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CASE REPORT

Apremilast Coadministered with Secukinumab for Effective Treatment of Acrodermatitis Continua of Hallopeau: A Case Report

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Background: Acrodermatitis continua of Hallopeau (ACH) is a chronic, relapsing variant of pustular psoriasis proven to be remarkably challenging to treat. There are cases in the literature describing successful treatment with biologic therapy for plaque psoriasis. However, there is less evidence on long-term management of the disease. Evidence from previous case reports suggests that for patients with plaque psoriasis who have failed monotherapy with biologics, the combination of biologics and small molecule drugs can be considered as a treatment option. For patients with ACH, there is currently a gap in research in this area. Further information is needed to help dermatologists formulate treatment plans for patients presenting with such diseases.

Case Summary: We report the case of a 44-year-old man with an 8-year history of acrodermatitis continua of ACH. The patient started treatment with secukinumab (300 mg, once every 4 weeks) four years ago. This dramatically improved disease symptoms, with clearance of pustules and absence of pain. Unfortunately, the rash recurred after 2 years of treatment. The patient was transitioned to secukinumab (300 mg, once every 4 weeks) and apremilast (30 mg, twice daily), well-controlled ACH lesions. After 5 months, secukinumab was tapered to 300 mg every 8 weeks. During the 2 years of treatment, laboratory workup was within normal limits.

Conclusion: This case underscores that the combination therapy of secukinumab and apremilast can offer a promising approach for the long-term management of ACH.

Keywords: apremilast, combination, phosphodiesterase inhibitor, secukinumab, acrodermatitis continua of hallopeau

Introduction

Acrodermatitis Continua of Hallopeau (ACH) is a rare chronic, relapsing variant of pustular psoriasis that is remarkably challenging to treat. It has been sparingly reported from across the globe. ACH impacts patients' quality of life, resulting in a physical and psychological burden. Common therapies for ACH include topical and oral treatments. Topical application of potent glucocorticoids and vitamin D3 derivatives controls inflammation, while stubborn cases require systemic use of acitretin and methotrexate. With the arrival of the biologics revolution, we have made great progress in treating refractory moderate-to-severe plaque psoriasis. Targeting the IL-17/IL-23 pathway, biologics widely used for plaque psoriasis (such as secukinumab and guselkumab) have also shown significant benefits for patients with ACH. However, for all diseases, the high clearance rate brought by biologic therapy is accompanied by the long-term use of the same biologics, often resulting in a decline in efficacy.

We report one case of ACH. Although secukinumab is effective as a treatment option within the first 2 years, the patient experienced a gradual decrease in response, repeated rashes, and produced secondary treatment failure with biologics over time. It made the management challenging. We added apremilast to his treatment regimen. Near-complete responses were rapidly achieved and maintained over 2 years of combination therapy, and the dose of secukinumab was halved.

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Case History

The patient is a 44-year-old male with a history of ACH for 8 years. Before this, he had been treated with topical medications primarily consisting of glucocorticoids, but due to difficulty in controlling the skin lesions and significant pain, he began treatment with secukinumab at a local hospital. At the time of this visit, the patient had been receiving secukinumab (300 mg, once every 4 weeks) for 2 years and noted that the disease had been stably relapsing for nearly 3 months.

Physical examination revealed Erythema at the fingertips, with dark red discoloration, accompanied by mild swelling, hyperkeratosis, and desquamation. The left index finger manifested periungual erythema and edema with multiple variably sized sterile pustules. The affected nail plate displayed onychodystrophy characterized by subungual hyperkeratosis and partial onycholysis. Histopathological evaluation of a representative pustular lesion in the left finger (Figure 1) revealed hyperkeratosis of the epidermis with parakeratosis, with psoriasiform hyperplasia, and neutrophils accumulate in the epidermis forming a pustule. Kogoj microabscess is seen above the spinous layer. Based on these findings, he was diagnosed with ACH.

After further communication with the patient, we learned that the patient had no other medical problems. Following the evaluation of laboratory test results, apremilast (30 mg orally twice a day) was added to the patient's current standard therapeutic dose regimen of secukinumab. After 3 months of combination therapy, the patient's skin lesions were significantly controlled. We attempted to discontinue secukinumab after its levels stabilized and switched the patient to treatment with only apremilast. However, using secukinumab alone resulted in the reappearance of skin lesions, as did using apremilast tablets alone. Fortunately, starting from the 5th month of combination therapy and continuing for the past 2 years, the addition of apremilast allowed for a reduction of secukinumab dosage by half, maintaining the disease state (300 mg, every 8 weeks) (Figure 2). The patient did not report any side effects, including common gastrointestinal adverse effects. Laboratory workup was within normal limits.

Discussion

ACH is a rare subtype of pustular psoriasis that presents as a sterile, pustular eruption in the fingertips and toes. ACH usually leads to abnormal changes in the nails and functional impairment. The disease is more common in adult women but can affect men and women of all ages.[1] The clinical course of ACH was chronic and recalcitrant.[2] Recurrence is common with dose reduction or cessation of treatment. Due to the rare nature of ACH, the limited reports are mainly case reports or case series, which leads to no standardized guidelines.

Biological therapies revolutionized the treatment of many chronic inflammatory skin diseases represented by psoriasis. Biological drugs allow, through the blockade of specific cytokines, to selectively stop the process of

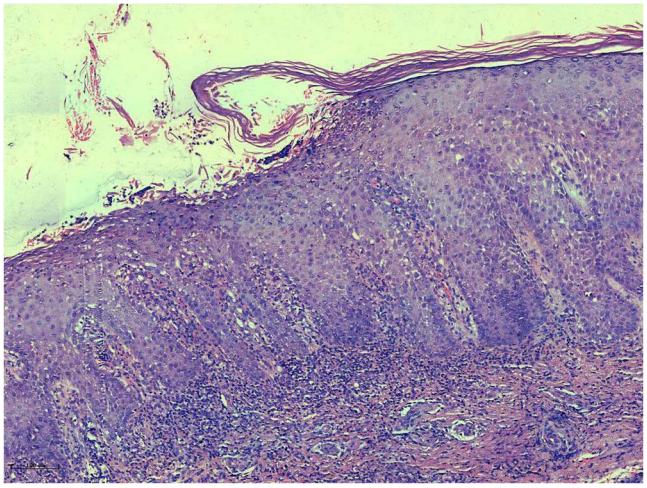

Figure 1 Hyperkeratosis of the epidermis with parakeratosis, and neutrophils accumulate in the epidermis forming a pustule. Kogoj microabscess is seen above the spinous layer. (HE ×100).

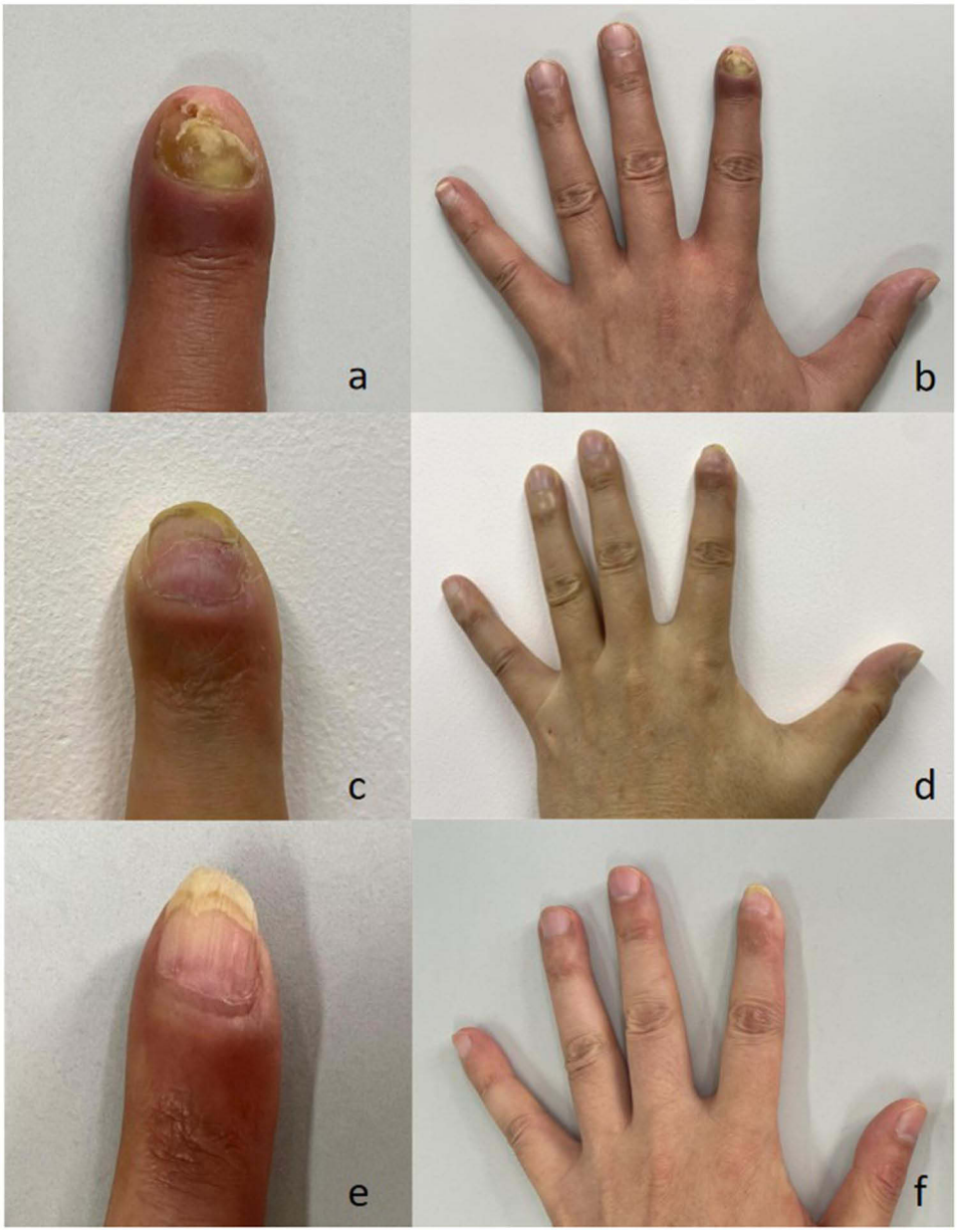

Figure 2 Obvious turbidity and thickening of the nail, with several pustules underneath the nail. (**a** and **b**) The normal nail had grown from the left side of the nail at week 24. (**c** and **d**) Complete clearance of pustules and erythema was achieved at week 48. The form of the nascent deck was normal (**e** and **f**).

inflammation and reduce skin lesions. It demonstrated a strong clinical response rate and usually higher safety and tolerability than traditional systemic oral drugs. Reports indicate that most of the biological therapies available for treating plaque psoriasis or pustular psoriasis (including TNF-α\IL-17A\IL-23\IL-36 inhibitors) have shown a response in the management of ACH as well.[3–7] This patient was no exception.

However, the pathogenesis of chronic immune-mediated inflammatory diseases depends on the role of multiple inflammatory pathways.[8] Some patients with long-term use of biologics may remain resistant to systemic monotherapy and gradually lose its effectiveness. Biologic monotherapy is insufficient to obtain or maintain global disease control. This leads to therapeutic failure. At such time, while increasing dosage is an option, this may raise the risk of side effects. On the other hand, switching to another biological drug is known to be associated with less efficacy and drug survival impairment.[9] Combination therapy incorporating biologics alongside other agents can be considered a treatment option for patients whose disease is refractory to treatment.[10]

Much less evidence exists on the combination of two biological drugs or biological drugs in combination with small molecules. Evidence from case series and case reports suggests IL-17i combination therapy with apremilast is a desirable treatment option for patients with plaque psoriasis and/or PsA who lose the efficacy of monotherapies.[11–14] Limited information indicates that the addition of apremilast to the methotrexate treatment regimen for palmoplantar psoriasis is also effective and safe, significantly improving the quality of life index for patients.[15] Apremilast addition to the treatment regimen can make sustained control of skin lesions and improve the clinical response rate of patients. Moreover, combining apremilast with biologics can prolong the dosing interval of biologics, reduce the dose, minimizing costs and side effects.[16] This leaves apremilast with the potential to be a cost-effective, add-on treatment in psoriasis.[13]

Apremilast is an oral phosphodiesterase 4 (PDE4) inhibitor that was the first small-molecule drug in almost 20 years to be approved by the US Food and Drug Administration (FDA). Apremilast can down-regulate the production of many proinflammatory cytokines. It has broader anti-inflammatory properties than biologic agents.[17] Its simplicity as an oral medication, along with a good safety profile, makes it a compelling choice for managing psoriasis.[18] The success of the combination therapy of Apremilast and biological agents may be related to the different mechanisms of action of the two types of drugs, which can control inflammation through multiple pathways, shorten the time for lesion clearance, and improve the quality of life for patients.[19] Meanwhile, no differences in Adverse events (AEs) were observed in studies comparing apremilast mono- and combination therapy.[12,20] Side effects of combination therapy are mostly mild and affect the gastrointestinal system.

Based on available data, the combination therapy of apremilast and biologics may be a safe, effective method to achieve disease control for patients with a disease that remains recalcitrant to biologic monotherapy. After in-depth communication with the patient, the patient agreed to choose the combination regimen of apremilast in addition to secukinumab. To our delight, the patient's condition has improved markedly. Not only was the efficacy saved, but the dose of secukinumab and the entire cost of treatment were reduced. In conclusion, the results of our patient indicate that same as in patients with plaque psoriasis, combined therapy with apremilast may be more beneficial in patients of ACH that those who had diminished response over time to biologic therapy. This type of program can use synergism between different mechanisms to maximize efficacy as much as possible.[21] Additional research is required to assess the long-term safety, efficacy, and cost-effectiveness of this approach.

Ethics Statement

The patient had given written informed consent for the publication of her clinical details and accompanying images. All personally identifiable information has been removed or altered to protect the patient's privacy and ensure confidentiality. Institutional approval was not required to publish the case details.

Consent Statement

Informed consent was provided by the patient for publication of the case.

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Disclosure

The authors declare no potential conflicts of interest in this work.

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