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Severe paradoxical generalized pustular psoriasis induced by adalimumab biosimilar successfully treated with brodalumab

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Conflicts of interest: MG and MT declare to have acted as speakers and/or consultants for AbbVie, Almirall, Eli-Lilly, Johnson & Johnson, LeoPharma, Novartis, and Sanofi outside the submitted work; LB declares to have acted as a speaker and/or consultant for AbbVie, Almirall, Eli-Lilly, Johnson & Johnson, LeoPharma, Novartis, Pfizer, Sanofi, and UCB outside the submitted work. The other authors declare no conflict of interest.

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Consent for publication: the patient gave her written consent to use her personal data for the publication of this case report and any accompanying images.

Availability of data and materials: data supporting the findings of this study are available upon reasonable request from the corresponding author.

Abstract

Paradoxical psoriasis is a rare but increasingly recognized adverse effect of anti-TNF-α therapy, characterized by the onset or exacerbation of psoriatic lesions in patients treated for other immune-mediated conditions. We report the case of a 47-year-old woman with chronic plaque psoriasis who developed severe generalized pustular psoriasis (GPP) after six months of treatment with an adalimumab biosimilar. Given the extent and severity of the eruption and following inadequate response to previous conventional therapies, the patient was treated with brodalumab, an IL-17RA inhibitor. Rapid and complete remission of both pustular and plaque psoriasis was achieved and maintained for over 60 weeks. This case supports the efficacy of IL-17 pathway blockade in managing paradoxical GPP and highlights the importance of prompt recognition and appropriate therapeutic switching in severe biologic-induced psoriasis.

Introduction

Tumor necrosis factor (TNF) inhibitors are well-established therapeutic options for patients with psoriasis. It is documented that TNF inhibitors, such as adalimumab, can worsen pre-existing psoriasis lesions or trigger the onset of new lesions, including pustular eruptions.[1] This is caused by an imbalance in cytokines, leading to what is known as “paradoxical reactions”. In this article, we share our experience with a paradoxical generalized pustular psoriasis (GPP) induced by adalimumab and treated very satisfactorily with brodalumab.

Case Report

A 47-year-old woman with a history of chronic plaque psoriasis since 2014, previously treated at another institution with topical corticosteroids, azathioprine, and cyclosporine, presented with recurrent disease flares unresponsive to these conventional therapies. In June 2016, she was hospitalized for widespread erythema and pustular/vesicular eruptions. Histopathological analysis from a skin biopsy suggested eczematous dermatitis, and oral corticosteroids led to temporary resolution. A subsequent flare in February 2017 required rehospitalization for similar erythematous-papular-pustular lesions. A second biopsy yielded overlapping features of eczema and psoriasis, again responsive to corticosteroid therapy. Between 2017 and 2022, the patient experienced recurrent psoriatic activity despite intermittent systemic therapy. In April 2022, during a worsening of the disease, she was referred to our center. A decision was made to initiate treatment with a biosimilar of adalimumab targeting persistent plaque psoriasis on the arms and trunk. Clinical improvement was noted for five months. However, by October 2022, the patient developed a sudden and extensive pustular eruption involving the majority of her body surface area, accompanied by diffuse erythema

and pruritus. No fever or systemic symptoms were present. Laboratory investigations, including hematologic and biochemical panels, were unremarkable. In the suspicion of a paradoxical reaction to adalimumab, the drug was discontinued, and since the patient refused a repeat biopsy, she was evaluated using confocal laser microscopy. Imaging revealed intracorneal pustules containing hyper-reflective neutrophils (Figure 1). Based on clinical presentation and confocal microscopy, a diagnosis of generalized pustular psoriasis was made. Disease severity assessments showed a Generalized Pustular Psoriasis Area and Severity Index (GPPASI) score of 40, body surface area (BSA) involvement of 60%, and a Dermatology Life Quality Index (DLQI) of 15. The Columbia-Suicide Severity Rating Scale (C-SSRS) screening was negative for depressive symptoms. Therapy with brodalumab was initiated at a dosage of 210 mg subcutaneously at weeks 0, 1, and 2, followed by maintenance dosing every two weeks. Significant clinical improvement was observed after the first two weeks, and by week 12, the patient achieved complete resolution of pustular lesions. Additionally, the plaque psoriasis was effectively controlled. After 60 weeks of continuous treatment, the patient remains in complete remission, without recurrence of either pustular or plaque-type lesions (Figures 2 and 3).

Discussion

Paradoxical psoriasis is a well-documented adverse event associated with anti-TNF-α therapies, often characterized by clinical and histopathologic features indistinguishable from idiopathic psoriasis.[2,3] Among its various clinical phenotypes, GPP is one of the most severe and challenging to manage, given its acute presentation, potential systemic involvement, and refractoriness to conventional therapies.[4] The immunopathogenesis of paradoxical psoriasis remains incompletely understood, but dysregulated cytokine signaling following TNF-α blockade appears to be central. Two predominant hypotheses have emerged. The first posits that inhibition of TNF-α leads to enhanced activation of plasmacytoid dendritic cells (PDCs), resulting in increased production of type I interferons (especially IFN-α) and subsequent T cell activation, thereby establishing a self-sustaining inflammatory loop. The second hypothesis involves an imbalance in T cell subsets: TNF-α blockade favors the expansion of Th17 cells while suppressing regulatory T cells, culminating in elevated IL-17 production – a key driver of psoriatic inflammation.[5] In the context of GPP, recent advances have delineated a distinct inflammatory pathway involving the IL-36 cytokine family.[6] Mutations in *IL36RN*, encoding the IL-36 receptor antagonist, have been identified in a subset of GPP patients, resulting in unopposed IL-36 activity. This promotes exaggerated neutrophilic inflammation and keratinocyte activation. Importantly, IL-36 and IL-17 exhibit a synergistic interplay: IL-36 promotes Th17 polarization and IL-17 secretion,[7] while IL-17 further upregulates IL-36 expression in keratinocytes.[8] This positive

feedback loop amplifies cutaneous inflammation and drives the hallmark features of GPP, including widespread sterile pustules and systemic symptoms. Given this pathogenic framework, targeting the IL-17 axis represents a rational therapeutic strategy.[9] Among IL-17 inhibitors, brodalumab offers a unique mechanism of action by antagonizing the IL-17 receptor A (IL-17RA), thereby blocking signaling from multiple IL-17 family cytokines (including IL-17A, IL-17F, and others).[10] This broader inhibition may be particularly effective in severe and refractory cases such as paradoxical GPP, where multiple IL-17 isoforms and cytokine loops are implicated. Our clinical case underscores this therapeutic potential. The temporal association with adalimumab administration, clinical presentation, and rapid improvement after discontinuation strongly support a diagnosis of paradoxical GPP. The lack of systemic symptoms and the confocal microscopy findings further supported this conclusion in the absence of histopathological confirmation. The patient achieved complete and sustained remission with brodalumab, with both pustular and plaque components resolving rapidly. Notably, confocal microscopy played a valuable diagnostic role in our case, providing real-time, non-invasive visualization of psoriasiform features and aiding in the differential diagnosis without the need for an invasive biopsy. This highlights its potential utility in complex or atypical dermatologic presentations. Management of paradoxical GPP typically necessitates discontinuation of the inciting anti-TNF agent.[4] While some patients respond to topical therapies, systemic treatment is often required. Switching to another anti-TNF agent may carry a risk of recurrence, suggesting a class effect.[11] In contrast, switching to a different biologic class, particularly IL-17 inhibitors, has shown superior efficacy. Brodalumab has demonstrated robust and durable responses in both clinical trials and real-world reports of paradoxical psoriasis, including pustular variants.[12-14]

Conclusions

In conclusion, paradoxical GPP represents a distinct inflammatory reaction triggered by TNF-α inhibition, driven by complex cytokine dysregulation involving the IL-17/IL-36 axis. IL-17 inhibitors, and especially brodalumab, due to their receptor-blocking mechanism, provide a targeted and effective treatment option. Our case illustrates not only the therapeutic success of brodalumab in this context but also the emerging role of confocal microscopy as a diagnostic adjunct in dermatology.

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Figure 1. Section details under focal laser microscopy examination exhibit intracorneal pustules with hyperreflective neutrophils.

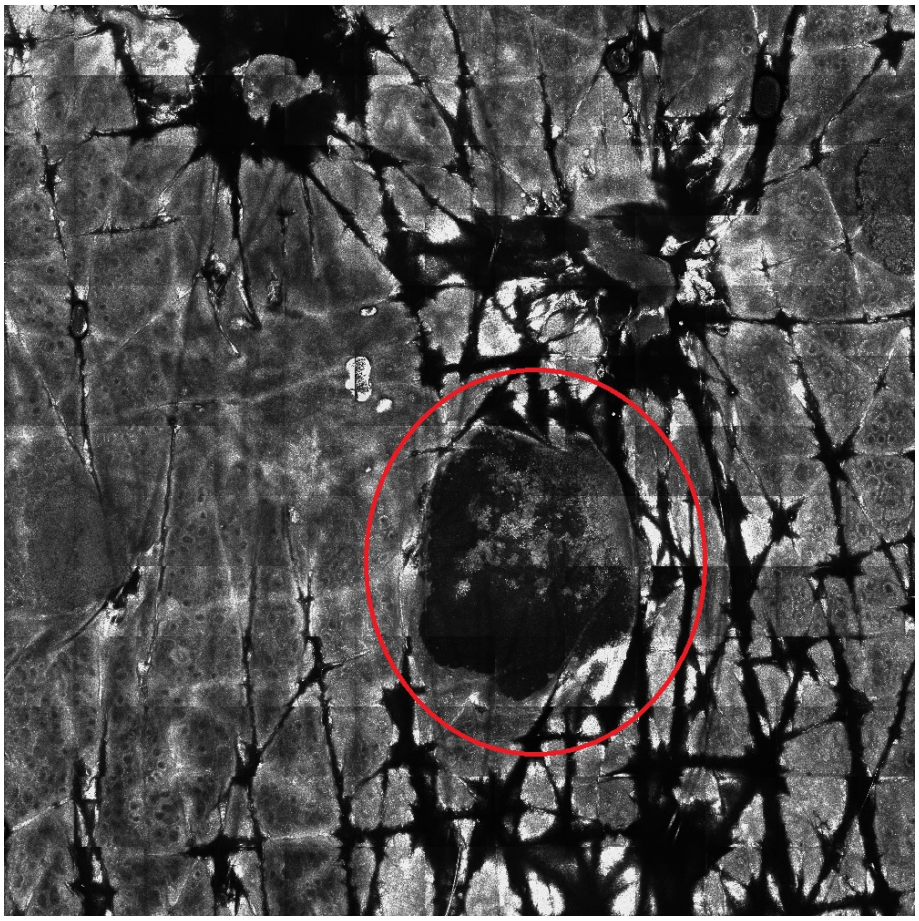

Figure 2. GPP eruption before (a) and after (b) treatment with brodalumab.

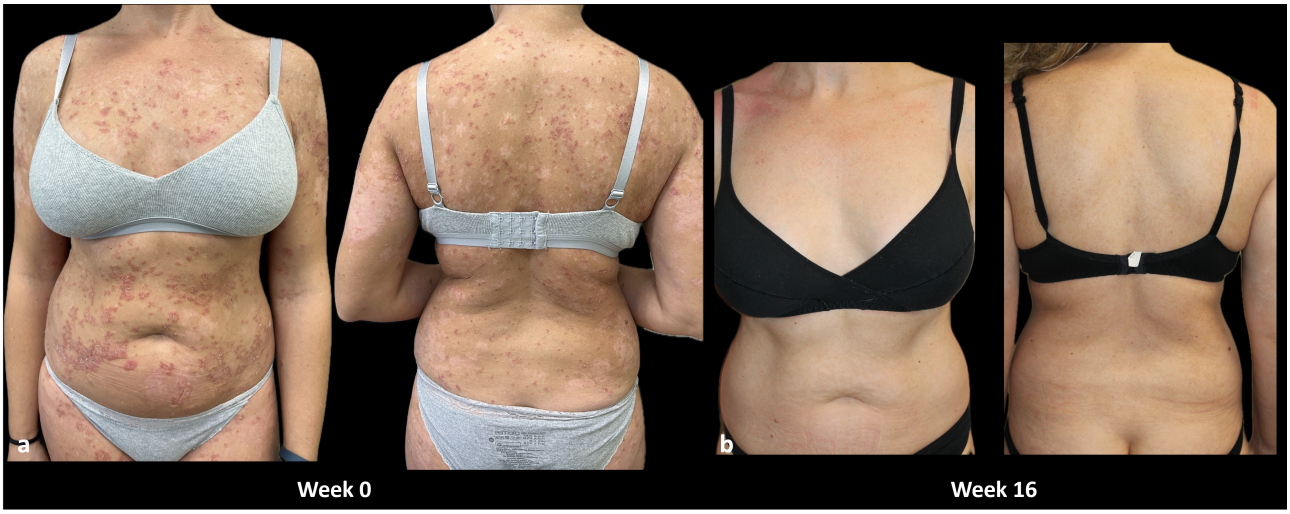

Figure 3. A particular of GPP eruption before (a-c) and after (b-d) treatment with brodalumab.