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CASE REPORT

A Patient with Adalimumab-Induced Refractory Paradoxical Palmoplantar Pustulosis Was Successfully Treated by Ixekizumab: A Case Report

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Abstract: Ankylosing spondylitis (AS) is a chronic immune-mediated inflammatory disorder involving the sacroiliac (SI) joints, the spine and often the hips. Biologic therapy has been shown to be efficacious in patients with AS and could improve patients' quality of life. With the increased use of tumor necrosis factor-α (TNF-α) inhibitors, more paradoxical reactions have been revealed. However, the treatment option for patients with AS is still a challenge when refractory paradoxical palmoplantar pustulosis appeared after the use of TNF-α inhibitors. We reported the case of a 45-year-old male patient with AS treated with adalimumab treatment who developed a refractory paradoxical palmoplantar pustulosis after failure of prior secukinumab treatment. A dramatic improvement was seen in all skin and low back pain after the use of ixekizumab. We conclude that, in TNF-α inhibitors induced refractory paradoxical palmoplantar pustulosis, ixekizumab should be considered as an alternative option to choose from.

Keywords: ankylosing spondylitis, refractory, paradoxical palmoplantar pustulosis, ixekizumab, biological agent

Introduction

Ankylosing spondylitis (AS) is a chronic progressive auto-inflammatory disease predominantly affecting the spine and the sacroiliac joints, presenting with chronic back pain.[1] The introduction of targeted therapy with tumor necrosis factor-α (TNF-α) inhibitors has largely revolutionized the treatment of AS.[2] However, in parallel to the increasing use of TNF-α inhibitor, the number of unacceptable side effects is increasing as well.[3]

TNF-α inhibitors, such as adalimumab, have been successfully utilized in the treatment of different immune-mediated inflammatory diseases, including psoriasis, psoriatic arthritis (PsA), rheumatoid arthritis and inflammatory bowel disease (IBD).[4–6] One of the side effects of anti-TNF-α therapy is several "paradoxical" adverse events. Paradoxical palmoplantar pustulosis has been reported following the administration of therapeutic TNF-α inhibition, which is characterized by an eruption of sterile pustules on the palms and soles. In the current case presentation, we reported a case of the successful use of ixekizumab for adalimumab-induced refractory paradoxical palmoplantar pustulosis in a patient with AS.

Case Report

A man aged 45 was diagnosed with ankylosing spondylitis for 2 years. No history of psoriasis before he received anti-TNF had been reported. After half year of adalimumab treatment, a painful eruption of pustules on both palms and soles developed (Figure 1A) along with scaly plaques on his scalp and left lower limb (Palmoplantar Pustulosis Area Severity Index, PPPASI: 26). The clinical features confirmed the diagnosis of paradoxical palmoplantar pustulosis, but with conventional therapy, the degree of pain relief and the skin condition of the patient showed no improvement. Adalimumab was stopped, and secukinumab with 150 mg was administered to control both ankylosing spondylitis and paradoxical psoriasis as a maintenance dose at 0, 2 and 4 weeks. However, after 3 months of secukinumab treatment with

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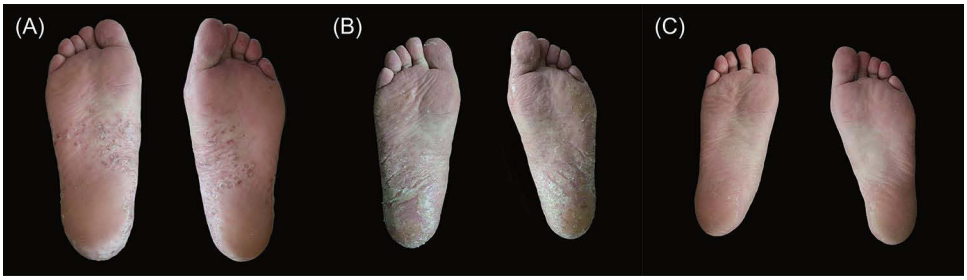

Figure 1 Paradoxical palmoplantar pustulosis lesions on patient's soles (**A**), after 3 months treatment with secukinumab (**B**) and 10 months treatment with ixekizumab (**C**).

a dosage of 300mg per injection, his lesions were not improved (Figure 1B) (PPPASI: 36). Therefore, he received an injection of ixekizumab at a dose of 160 mg. Thereafter, 80 mg ixekizumab was injected every 2 weeks. After 3 months, the lesions of pustules on his palms and soles were improved (PPPASI: 10). After 10 months follow-up, his paradoxical psoriasis went into complete remission (Figure 1C).

Discussion

AS is a chronic inflammatory disease involving primarily the axial skeleton and is characterized by new bone formation, leading to progressive ankylosis of the spine and sacroiliac joints. Recently, TNF-α inhibitors have been shown to be effective in the treatment of AS. However, a number of undesirable side effects can be observed after starting treatment with TNF-α inhibitors. A previous review reported that TNF-α inhibitors treatment for patients with AS leads to paradoxical reactions in 19 per 1000 patient years, compared with conventional treatment.[7]

TNF-α inhibitor-induced psoriasis is not uncommon. TNF-α inhibitors can also induce new psoriasis-like skin lesions in about 2–5% of treated patients.[8] These skin manifestations are called "paradoxical psoriasis", as TNF blockade is usually highly efficacious in psoriasis treatment. These cutaneous adverse events can manifest in several forms including paradoxical palmoplantar pustulosis, plaque psoriasis, psoriasiform, guttate, and inverse psoriasis.

The pathogenesis of paradoxical psoriasiform skin lesions seems to be related to the balance between the levels of TNF-α and interferon (IFN). Increased IFN-α production by plasmacytoid dendritic cells, which is secondary to TNF-α antagonism, stimulates the activation of T cells and an increase in TNF-α production.[9] Another hypothesis is that T helper 17 (Th17) cell enhancement and regulatory T cells (Treg) downregulation after blockade of TNF-α can lead to increased production of IL-17.[10] Ixekizumab, a high affinity monoclonal antibody that selectively targets IL-17A, is highly efficacious and safe for the treatment of AS. Although a few cases reported that paradoxical palmoplantar pustular is induced by ixekizumab,[11] they still show a significant and continuous efficacy in the treatment of patients with AS when TNF-α inhibitors is contraindicated. Our patient showed no improvement from conventional therapy and secukinumab. However, a fast response to treatment was observed when ixekizumab was started, which suggested that ixekizumab could be a great treatment alternative for paradoxical palmoplantar pustulosis induced by TNF-α inhibitors for patients with AS. Intriguingly, the efficacy of two IL-17 antibodies, ixekizumab and secukinumab, is completely different. This result may be related to the different affinity of the two anti-IL17 drugs. The in vitro affinity of ixekizumab is about 50–100 times higher than secukinumab.[12] However, it should be noted that the main limitation of this article is its nature as a case report. Prospective clinical trials for patients with refractory paradoxical palmoplantar pustulosis that consider the onset of action and efficacy of ixekizumab are therefore warranted in the future.

Conclusion

To conclude, paradoxical palmoplantar pustulosis is commonly induced by TNF-α inhibitors among patients with AS. While conventional therapy and other biological medications were ineffective, ixekizumab may be an alternative option for patients with AS.

Ethics Approval and Informed Consent

A written informed consent was obtained from the patient to publish the case details and the images. Institutional approval is not required to publish the case details.

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Disclosure

The authors declare no conflicts of interest in this work.

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