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Successful Management of Anti-TNF-Induced Psoriasis Despite Continuation of Therapy in a Pyoderma Gangrenosum Patient

Atrin Toussi BS BA,[a,b] Stephanie T. Le MD,[a] Virgina R. Barton MD,[a] Chelsea Ma MD,[a] Michelle Y. Cheng MD,[a] Andrea Sukhov MD,[c] Reason Wilken MD,[d] Forum Patel MD,[a] Elizabeth Wang MD,[e] Emanual Maverakis MD[a]

[a]University of California, Davis, Department of Dermatology, Sacramento, CA
[b]University of California, Davis, School of Medicine, Sacramento, CA
[c]University of Colorado, Denver, Department of Dermatology, Denver, CO
[d]New York University, Langone Health, Department of Dermatology, New York, NY
[e]Stanford University School of Medicine, Department of Dermatology, Redwood City, CA

ABSTRACT

Pyoderma gangrenosum is an inflammatory, neutrophil-mediated disorder that is difficult to treat. Tumor necrosis factor and other inflammatory mediators are among the most promising therapeutic targets. We present a case of a 60-year-old woman with recalcitrant pyoderma gangrenosum treated with adalimumab, who paradoxically developed psoriasis. Secukinumab, an interleukin-17 inhibitor, was added to her regimen, resulting in successful treatment of her psoriasis. Secukinumab was later replaced by methotrexate, resulting in remission of both pyoderma gangrenosum and maintenance of a psoriasis-free state. We conclude that paradoxically induced psoriatic lesions can resolve with adjunct therapy despite continuation of anti-tumor necrosis factor agents.

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INTRODUCTION

Pyoderma gangrenosum (PG) is a rare, ulcerating, inflammatory skin disease that commonly arises at sites of minor trauma, a phenomenon known as pathergy. Although its etiology is mostly unknown, T cell activation, abnormal neutrophil migration, and tumor necrosis factor (TNF), and interleukin (IL)-17 signaling appear to play major roles in pathogenesis.[1-3]

Despite their therapeutic efficacy in psoriasis, TNF inhibitors, such as adalimumab, have been implicated in paradoxical anti-TNF-induced psoriasis. In these cases, it is commonly thought that the offending TNF inhibitor should be immediately discontinued. However, we demonstrate that anti-TNF agents can be continued for treatment of underlying disease in the setting of paradoxical psoriasis. We also demonstrate the utility of adjunct treatment, specifically secukinumab and methotrexate, in the respective induction and maintenance of remission from anti-TNF-induced psoriasis.

CASE REPORT

A 60-year-old woman with a history of severe, relapsing PG requiring multi-drug therapy presented with an ulcer at the site of a recent skin biopsy (Figure 1a). Her treatment regimen for PG included adalimumab 40 mg twice monthly and a multidrug combination of mycophenolate mofetil and cyclosporine, which she had previously responded well to. Upon presentation, adalimumab was increased to 40 mg weekly alongside adjuvant therapy, which resulted in remission of her PG flare (Figure 1b). She then continued this regimen as maintenance therapy (Figure 2).

FIGURE 1. Pyoderma gangrenosum of the leg. (A) Our patient developed a lower extremity ulcer with undermined borders and peripheral erythema. Granulation tissue and neutrophilic exudates are present at the ulcer base. (B) The ulcer resolved on a regime of adalimumab 40 mg weekly, cyclosporine 100 mg twice daily, and mycophenolate mofetil 500 mg twice daily, leaving an atrophic scar.

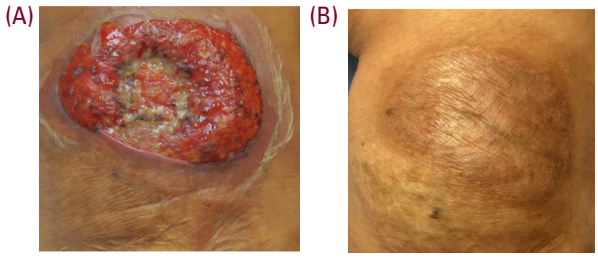
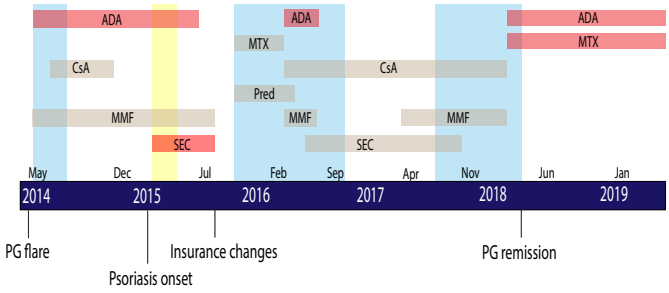
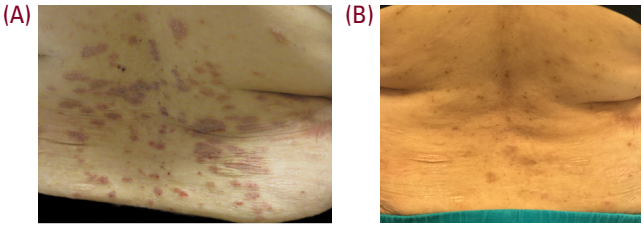


FIGURE 2. Timeline of medication changes from 2014 to 2019, not to scale. Regions in blue denote pyoderma gangrenosum flares. Regions in yellow denote psoriasis flare. Medications of interest are denoted in red. Other than those noted in the text, some medications were either self-discontinued or insurance changes necessitated their discontinuation. Note that cyclosporine and mycophenolate mofetil were titrated down in 2018 until replaced by adalimumab and methotrexate. ADA = adalimumab, CsA = cyclosporine, Pred = prednisone, MMF = mycophenolate mofetil, MTX = Methotrexate, SEC = secukinumab.



Nine months after starting her modified regimen, she returned to clinic with several new, well-demarcated, erythematous post-auricular plaques. She was treated with topical corticosteroids for presumed seborrheic dermatitis. Over the course of two months, the lesions expanded to include well-demarcated, erythematous scaling plaques on her arms, trunk, scalp, and lower extremities (Figure 3a). Evaluation for fungal etiologies with KOH staining was negative. A diagnosis of adalimumab-induced psoriasis was favored, and she was started on secukinumab.

FIGURE 3. Adalimumab-induced psoriasis. (A) Nine months after increasing adalimumab, our patient developed well-demarcated, erythematous plaques distributed to the arms, trunk, and lower extremities. The background was digitally darkened, but the cutaneous lesions were not altered. (B) Within one month of initiating secukinumab, there was complete resolution of the psoriasiform lesions.



Within weeks of starting secukinumab, her psoriasis resolved despite remaining on adalimumab concurrently (Figure 3b). At this point, she had complications with insurance coverage and underwent numerous lapses in follow up visits, necessitating multiple medication changes (Figure 2). She later transitioned to secukinumab-only therapy but when her PG symptoms returned, secukinumab was discontinued and she was treated instead with a multidrug regimen of prednisone, cyclosporine, and mycophenolate mofetil.

When adalimumab (40 mg weekly) was approved by her insurance, it was restarted with the addition of methotrexate prophylactically to prevent another episode of adalimumab-induced psoriasis. With this combination, her PG symptoms went into remission without evidence of psoriasiform lesions for greater than one year to date (Figure 2).

DISCUSSION

Treatment of Pyoderma Gangrenosum

PG is a complex and multifactorial neutrophilic dermatosis requiring multi-drug therapy.[4,5] It is estimated to occur in approximately 3 to 10 people per million per year.[6] Although this disease is traditionally difficult to diagnose,[7] recent diagnostic guidelines have been proposed.[8,9] Currently, there are two randomized controlled trials (RCTs), multiple cohort studies , and limited open-label and case-control studies detailing treatment.[10,11] In these, systemic steroids are most often used, followed by cyclosporine and biologics, with equivalent efficacy noted between prednisolone and cyclosporine.[10]

Infliximab, a TNF antagonist, is typically used in refractory cases of PG.[10] Additional studies have documented PG remission with similar biologics, including adalimumab, etanercept, anakinra, and ustekinumab, but responses are often partial.[12,13] In addition to partial response, TNF inhibitors can have unanticipated side effects, including paradoxical psoriasis. In fact, psoriasis is the third leading skin complication of anti-TNF therapy, behind xerosis and atopic dermatitis.[14] And while there are over one hundred reported cases of TNF inhibitor-induced psoriasis,[15] ours is the first to demonstrate this phenomenon in a PG patient.

Treatment of TNF-Inhibitor Induced Psoriasis

When TNF-inhibitor paradoxical reactions occur, the first step in management is commonly thought to be discontinuation of the offending agent. However, current literature provides conflicting data on this point. A recent review of anti-TNF-induced psoriasis recommends switching to a different agent or class of medications only in the setting of uncontrolled underlying disease.[16] Another review of 222 cases of paradoxical psoriasis found that nearly 40% of patients continue therapy with either the same or a different TNF inhibitor and 74% of these patients achieve complete remission of their paradoxical psoriasis.[17] As a result, in at least some cases of paradoxical psoriasis with controlled underlying disease, patients can seemingly tolerate the causative TNF inhibitor. Our case demonstrates that paradoxical psoriatic lesions can resolve in patients who continue the offending anti-TNF agent with the addition of a second immunosuppressive therapy, even in the setting of uncontrolled underlying disease.

Here we illustrated the efficacy of secukinumab and, subsequently, methotrexate as adjunct agents in treating TNF-inhibitor-induced psoriasis. These treatments have yet to be

established for the induction and maintenance of remission from paradoxical psoriasis in the setting of uncontrolled underlying disease while maintaining anti-TNF therapy.[18,19]

Secukinumab has been used to treat recalcitrant anti-TNF induced psoriasis, but is not typically a first-line agent.[16] As an IL-17 inhibitor, it is suited to treat both psoriasis and anti-TNF-induced psoriasis, which evidently must also be mediated by IL-17 producing Th17 cells.[20] In addition to secukinumab's efficacy in psoriasis, its mechanism of action is also implicated in PG treatment, as IL-17 mediates neutrophil migration and homeostasis.[21,22] Additionally, IL-17 and its receptor are overexpressed in PG lesions and a greater ratio of IL-17-producing Th17 cells is seen in PG patients.[23] For these reasons, IL-17 targeted therapy in PG has already been suggested.[24,25]

In our case, secukinumab was initiated for anti-TNF-induced psoriasis with the hope of also controlling the patient's PG. In the end, while secukinumab induced remission of psoriasis, it only temporarily alleviated PG symptoms. One possible reason for this failure is that PG pathophysiology does not solely rely on IL-17 signaling and other inflammatory pathways are likely involved. Towards this end, new investigations of PG-associated conditions suggest it to be a disease of the innate immune system in which inflammasomes activate IL-8.[1] As a result, IL-17 therapy may not be sufficient for all cases of PG.

Lastly, we examine methotrexate, a folate antimetabolite and dihydrofolate reductase inhibitor. It is a commonly cited systemic agent used to induce remission of mild to severe psoriasis as well as in anti-TNF-induced psoriasis.[16,26] Our case demonstrates that as an adjunctive medication, methotrexate can effectively prevent the development of anti-TNF-induced psoriasis in a patient with a history of this paradoxical reaction.

CONCLUSION

Anti-TNF-induced psoriasiform lesions fully remit with adjunct secukinumab therapy despite continuation of anti-TNF therapy. These lesions stay in remission with adjunct methotrexate therapy.

DISCLOSURES

All authors have no relevant conflicts of interest to disclose.

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AUTHOR CORRESPONDENCE

Emanual Maverakis MD
E-mail:..... emaverakis@ucdavis.edu