasing, particularly in immune-mediated conditions, including severe and treatment-refractory inflammatory bowel disease, rheumatologic disorders, and dermatologic conditions such as atopic dermatitis (AD). By inhibiting the JAK/signal transducer and activator of transcription signaling pathway, these agents suppress proinflammatory cytokine production and modulate immune responses. However, as a consequence of this potent immunomodulatory activity, immune-mediated paradoxical reactions—most notably paradoxical psoriasis—may occasionally occur. Although paradoxical psoriasis associated with JAK inhibitors has only rarely been reported in the literature, its true incidence is likely higher. This review synthesizes the current evidence, discusses the proposed pathophysiological mechanisms, and provides an updated perspective on clinical management strategies. This comprehensive evaluation is expected to enhance clinical awareness of paradoxical psoriasis arising during JAK inhibitor therapy and to contribute to improved diagnostic and therapeutic approaches.

Keywords: Immune-mediated adverse reactions, Janus kinase inhibitors, JAK/STAT pathway, paradoxical psoriasis

Introduction

Janus kinase (JAK) inhibitors are pharmacologic agents that inhibit intracellular enzymes of the JAK family involved in cytokine and growth-factor signaling. In recent years, they have gained a prominent role in the treatment of a wide range of immune-mediated diseases, including inflammatory bowel disease (IBD), rheumatoid arthritis (RA), spondyloarthropathies, psoriasis, psoriatic arthritis, atopic dermatitis (AD), and alopecia areata. By selectively or broadly inhibiting the JAK/signal transducer and activator of transcription signaling pathway, these agents simultaneously modulate multiple cytokine-driven immune mechanisms, resulting in rapid and potent anti-inflammatory effects.

While these broad immunological effects offer therapeutic advantages, the multidimensional modulation of immune responses may also lead to unexpected immunological disequilibrium in some patients. One of the most notable examples of this phenomenon is paradoxical psoriasis. This entity is defined as the new onset of psoriasis or the exacerbation of pre-existing psoriasis during treatment for another condition. Unlike classical psoriasis, paradoxical psoriasis typically regresses after discontinuation of the offending agent, and relapse is uncommon. Although initially most frequently associated with tumor necrosis factor (TNF) inhibitors, cases have also been described with interleukin (IL)-

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4/13 and IL-17A inhibitors.[1] Although still rare, paradoxical psoriasis associated with JAK inhibitors has increasingly been recognized and has drawn clinical attention (Table 1).[2-8]

The aim of this narrative review is to summarize the currently available evidence regarding paradoxical psoriasis associated with JAK inhibitors, to discuss the proposed pathophysiological mechanisms, to review clinical management strategies, and to present an illustrative case of a psoriasiform eruption occurring during upadacitinib therapy. Although the number of reported cases remains limited, the available literature provides valuable insights into the clinical spectrum, potential mechanisms, and therapeutic approaches to this uncommon adverse event.

Reported Cases in the Literature

One of the first reported cases of paradoxical psoriasis associated with JAK inhibitors was described by Shibata et al.[2] in a 25-year-old patient with juvenile idiopathic arthritis. Shortly after initiation of tofacitinib, sterile palmoplantar pustular lesions developed on the palms and soles, which regressed markedly upon drug discontinuation and recurred after re-introduction. This clinical course provided some of the earliest evidence that tofacitinib may trigger palmoplantar pustulosis-like psoriasiform eruptions.[2]

Koumaki et al.[3] reported a case of palmoplantar pustulosis in a patient receiving baricitinib for RA, in whom the lesions resolved after withdrawal of the drug and recurred upon re-challenge. The authors suggested that the mechanism of baricitinib-associated palmoplantar pustulosis remains unclear, but alterations in T-cell–mediated cytokine pathways may be involved.[3] Similarly, Di Domizio et al.[4] described a psoriasiform eruption in a patient with RA who was treated with baricitinib and suggested that JAK1/2 inhibition led to a cytokine imbalance, particularly increased expression of IL-6, IL-8(CXCL8), and IL-36G. These cytokines were proposed to promote neutrophil accumulation and IL-23A activation, thereby driving JAK-independent inflammatory pathways and triggering paradoxical psoriasis.[4]

Erol and Ertaş[5] reported the development of psoriasiform plaques in a patient with RA during the third month of tofacitinib therapy. The lesions were clinically and histopathologically consistent with psoriasis and showed marked improvement after drug discontinuation, leading to their classification as a paradoxical psoriasiform reaction. The authors hypothesized that suppression of several downstream cytokines, including interferon-α (IFN-α), may disturb the balance between IFN-α and IFN-γ and/or reshape Th1/Th17 responses, thereby contributing to the development of paradoxical psoriatic inflammation.[5]

Table 1. Reported cases of paradoxical psoriasis and psoriasiform eruptions associated with JAK inhibitor therapy in the literature and the present case

Author year	Age/ gender	JAK inhibitor	Indication	Clinical phenotype	Onset	Previous psoriasis	Family history	Biopsy	Outcome
Shibata et al.[2]	25/F	Tofacitinib	Juvenile idiopathic arthritis	Palmoplantar pustulosis–like eruption	10 days	No	No	Yes	Near-complete clearance after discontinuation; recurrence after reintroduction
Koumaki et al.[3]	56/M	Baricitinib	Rheumatoid arthritis	Palmoplantar pustulosis–like eruption	5 years	No	No	Yes	Near-complete clearance after discontinuation; recurrence after rechallenge
Di Domizio et al.[4]	68/F	Baricitinib	Rheumatoid arthritis	Plaque-type psoriasiform eruption	3 weeks	No	No	Yes	Resolved within 2 months after discontinuation and topical corticosteroids
Erol and Ertaş[5]	45/M	Tofacitinib	Rheumatoid arthritis	Plaque-type psoriasiform eruption	3 months	No	No	Yes	Improved after discontinuation
Ferrucci et al.[6]	44/M	Upadacitinib	Atopic dermatitis	Plaque psoriasis	3 weeks	Yes	NR	Yes	Recurrence of psoriasis during upadacitinib treatment; improvement after discontinuation and methotrexate reintroduction
Becker et al.[7]	20/M	Abrocitinib	Atopic dermatitis	Plaque psoriasis	7 months	No	No	Yes	Resolution after dose reduction
Özkır et al.[8]	12/F	Tofacitinib	Alopecia totalis	Psoriasis flare	4 months	Yes	NR	No	Significant regression after discontinuation, NB-UVB phototherapy, and topical treatment
Present case 2025	43/M	Upadacitinib	Ulcerative colitis	Plaque-type psoriasiform eruption with pustulation	6 months	No	No	Yes	Marked improvement with topical mometasone furoate while continuing upadacitinib (3-month follow-up)

F: Female, M: Male, NR: Not reported, NB-UVB: Narrowband ultraviolet B phototherapy, JAK: Janus kinase

Two patients with AD who developed paradoxical psoriasis during JAK inhibitor therapy have also been reported. In a patient with severe AD who developed psoriasis while receiving dupilumab, disease flares recurred shortly after switching to upadacitinib. This clinical course suggests that Th2 blockade may relatively enhance the Th1/Th17 axis, thereby promoting psoriasiform inflammation, and that JAK1 inhibitors may not fully prevent a phenotypic shift in some individuals. It has also been proposed that incomplete suppression of TYK2-mediated IL-12/IL-23 pathways may contribute to the persistence of psoriatic responses.[6] In another reported patient with severe AD, new eruptions clinically and histologically compatible with psoriasis appeared approximately seven months after initiation of abrocitinib. This observation supports the notion that, despite broad cytokine inhibition, JAK1 inhibitors may paradoxically induce a Th2 → Th17 phenotypic shift.[7] Although JAK inhibitors are theoretically effective for both AD and psoriasis due to their wide-ranging cytokine blockade, they may paradoxically precipitate psoriatic inflammation.

Another case in the literature involved an adolescent patient with alopecia totalis receiving tofacitinib.[8] The patient had a history of psoriasis, and it was postulated that JAK inhibitor–induced cytokine disequilibrium, particularly disruption of the IFN-α/IFN-γ axis, may have triggered psoriatic inflammation. Marked regression of the lesions after drug discontinuation supported the diagnosis of a drug-induced paradoxical reaction.

In our case, a 43-year-old male with ulcerative colitis presented to our dermatology outpatient clinic with a one-month history of erythema and scaling on the soles of both feet that began after approximately six months of treatment with upadacitinib 30 mg/day. The patient had previously failed multiple therapies for ulcerative colitis, including 5-aminosalicylic acid derivatives, systemic corticosteroids, azathioprine, adalimumab, and infliximab. No concomitant medications were used at the time of lesion onset. There was no personal or family history of psoriasis. Dermatological examination revealed erythematous, scaly plaques with scattered pustules on the bilateral plantar surfaces (Figure 1). Histopathological examination demonstrated epidermal parakeratosis, hyperkeratosis, focal areas of hypogranulosis, and focal intraepidermal pustule formation, accompanied by occasional eosinophils within the dermis (Figure 2). Based on the clinical and histopathological findings, a diagnosis of paradoxical psoriasis was favored. Given the excellent control of ulcerative colitis and the localized nature of the lesions, upadacitinib therapy was continued, and topical mometasone furoate was initiated, resulting in marked clinical improvement during a three-month follow-up. Although the temporal relationship between upadacitinib exposure and lesion onset, the absence of personal or family history of psoriasis, and the lack of concomitant medications support a possible association, causality should be interpreted with caution. Because upadacitinib therapy was continued and neither dechallenge nor rechallenge could be assessed, a definitive causal relationship cannot be established in this case.

The pathogenesis and molecular mechanisms of paradoxical psoriasis associated with upadacitinib have not yet been fully elucidated; however, it has been proposed that selective JAK1 inhibition may disturb cytokine homeostasis in genetically predisposed individuals and thereby precipitate this adverse event. To the best of our knowledge, paradoxical psoriasis associated with JAK inhibitor therapy in the context of UC has not previously been reported. Although this case is compatible with a paradoxical dermatologic reaction associated with upadacitinib, causality should be interpreted with caution because neither dechallenge nor rechallenge could be assessed.

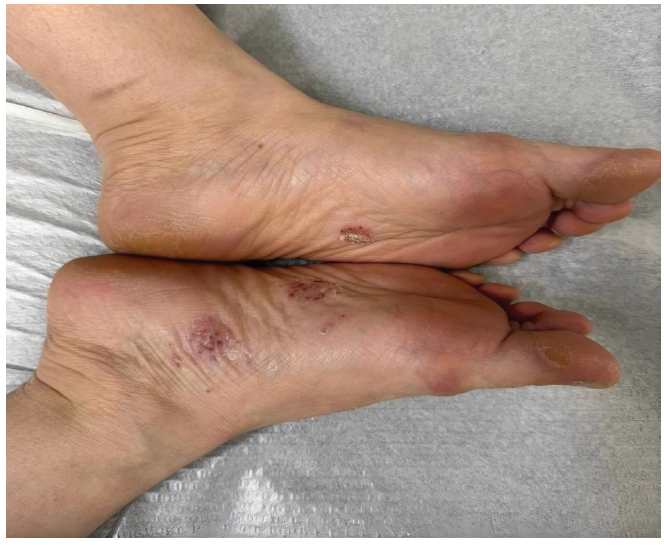

Figure 1. Clinical image of the lesion on the foot

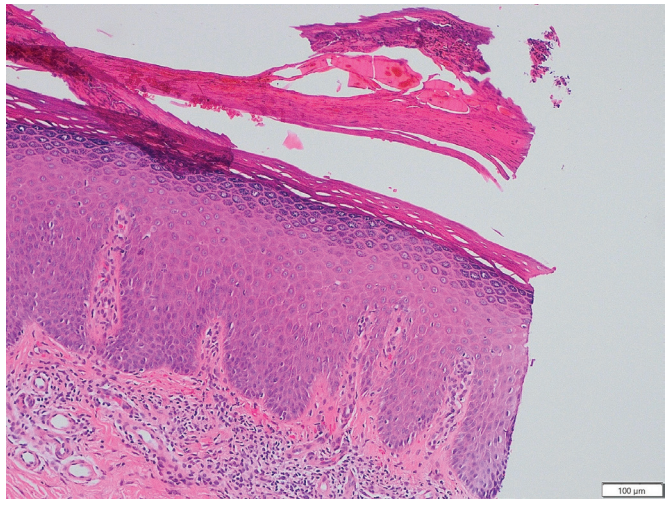

Figure 2. Histopathology showing psoriasiform epidermal hyperplasia with focal intraepidermal pustules and parakeratosis (H&E ×100)
H&E: Hematoxylin and eosin

Nevertheless, it adds to the limited literature on paradoxical dermatologic reactions associated with JAK inhibitor therapy. It also has clinical relevance for improving the understanding of the safety profile of JAK inhibitors and for optimizing patient selection.

Proposed Pathophysiological Mechanisms of Paradoxical Psoriasis

Paradoxical reactions comprise various inflammatory manifestations that may both respond to and be triggered by modern immunomodulatory therapies targeting similar immunologic pathways. These reactions include paradoxical psoriasis, hidradenitis suppurativa, lichenoid eruptions, granulomatous reactions, eczematous eruptions, and neutrophilic dermatoses. Their pathogenesis is multifactorial, involving both drug-related immunologic effects and patient-specific genetic or microbial factors. Most frequently implicated mechanisms include shifts in T-cell polarization, disruption of negative feedback loops, secondary immune responses driven by anti-drug antibodies, and immune activation mediated by interactions between monoclonal antibodies and Fc receptors on myeloid cells.[9] Although paradoxical psoriasis has been most commonly associated with TNF inhibitors due to their long-standing clinical use, reports of paradoxical psoriasis linked to other biologic agents have increasingly accumulated.

Biologic agents remain the class of drugs most frequently associated with paradoxical reactions; however, in recent years a limited but growing number of similar cutaneous phenomena have also been reported with oral small-molecule JAK inhibitors. These agents suppress multiple cytokine pathways simultaneously, generating a broad immunomodulatory effect. Paradoxical psoriasis associated with JAK inhibition appears to arise from a complex immunologic process that cannot be explained by a single mechanism. One prominent hypothesis suggests that JAK inhibition suppresses IFN-α signaling while relatively enhancing IFN-γ–mediated responses, thereby increasing inflammatory gene expression in keratinocytes and triggering psoriatic changes.[10] This hypothesis resembles the pathogenic model proposed for paradoxical psoriasis associated with TNF inhibitors.

Another proposed mechanism, particularly in RA, involves suppression of Th1/Th17 cells within the synovium, leading to expansion of pathogenic T-cell subsets in peripheral lymph nodes—similar to mechanisms described for TNF inhibitors.[11] This aberrant T-cell redistribution may facilitate cutaneous psoriasiform reactions.

Additional studies have suggested that JAK1/2 blockade may shift cytokine balance toward JAK-independent inflammatory axes, particularly IL-8/IL-36–driven pathways, resulting in increased expression of epithelial gene products involved in psoriatic inflammation.[12] This immunologic reprogramming can promote keratinocyte proliferation, neutrophilic infiltration, and the amplification of psoriatic inflammation, creating a permissive environment for paradoxical psoriasis.

In AD, psoriasiform eruptions arising during JAK inhibitor therapy have been interpreted as supporting the Th2 → Th17 phenotypic shift hypothesis. Reduction of Th2 activity—especially following potent IL-4/IL-13 inhibition—may lead to relative dominance of the Th17/IL-23 axis. Such a shift may increase susceptibility to paradoxical psoriasis, particularly in AD subsets characterized by heightened IL-17 expression and histopathologic features overlapping with psoriasis.

Collectively, these mechanisms highlight the complex interplay of genetic predisposition, cytokine imbalance, and treatment-related modulation of immune pathways, which likely underpins the clinical heterogeneity of paradoxical psoriasis observed across rheumatologic, dermatologic, and IBD populations. Considering the shared features of our case with previously published reports, it may be hypothesized that JAK blockade contributes to cytokine alterations in genetically predisposed individuals, thereby facilitating paradoxical psoriatic inflammation. However, the exact mechanisms remain uncertain and require further investigation. Future studies incorporating cytokine profiling and genetic biomarkers may facilitate the development of risk-stratification strategies to predict psoriasiform reactions in patients receiving JAK inhibitors.

Clinical Presentation and Diagnosis

Paradoxical psoriasis typically differs from classic psoriasis in that lesions may exhibit eczema-like areas, less sharply demarcated borders, focal erosions, and incompletely developed silvery scale.[13] Although paradoxical psoriasis associated with JAK inhibitors presents a heterogeneous clinical spectrum, several recurring features have been noted in the literature. The most commonly reported phenotype resembles classic plaque-type psoriasis, followed by a palmoplantar pustulosis–like pustular variant.

Histopathologically, paradoxical psoriasis is often indistinguishable from *de novo* psoriasis. However, cases associated with TNF inhibitors demonstrate a wide histologic spectrum, including eczematous spongiotic patterns, psoriasiform patterns mimicking classic psoriasis (with intraepidermal or subcorneal neutrophilic microabscesses), and lichenoid interface dermatitis.[14] The presence of scattered eosinophils or plasma cells may provide supportive evidence for a drug-related process.

Across all reported cases of JAK inhibitor–associated paradoxical psoriasis, the histopathology consistently demonstrates psoriasiform epidermal hyperplasia, neutrophilic infiltration, and varying degrees of parakeratosis. These features suggest that JAK inhibitors may alter cytokine balance in a way that promotes keratinocyte proliferation and neutrophil-mediated inflammation, thereby initiating paradoxical psoriatic disease.

Clinical Management and Therapeutic Approach

The primary step in clinical management is confirming the possibility of a drug-induced paradoxical reaction. Accurate recognition of paradoxical psoriasis is essential to avoid unnecessary treatment changes and to maintain drug survival. Although no universal treatment algorithm has been established, evidence from published cases indicates that management strategies should be guided by the severity of the paradoxical psoriasis, the pattern of psoriatic involvement, and the status of the underlying disease for which the drug was initiated. Accordingly, individualized decision-making and a multidisciplinary approach are crucial.

Management strategies should be tailored according to disease severity. In patients with mild and localized eruptions, continuation of JAK inhibitor therapy is often feasible, with adequate symptom control achieved through topical therapies and/or phototherapy. In moderate disease, additional therapeutic interventions may be warranted while carefully balancing the benefits of ongoing JAK inhibitor treatment against the severity of the cutaneous adverse event. In severe, extensive, or treatment-refractory cases, dose reduction or discontinuation of the offending agent should be considered, taking into account the activity of the underlying disease and the availability of alternative treatment options.

In most patients, lesions improve following discontinuation or dose reduction of the implicated drug. Topical corticosteroids, keratolytics, vitamin D analogues, and narrowband ultraviolet B phototherapy are commonly employed to control cutaneous manifestations. When continuation of JAK inhibitor therapy is necessary because of active underlying disease, close multidisciplinary collaboration is essential. Ultimately, treatment decisions should be individualized according to the severity of skin involvement, the degree of disease control, and the feasibility of maintaining JAK inhibitor therapy.

Conclusion

JAK inhibitors have emerged as highly effective therapies for a broad range of immune-mediated conditions due to their extensive cytokine blockade. Nonetheless, they may rarely induce unexpected cutaneous reactions such as paradoxical psoriasis. The limited number of published cases suggests that this reaction cannot be explained by a single pathogenic pathway but rather reflects a complex interplay among cytokine imbalance, T-cell polarization, and individual genetic susceptibility. Early recognition and personalized management are essential to achieving adequate control of psoriatic reactions and to ensuring continuity of JAK inhibitor therapy. Future studies focusing on immunologic and genetic predictors of risk are expected to deepen our understanding of these reactions and enhance clinical decision-making.

Ethics

Informed Consent: Written informed consent was obtained from the patient.

Authorship Contributions

Surgical and Medical Practices: S.Y., Concept: S.Y., S.A.T., Design: S.Y., S.A.T., Data Collection or Processing: S.Y., S.A.T., M.A., Literature Search: S.Y., S.A.T., M.A., S.D., P.O., Writing: S.Y., S.A.T., M.A., S.D., P.O.

Footnotes

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