10.58931/cdt.2024.54130

ABOUT THE AUTHOR

David O. Croitoru, MD

Dr. David Croitoru is a full-time Clinician Investigator at University Health Network, Toronto, Canada, with an interest in autoimmune and inflammatory dermatoses as well as cutaneous manifestations of chemotherapy. He is cross appointed at Women's College Hospital where he practices Wound Care and is the medical lead of specialized Pyoderma Gangrenosum and Hidradenitis Suppurativa surgery clinics. To further resident engagement with research, he is the co-chair of the CIHR-funded SKiN Canada's trainee development committee as well as for the SPoT (Skin Pathophysiology Therapeutics).

Affiliations: Temerty Faculty of Medicine, University of Toronto, Toronto, ON.
Division of Dermatology, Department of Medicine, Temerty Faculty of Medicine, University of Toronto, Toronto, ON.
Division of Dermatology, Department of Medicine and Research and Innovation Institute, Women's College Hospital, Toronto, ON.
Division of Dermatology, Department of Medicine, University Health Network, Toronto, ON.

Paradoxical Psoriasis Induced by TNF Inhibitors and Beyond: A Review

David O. Croitoru, MD

Introduction

Paradoxical psoriasis (PP) represents an uncommon but well-documented adverse effect that occurs following exposure to tumour necrosis factor-alpha (TNF-α) inhibitors.[1] There is growing evidence that this reaction may not be class-specific, as the indications for biologic interventions (interleukin [IL]12/23, IL23, IL17, IL4/13) broaden in chronic inflammatory diseases. However, cumulative evidence amongst other classes remains limited to case reports.[2,3]

The pathogenesis of this reaction to TNF inhibitors has been postulated and experimentally supported as a switch toward interferon (IFN) production by antigen-presenting cells, however, the mechanism with other biologics remains elusive.[4] The baseline association of classical psoriasis (non-drug induced) with the seronegative rheumatic and gastrointestinal inflammatory diseases treated by TNF inhibitors, initially made this reaction a challenge to define and study. As evidence has grown, PP has been defined as psoriatic lesions that arise *de novo* or as morphologically atypical exacerbations of pre-existing known psoriasis during TNF-α therapy. These lesions may persist and worsen unless treated, commonly requiring systemic therapeutic adjustments. This review explores the epidemiology, pathogenesis, clinical manifestations, and management of PP, with an emphasis on patient outcomes and recommendations based on primary data, systematic reviews, and contributions from key researchers in the field.

Epidemiology

The incidence of PP varies by therapeutic agent, clinical context, and patient demographic. Anti-TNF agents, such as infliximab, adalimumab, and etanercept, are frequently implicated. A systematic review conducted in 2022 involving 2,049 cases found that infliximab accounted for over half of the reported cases.[5] Studies suggest that up to 5% of patients on TNF inhibitors experience PP, with higher rates observed in inflammatory bowel disease (IBD) patients compared to those with other autoimmune diseases. Among patients with IBD, those with Crohn's disease are at over a 1.5 times greater risk of developing PP than those with ulcerative colitis.[6] Females appear more predisposed to PP, comprising approximately 60-70% of cases.[6,7] Anti-IL-17 therapies, often prescribed for psoriasis, psoriatic arthritis, and ankylosing spondylitis, are also associated with PP, though the number of reported cases has been significantly lower than that observed with anti-TNF agents. Among the approximately 30 documented cases, most involve IL-17A-specific inhibitors such as secukinumab, with fewer reports for agents such as ixekizumab, the

IL-17A/F inhibitor bimekizumab, and the receptor antagonist brodalumab.[8] While p19 and p40 inhibitors of Il-12 and IL-23 pathways are commonly described in the treatment of TNF-induced PP, they have also been occasionally described as potential culprits.[2] Recently, IL-4/IL-13 inhibitors, such as dupilumab, have also been described with a lower frequency of PP following exposure (1-2%) with an increased risk noted in those with a familial or personal history of psoriasis, suggesting that this may represent an 'unmasking' of psoriasis in predisposed patients.[3]

Pathogenesis

The pathogenesis of PP is distinct from idiopathic psoriasis and hinges on the tight immunological regulation of TNF, IFN, and likely IL-4/13 and Il-17. Evidence suggests that the mechanism for TNF-α induced PP occurs due to TNF inhibition, which causes an overcompensation in interferon-alpha (IFN-α) activity via plasmacytoid dendritic cell activation. This causes a T-cell independent, innate psoriasiform inflammatory response, as well as the recruitment of Th17 and Th1 cells.[4,9] In contrast, emerging data on the pathogenesis of IL-4/IL-13-induced PP supports the theory that dysregulation of the homeostasis of Th17 and Th2 inflammation is the underlying event for these agents.[10,11] Both IL-4-Rα and specific IL-13 inhibition have been demonstrated to shift toward a Th1/Th17 phenotype, resulting in the development of PP. Patients with this presentation have demonstrated increased relative Il-17A levels in peripheral blood, along with a corresponding increase in IL-23 in lesional skin. Conceptually, it is believed that psoriasis and atopic dermatitis may represent two poles of an interrelated immunological spectrum, with switches hinging on Il-17; emerging translational data may support baseline Il-17A levels as predictive of this immunological switch.[12]

Clinical Manifestations

PP presents with a spectrum of clinical forms, often mirroring classical psoriasis but with some variations. The most frequently observed morphologies include plaque-type (vulgaris) and palmoplantar pustulosis, which can occur either in isolation or with corporal involvement. Other documented forms include inverse, guttate, psoriasiform dermatitis and generalized pustular forms.[6] Palmoplantar pustules, observed in approximately one-third of cases, may be seen in conjunction with other morphologies simultaneously. Despite the predilection for pustular eruptions, generalized pustulosis is a rare occurrence with <3% of cases described in larger cohorts.[13] A notable feature of TNF-induced PP, which occurs in a minority of patients (approximately 10%), is the potential for scalp involvement with regional alopecia, which is not observed in classical psoriasis.[6,7] This scalp involvement typically manifests as psoriatic erythematous, hyperkeratotic, and sometimes exudative/pustular lesions.

The pleomorphic nature of PP coupled with the variable latency period from initial drug exposure can make the etiology of the eruption challenging to pinpoint. The timing of PP generally occurs within the first year of TNF inhibitor initiation, with an average onset of approximately 11 months in adults and 22 months in children.[14]

Factors that predict extensive or severe PP with alopecia include female sex, younger age, smoking, and having Crohn's disease, with a particularly elevated risk among patients on adalimumab.[6]

In rare cases, PP may involve articular manifestations, resembling both arthralgia secondary to IFN upregulation as well as true psoriatic arthritis with synovitis, associated with upregulations in IL-17 and IL-23 pathways.

An important diagnostic consideration for clinicians when managing patients with suspected PP on less commonly described agents (e. g., IL-17) is whether the eruption represents a breakthrough of classical psoriasis or multiple competing pathologies.

Management

Managing PP is often a multidisciplinary decision that involves a reassessment of biologic therapy, without a standard treatment ladder or published guideline. For mild cases, topical therapies may be considered as the first line of treatment, either alone or in conjunction with phototherapy.[15] These include vitamin D agonists, corticosteroids, calcineurin inhibitors, salicylic acid/retinoids, and more recently, phosphodiesterase inhibitors. Discontinuing or alternating biologic therapy is the most straightforward approach, with symptomatic resolution observed in many patients after cessation. However, this decision must be weighed against the risk of exacerbating the underlying inflammatory condition, particularly in patients with severe rheumatoid arthritis or Crohn's disease. Some clinicians will arrange for interval disease staging with synovial exams, serum and stool studies (fecal calprotectin), and/or imaging modalities to define the underlying disease before committing to a management strategy. For patients who cannot discontinue TNF inhibitors, alternative biologic therapies, such as IL-17 or IL-12/23 inhibitors, have shown promise.

In one systematic review on PP in patients with IBD following TNF inhibitor exposure, ustekinumab

resulted in a complete or partial resolution in 83.1% of patients (n=74/89), with 75.4% maintaining their IBD remission.[13,16] Clinical outcomes following interclass transitions vary, but they are generally favourable, with improved symptom control and reduced lesion progression.

Intraclass switches may also be of benefit but have been associated with persistence or worsening of their PP in large cohort studies. Therefore, this approach should be employed cautiously and on an as-needed basis.

Systemic agents, such as methotrexate or cyclosporine, may also be considered for moderate-to-severe cases using a treat-through approach, though the risk-benefit profile of these treatments must be assessed carefully. Studies underscore the importance of regular monitoring for side effects, particularly when systemic agents are prescribed concurrently with TNF inhibitors. For refractory cases, small-molecule inhibitors such as apremilast, which modulate intracellular inflammatory pathways, have shown potential in small cohort studies but require further validation in larger studies and trials.

Conclusion

PP presents a unique therapeutic challenge, reflecting the complexity of immune modulation through TNF-α inhibition and the polarization of Th17/Th2 immunity. This review highlights the unpredictable epidemiology, complex pathogenesis, and diverse clinical manifestations associated with this condition. Although TNF inhibitors are indispensable for treating various autoimmune disorders, the emergence of PP necessitates ongoing vigilance and a tailored management approach. Current therapeutic options, particularly IL-17 and IL-12/23 inhibitors, offer promising alternatives for managing PP while maintaining disease control of the primary autoimmune condition. Ongoing research into the immunologic mechanisms and long-term outcomes of PP is essential for refining treatment protocols and improving patient care.

Correspondence

David O. Croitoru, MD
Email: david.croitoru@utoronto.ca

Financial Disclosures

Consultancy: AbbVie, Amgen, Bausch Health, BioJAMP, Boehringer-Ingelheim, Bristol Myers Squibb, Eli Lilly, Janssen, Leo, Novartis, Pfizer, Sanofi-Regeneron, Sun Pharma, and UCB.

References

1. Tillack C, Ehmann LM, Friedrich M, Laubender RP, Papay P, Vogelsang H, et al. Anti-TNF antibody-induced psoriasiform skin lesions in patients with inflammatory bowel disease are characterised by interferon-γ-expressing Th1 cells and IL-17A/IL-22-expressing Th17 cells and respond to anti-IL-12/IL-23 antibody treatment. Gut. 2014;63(4):567-577. doi:10.1136/gutjnl-2012-302853
2. Klimko A, Olteanu AO, Tieranu I, Orzan OA, Toma CV, Ionescu EM, et al. Paradoxical psoriasis induced by ustekinumab: a comprehensive review and case report. Medicina (Kaunas). 2024;60(1). doi:10.3390/medicina60010106
3. Brumfiel CM, Patel MH, Zirwas MJ. Development of psoriasis during treatment with dupilumab: a systematic review. J Am Acad Dermatol. 2022;86(3):708-709. doi:10.1016/j.jaad.2021.05.013
4. Conrad C, Di Domizio J, Mylonas A, Belkhodja C, Demaria O, Navarini AA, et al. TNF blockade induces a dysregulated type I interferon response without autoimmunity in paradoxical psoriasis. Nat Commun. 2018;9(1):25. doi:10.1038/s41467-017-02466-4
5. Murphy MJ, Cohen JM, Vesely MD, Damsky W. Paradoxical eruptions to targeted therapies in dermatology: a systematic review and analysis. J Am Acad Dermatol. 2022;86(5):1080-1091. doi:10.1016/j.jaad.2020.12.010
6. Croitoru DO, Brooks SG, Nathanielsz N, Silverberg O, Nicolau I, Drucker AM, et al. Predictors of severity in paradoxical psoriasis from biologic therapies: a systematic review. J Am Acad Dermatol. 2023;88(2):471-473. doi:10.1016/j.jaad.2022.06.019
7. Brown G, Wang E, Leon A, Huynh M, Wehner M, Matro R, et al. Tumor necrosis factor-α inhibitor-induced psoriasis: systematic review of clinical features, histopathological findings, and management experience. J Am Acad Dermatol. 2017;76(2):334-341. doi:10.1016/j.jaad.2016.08.012
8. Alnaqbi KA, Zeyoudi JA, Fazal F, Alhaj OM, Jassim I, Albreki FA. Paradoxical psoriasis and worsening spondylitis due to secukinumab in a patient with ankylosing spondylitis: a case report and literature review. Cureus. 2023;15(12):e50726. doi:10.7759/cureus.50726
9. Moran B, Gallagher C, Tobin AM, Fletcher JM. Enrichment of polyfunctional IL-17-producing T cells in paradoxical psoriasis skin lesions. J Invest Dermatol. 2020;140(5):1094-1097. doi:10.1016/j.jid.2019.10.010
10. Safa G, Paumier V. Psoriasis induced by dupilumab therapy. Clin Exp Dermatol. 2019;44(3):e49-e50. doi:10.1111/ced.13901
11. Ahmad M, Murphy MJ, Damsky W, Leventhal J. Dupilumab-induced psoriasis in the setting of pembrolizumab therapy: an analysis of cytokine expression. Int J Dermatol. 2023;62(8):e424-e426. doi:10.1111/ijd.16538
12. Guttman-Yassky E, Krueger JG. Atopic dermatitis and psoriasis: two different immune diseases or one spectrum? Curr Opin Immunol. 2017;48:68-73. doi:10.1016/j.coi.2017.08.008
13. Maronese CA, Valenti M, Moltrasio C, Romagnuolo M, Ferrucci SM, Gilliet M, et al. Paradoxical psoriasis: an updated review of clinical features, pathogenesis, and treatment options. J Invest Dermatol. 2024;144(11):2364-2376. doi:10.1016/j.jid.2024.05.015
14. Böhner A, Jargosch M, Müller NS, Garzorz-Stark N, Pilz C, Lauffer F, et al. The neglected twin: Nummular eczema is a variant of atopic dermatitis with codominant T(H)2/T(H)17 immune response. J Allergy Clin Immunol. 2023;152(2):408-419. doi:10.1016/j.jaci.2023.04.009
15. Mazloom SE, Yan D, Hu JZ, Ya J, Husni ME, Warren CB, et al. TNF-α inhibitor-induced psoriasis: a decade of experience at the Cleveland Clinic. J Am Acad Dermatol. 2020;83(6):1590-1598. doi:10.1016/j.jaad.2018.12.018
16. Karadeniz H, Ataş N, Avanoğlu Güler A, Tufan A. Treatment of anti-TNF-related paradoxic palmoplantar psoriasis in Behçet's disease with azathioprine. Clin Exp Rheumatol. 2019;37 Suppl 121(6):168.