

Paradoxical Reaction to TNF- α Inhibitor Therapy in a Patient With Hidradenitis Suppurativa

Leila K. Asadi; Leonard H. Goldberg, MD; Ming H. Jih, MD, PhD

PRACTICE POINTS

- Clinicians need to be aware of the potential risk for a paradoxical reaction in patients receiving a tumor necrosis factor α (TNF- α) inhibitor for hidradenitis suppurativa.
- Although uncommon, developing more than 1 type of paradoxical skin reaction is possible with a TNF- α inhibitor.
- Early recognition and appropriate management of these paradoxical reactions are critical.

To the Editor:

Hidradenitis suppurativa (HS) is a chronic inflammatory condition of the pilosebaceous unit that occurs in concert with elevations of various cytokines, including tumor necrosis factor α (TNF- α), IL-1 β , IL-10, and IL-17.^{1,2} Adalimumab is a TNF- α inhibitor approved by the US Food and Drug Administration for the treatment of HS. Although TNF- α inhibitors are effective for many immune-mediated inflammatory disorders, paradoxical drug reactions have been reported following treatment with these agents.³⁻⁶ True paradoxical drug reactions likely are immune mediated and directly lead to new onset of a pathologic condition that would otherwise respond to that drug. For example, there are reports of rheumatoid arthritis patients who were treated with a TNF- α inhibitor and developed psoriatic skin lesions.^{3,6} Paradoxical drug reactions also have been reported with acute-onset inflammatory bowel disease and HS or less commonly

pyoderma gangrenosum (PG), uveitis, granulomatous reactions, and vasculitis.^{4,5} We present the case of a patient with HS who was treated with a TNF- α inhibitor and developed 2 distinct paradoxical drug reactions. We also provide an overview of paradoxical drug reactions associated with TNF- α inhibitors.

A 38-year-old woman developed a painful “boil” on the right leg that was previously treated in the emergency department with incision and drainage as well as oral clindamycin for 7 days, but the lesion spread and continued to worsen. She had a history of HS in the axillae and groin region that had been present since 12 years of age. The condition was poorly controlled despite multiple courses of oral antibiotics and surgical resections. An oral contraceptive also was attempted, but the patient discontinued treatment when liver enzyme levels became elevated. The patient had no other notable medical history, including skin disease. There was a family history of HS in her father and a sibling. Seeking more effective treatment, the patient was offered adalimumab approximately 4 months prior to clinical presentation and agreed to start a course of the drug. She received a loading dose of 160 mg on day 1 and 80 mg on day 15 followed by a maintenance dosage of 40 mg weekly. She experienced improvement in HS symptoms after 3 months on adalimumab; however, she developed scaly pruritic patches on the scalp, arms, and legs that were consistent with psoriasis. Because of the absence of a personal or family history of psoriasis, the patient was informed of the probability of paradoxical psoriasis resulting from adalimumab. She elected to continue adalimumab

From DermSurgery Associates, Houston, Texas. Dr. Goldberg also is from the Department of Dermatology, Houston Methodist Hospital. The authors report no conflict of interest.

Correspondence: Ming H. Jih, MD, PhD, DermSurgery Associates, 7515 Main St, Ste 240, Houston, TX 77030 (ming_jih@yahoo.com). doi:10.12788/cutis.0898

because of the improvement in HS symptoms, and the psoriatic lesions were mild and adequately controlled with a topical steroid.

At the current presentation 1 month later, physical examination revealed a large indurated and ulcerated area with jagged edges at the incision and drainage site (Figure 1). Pyoderma gangrenosum was clinically suspected; a biopsy was performed, and the patient was started on oral prednisone. At 2-week follow-up, the ulcer was found to be rapidly resolving with prednisone and healing with cribriform scarring (Figure 2). Histopathology revealed an undermining neutrophilic inflammatory process that was consistent with PG. A diagnosis of PG was made based on previously published criteria⁷ and the following major/minor criteria in the patient: pathology; absence of infection on histologic analysis; history of pathergy related to worsening ulceration at the site of incision and drainage of the initial boil; clinical findings of an ulcer with peripheral violaceous erythema; undermined borders and tenderness at the site; and rapid resolution of the ulcer with prednisone.

Cessation of adalimumab gradually led to clearance of both psoriasiform lesions and PG; however, HS lesions persisted. At 2-month follow-up, the patient remained clear of new psoriatic and PG lesions. Alternative treatment options for HS, including isotretinoin and other biologic agents, were discussed with the patient. She was subsequently lost to follow-up.

Although the precise pathogenesis of HS is unclear, both genetic abnormalities of the pilosebaceous unit and a dysregulated immune reaction appear to lead to the clinical characteristics of chronic inflammation and scarring seen in HS. A key effector appears to be helper T-cell (T_H17) lymphocyte activation, with increased secretion of $TNF-\alpha$, $IL-1\beta$, and $IL-17$.^{1,2} In turn, $IL-17$ induces higher expression of $TNF-\alpha$, leading to a persistent cycle of inflammation. Peripheral recruitment of $IL-17$ -producing neutrophils also may contribute to chronic inflammation.⁸

Adalimumab is the only US Food and Drug Administration–approved biologic indicated for the

treatment of HS. Our patient initially responded to adalimumab with improvement of HS; however, treatment had to be discontinued because of the unusual occurrence of 2 distinct paradoxical reactions in a short span of time. Psoriasis and PG are both considered true paradoxical reactions because primary occurrences of both diseases usually are responsive to treatment with adalimumab.

Tumor necrosis factor α inhibitor–induced psoriasis arises *de novo* and is estimated to occur in approximately 5% of patients with rheumatoid arthritis.^{3,6} Palmoplantar pustular psoriasiform reactions are the most common form of paradoxical psoriasis. Topical medications can be used to treat skin lesions, but systemic treatment is required in many cases. Switching to an alternate class of a biologic, such as an $IL-17$, $IL-12/23$, or $IL-23$ inhibitor, can improve the skin reaction; however, such treatment is inconsistently successful, and paradoxical drug reactions also have been seen with these other classes of biologics.^{4,9}

Recent studies support distinct immune causes for classical and paradoxical psoriasis. In classical psoriasis, plasmacytoid dendritic cells (pDCs) produce $IFN-\alpha$, which stimulates conventional dendritic cells to produce $TNF-\alpha$. However, $TNF-\alpha$ matures both pDCs and conventional dendritic cells; upon maturation, both types of dendritic cells lose the ability to produce $IFN-\alpha$, thus allowing $TNF-\alpha$ to become dominant.¹⁰ The blockade of $TNF-\alpha$ prevents pDC maturation, leading to uninhibited $IFN-\alpha$, which appears to drive inflammation in paradoxical psoriasis. In classical psoriasis, oligoclonal dermal $CD4^+$ T cells and epidermal $CD8^+$ T cells remain, even in resolved skin lesions, and can cause disease recurrence through reactivation of skin-resident memory T cells.¹¹ No relapse of paradoxical psoriasis occurs with discontinuation of anti- $TNF-\alpha$ therapy, which supports the notion of an absence of memory T cells.



FIGURE 1. Pyoderma gangrenosum on the right posterior leg.



FIGURE 2. Multiple tender nodules of pyoderma gangrenosum on the leg at the site of an ulcer that started healing within 2 weeks of prednisone therapy with cribriform scarring.

The incidence of paradoxical psoriasis in patients receiving a TNF- α inhibitor for HS is unclear.¹² There are case series in which patients who had concurrent psoriasis and HS were successfully treated with a TNF- α inhibitor.¹³ A recently recognized condition—PASH syndrome—encompasses the clinical triad of PG, acne, and HS.¹⁰

Our patient had no history of acne or PG, only a long-standing history of HS. New-onset PG occurred only after a TNF- α inhibitor was initiated. Notably, PASH syndrome has been successfully treated with TNF- α inhibitors, highlighting the shared inflammatory etiology of HS and PG.¹⁴ In patients with concurrent PG and HS, TNF- α inhibitors were more effective for treating PG than for HS.

Pyoderma gangrenosum is an inflammatory disorder that often occurs concomitantly with other conditions, such as inflammatory bowel disease. The exact underlying cause of PG is unclear, but there appears to be both neutrophil and T-cell dysfunction in PG, with excess inflammatory cytokine production (eg, IL-1 β , TNF- α , IL-17).¹⁵

The mainstay of treatment of PG is systemic corticosteroids and immunosuppressives, such as cyclosporine. Tumor necrosis factor α inhibitors as well as other interleukin inhibitors are increasingly utilized as potential therapeutic alternatives for PG.^{16,17}

Unlike paradoxical psoriasis, the underlying cause of paradoxical PG is unclear.^{18,19} A similar mechanism may be postulated whereby inhibition of TNF- α leads to excessive activation of alternative inflammatory pathways that result in paradoxical PG. In one study, the prevalence of PG among 68,232 patients with HS was 0.18% compared with 0.01% among those without HS; therefore, patients with HS appear to be more predisposed to PG.²⁰

This case illustrates the complex, often conflicting effects of cytokine inhibition in the paradoxical elicitation of alternative inflammatory disorders as an unintended consequence of the initial cytokine blockade. It is likely that genetic predisposition allows for paradoxical reactions in some patients when there is predominant inhibition of one cytokine in the inflammatory pathway. In rare cases, multiple paradoxical reactions are possible.

REFERENCES

- Vossen ARJV, van der Zee HH, Prens EP. Hidradenitis suppurativa: a systematic review integrating inflammatory pathways into a cohesive pathogenic model. *Front Immunol*. 2018;9:2965. doi:10.3389/fimmu.2018.02965
- Goldburg SR, Strober BE, Payette MJ. Hidradenitis suppurativa: epidemiology, clinical presentation and pathogenesis. *J Am Acad Dermatol*. 2020; 82:1045-1058. doi:10.1016/j.jaad.2019.08.090
- Brown G, Wang E, Leon A, et al. Tumor necrosis factor- α inhibitor-induced psoriasis: systematic review of clinical features, histopathological findings, and management experience. *J Am Acad Dermatol*. 2017;76:334-341. doi:10.1016/j.jaad.2016.08.012
- Puig L. Paradoxical reactions: anti-tumor necrosis factor alpha agents, ustekinumab, secukinumab, ixekizumab and others. *Curr Prob Dermatol*. 2018;53:49-63. doi:10.1159/000479475
- Faivre C, Villani AP, Aubin F, et al; French Society of Dermatology and Club Rheumatism and Inflammation. Hidradenitis suppurativa (HS): an unrecognized paradoxical effect of biologic agents (BA) used in chronic inflammatory diseases. *J Am Acad Dermatol*. 2016;74:1153-1159. doi:10.1016/j.jaad.2016.01.018
- Ko JM, Gottlieb AB, Kerbleski JF. Induction and exacerbation of psoriasis with TNF-blockade therapy: a review and analysis of 127 cases. *J Dermatolog Treat*. 2009;20:100-108. doi:10.1080/09546630802441234
- Maverakis E, Ma C, Shinkai K, et al. Diagnostic criteria of ulcerative pyoderma gangrenosum: a delphi consensus of international experts. *JAMA Dermatol*. 2018;154:461-466. doi:10.1001/jamadermatol.2017.5980
- Lima AL, Karl I, Giner T, et al. Keratinocytes and neutrophils are important sources of proinflammatory molecules in hidradenitis suppurativa. *Br J Dermatol*. 2016;174:514-521. doi:10.1111/bjd.14214
- Li SJ, Perez-Chada LM, Merola JF. TNF inhibitor-induced psoriasis: proposed algorithm for treatment and management. *J Psoriasis Psoriatic Arthritis*. 2019;4:70-80. doi:10.1177/2475530318810851
- Conrad C, Di Domizio J, Mylonas A, et al. TNF blockade induces a dysregulated type I interferon response without autoimmunity in paradoxical psoriasis. *Nat Commun*. 2018;9:25. doi:10.1038/s41467-017-02466-4
- Matos TR, O'Malley JT, Lowry EL, et al. Clinically resolved psoriatic lesions contain psoriasis-specific IL-17-producing $\alpha\beta$ T cell clones. *J Clin Invest*. 2017;127:4031-4041. doi:10.1172/JCI93396
- Faivre C, Villani AP, Aubin F, et al. Hidradenitis suppurativa (HS): an unrecognized paradoxical effect of biologic agents (BA) used in chronic inflammatory diseases. *J Am Acad Dermatol*. 2016;74:1153-1159. doi:10.1016/j.jaad.2016.01.018
- Marzano AV, Damiani G, Ceccherini I, et al. Autoinflammation in pyoderma gangrenosum and its syndromic form (pyoderma gangrenosum, acne and suppurative hidradenitis). *Br J Dermatol*. 2017;176:1588-1598. doi:10.1111/bjd.15226
- Cugno M, Borghi A, Marzano AV. PAPA, PASH, PAPASH syndromes: pathophysiology, presentation and treatment. *Am J Clin Dermatol*. 2017;18:555-562. doi:10.1007/s40257-017-0265-1
- Wang EA, Steel A, Luxardi G, et al. Classic ulcerative pyoderma gangrenosum is a T cell-mediated disease targeting follicular adnexal structures: a hypothesis based on molecular and clinicopathologic studies. *Front Immunol*. 2018;8:1980. doi:10.3389/fimmu.2017.01980
- Patel F, Fitzmaurice S, Duong C, et al. Effective strategies for the management of pyoderma gangrenosum: a comprehensive review. *Acta Derm Venereol*. 2015;95:525-531. doi:10.2340/00015555-2008
- Partridge ACR, Bai JW, Rosen CF, et al. Effectiveness of systemic treatments for pyoderma gangrenosum: a systematic review of observational studies and clinical trials. *Br J Dermatol*. 2018;179:290-295. doi:10.1111/bjd.16485
- Benzaquen M, Monnier J, Beaussault Y, et al. Pyoderma gangrenosum arising during treatment of psoriasis with adalimumab: effectiveness of ustekinumab. *Australas J Dermatol*. 2017;58:e270-e271. doi:10.1111/ajd.12545
- Fujimoto N, Yamasaki Y, Watanabe RJ. Paradoxical uveitis and pyoderma gangrenosum in a patient with psoriatic arthritis under infliximab treatment. *J Dtsch Dermatol Ges*. 2018;16:1139-1140. doi:10.1111/ddg.13632
- Tannenbaum R, Strunk A, Garg A. Overall and subgroup prevalence of pyoderma gangrenosum among patients with hidradenitis suppurativa: a population-based analysis in the United States. *J Am Acad Dermatol*. 2019;80:1533-1537. doi:10.1016/j.jaad.2019.02.004