Case Report

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Successful treatment of synovitis, acne, pustulosis, hyperostosis, and osteitis and paradoxical skin lesions by *Tripterygium wilfordii* hook f: a case report

Xinlu Zhang[1,2,*], Xia Wu[3,*] and Chen Li[4]

Abstract

Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome is a rare autoinflammatory disorder without standardized therapy. Anti-tumor necrosis factor (TNF)-α agents, which have been widely used in recent treatment of SAPHO syndrome, may elicit severe paradoxical psoriasiform lesions. Therefore, physicians must reverse the paradoxical skin lesions in affected patients, while improving their clinical symptoms of SAPHO syndrome. Herein, we describe a patient with SAPHO who exhibited TNF-α antagonist-induced paradoxical skin lesions and benefitted from treatment with *Tripterygium wilfordii* hook f (TwHF). A 58-year-old woman with SAPHO developed paradoxical psoriasiform lesions and exacerbation of primary palmoplantar pustulosis after 7 weeks of etanercept treatment. She then received TwHF treatment, which resulted in rapid and remarkable improvement in her skin lesions and osteoarticular pain. These findings suggest that TwHF might be a suitable treatment option for patients with SAPHO who exhibit TNF-α antagonist-induced paradoxical skin lesions.

[1]School of Clinical Medicine, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
[2]Institute of Clinical Medicine, Peking Union Medical College Hospital, Beijing, China
[3]Department of Hematology, Peking Union Medical College Hospital, Beijing, China
[4]Department of Traditional Chinese Medicine, Peking Union Medical College Hospital, Beijing, China

*These authors contributed equally to this work.

Corresponding author:
Chen Li, Department of Traditional Chinese Medicine, Peking Union Medical College Hospital, Dongcheng-qu, Beijing 100730, China.
Email: casio1981@163.com

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Introduction

Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome is a rare autoinflammatory disorder with unknown pathogenesis, for which no standardized therapy is widely accepted.[1] In recent decades, tumor necrosis factor (TNF)-α antagonists have been extensively used for treatment of patients with SAPHO syndrome; they have shown promising results in terms of relieving osteoarticular pain and cutaneous lesions.[2] However, as we previously reported, patients with SAPHO may develop severe psoriasiform lesions as a paradoxical side effect of treatment with TNF-α antagonists, including etanercept and infliximab.[3] These adverse events generally lead to the suspension of TNF-α antagonist therapy, which requires physicians to select new therapeutic regimens for SAPHO syndrome while controlling the paradoxical cutaneous lesions in affected patients.

Tripterygium wilfordii hook f (TwHF) is a Chinese herb with immunosuppressive effects that has been used in treatment of ankylosing spondylitis, rheumatoid arthritis, and several other chronic inflammatory diseases.[4–6] Our group was the first to report the application of TwHF in treatment of SAPHO syndrome.[7] Herein, we describe a patient with both TNF-α antagonist-induced paradoxical skin lesions and primary SAPHO syndrome, for whom TwHF treatment led to rapid and durable remission.

Case report

Ethical approval and patient consent

This case report was reviewed and approved by the institutional ethics committee of Peking Union Medical College Hospital, and informed consent for publication was obtained from the patient.

Patient history

A 58-year-old woman with postmenopausal status presented to her local hospital with pain at the left shoulder and back, along with pustular lesions on her scalp, trunk, palms, and foot soles. The symptoms were partially relieved with the empirical administration of nonsteroidal anti-inflammatory drugs. Three months later, the patient's osteoarticular pain recurred, accompanied by new-onset pain in the anterior chest wall; her skin lesions also worsened. Her overall pain intensity score was 9 points, according to Visual Analog Scale (VAS) assessment. Laboratory tests revealed that her erythrocyte sedimentation rate (ESR) was 70 mm/hour (reference range, 0–20 mm/h) and her hypersensitivity C-reactive protein (hsCRP) level was 24.35 mg/L (reference range, 0–3.00 mg/L). Skin biopsy findings for the patient's right palm suggested palmoplantar pustulosis.

Because the patient was suspected to have SAPHO syndrome, the local hospital administered etanercept at 25 mg/week for 4 weeks; her VAS score of osteoarticular pain improved to 5 points.

However, primary pustular lesions on her scalp, trunk, palms, and foot soles were exacerbated; and new-onset psoriasiform skin lesions also appeared on the extensor surfaces of her upper and lower limbs, palms, and foot soles. Another 3-week course of etanercept reduced her pain VAS score to 3 points, while the paradoxical skin lesions worsened. Notably, the patient had no family history of similar symptoms. Consequently, she discontinued etanercept treatment and presented to our hospital for treatment.

Clinical, laboratory, and imaging findings

On admission to our hospital, the patient exhibited patchy erythematous macules containing dense tiny superficial pustules and covered with silver scales; these were present on the scalp, trunk, and extensor surfaces of upper and lower limbs, palms, and foot soles (Figure 1b, 1e, 1h, 1k). Other physical examination findings were unremarkable. Blood analysis showed that complete blood count and liver and renal function test results were within normal ranges. The patient exhibited elevated ESR (67 mm/hour), hsCRP level (11.11 mg/dL), and TNF-α level (87.0 pg/mL; reference range, <8.1 pg/mL); these baseline values are shown in Figure 2. The patient's results for antinuclear antibody, rheumatoid factor, and human leukocyte antigen-B27 tests were all negative. Histological findings of skin biopsy lesions in the right palm included parakeratosis and hyperkeratosis, thickened spinous cell layer, irregular elongation of rete ridges, Kogoj's microabscesses, and slight perivascular lymphocyte infiltration, which supported a pathological diagnosis of palmoplantar pustulosis (Figure 1a). ^{99m}Tc-methylenediphosphonate whole-body bone scintigraphy findings indicated enhanced radionuclide uptake in bilateral sternoclavicular joints, sternum, left first anterior rib, multiple vertebrae, and bilateral knees and feet; a typical "bull's head" sign was evident in the anterior chest wall (Figure 3).

Diagnosis, treatment, and outcomes

Considering the patient's osteoarticular pain, characteristic bone scintigraphy findings, and palmoplantar pustulosis, she was diagnosed with SAPHO syndrome in accordance with criteria proposed by Benhamou et al.[8] As treatment, TwHF was cautiously administered with a priming dose of 60 mg per day for 3 months, 50 mg per day for the fourth month, 40 mg for the fifth month, and 30 mg for an additional 5 months. One month after the initiation of TwHF, the patient's clinical symptoms showed considerable improvement: her pain VAS score decreased to 1 point; pustules and silver scales disappeared from extensor surfaces of upper limbs, extensor surfaces of lower limbs, palms, and left foot sole (only patchy erythematous macules remained; Figure 1c, 1f, 1i, 1l); ESR and hsCRP level declined to 34 mm/hour and 0.83 mg/dL, respectively (Figure 2a); and serum TNF-α level decreased to 14.9 pg/mL (Figure 2b). After 4 months of TwHF treatment, all skin lesions had disappeared entirely (Figure 1d, 1g, 1j, 1m); osteoarticular pain had decreased to VAS score of 0 points. After 10 months of TwHF treatment, the patient did not exhibit recurrence of skin manifestations or osteoarticular pain; ESR and hsCRP level remained at 37 mm/hour and 2.44 mg/dL, respectively (Figure 2a). The patient maintained strict medication compliance; she reported no adverse events (e.g., gastrointestinal discomfort). No abnormalities were observed in her blood routine test results or blood biochemical examinations of liver and kidney function during the follow-up period. A timeline depicting changes in the patient's clinical symptoms and treatments is shown in Figure 4.

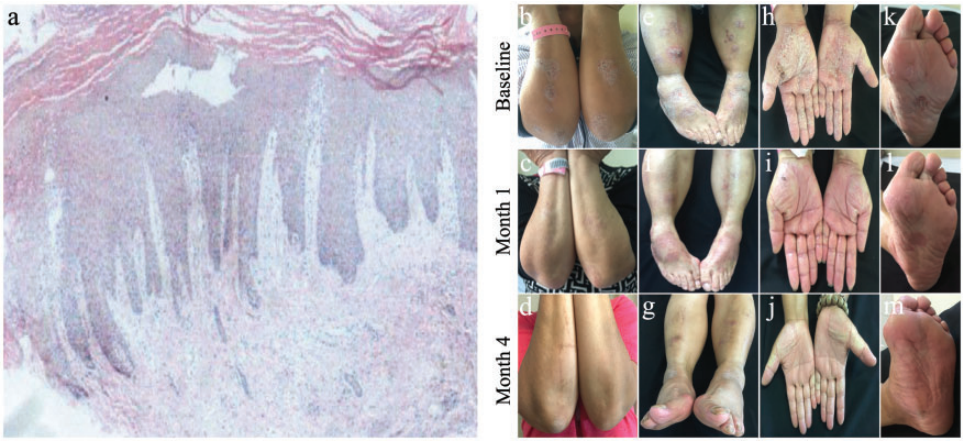

Figure 1. Skin biopsy on admission and changes in etanercept-induced paradoxical skin lesions following administration of TwHF. a: skin biopsy of lesions on the right palm on admission revealed parakeratosis and hyperkeratosis, thickened spinous cell layer, irregular elongation of rete ridges, Kogoj's microabscesses, and slight perivascular lymphocyte infiltration. b–d: bilateral extensor surfaces of upper limbs; e–g: bilateral extensor surfaces of lower limbs; h–j: palms; k–m: left foot sole. b, e, h, k: paradoxical skin lesions upon admission to our hospital (baseline); c, f, i, l: improvement of the skin lesions after TwHF treatment for 1 month; d, g, j, m: improvement of the skin lesions after TwHF treatment for 4 months.
Abbreviation: TwHF, *Tripterygium wilfordii* hook F.

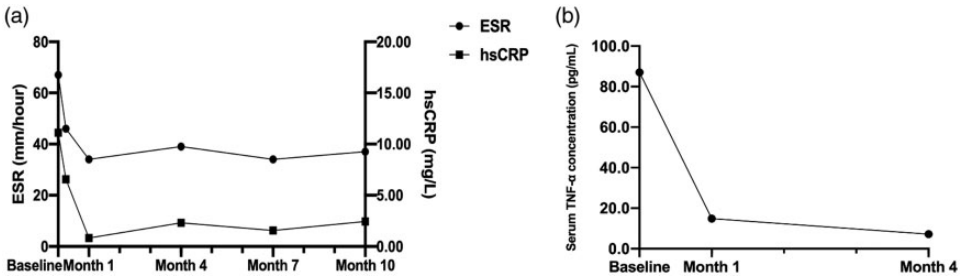

Figure 2. Reductions of ESR and hsCRP (a) and serum TNF-α levels (b) after administration of TwHF. Baseline data were collected upon admission to our hospital.
Abbreviations: hsCRP, high-sensitivity C-reactive protein; ESR, erythrocyte sedimentation rate; TNF, tumor necrosis factor; TwHF, *Tripterygium wilfordii* hook F.

Discussion

In this report, we have described a patient who developed paradoxical skin lesions after 7 weeks of etanercept treatment, which manifested as new-onset psoriasiform lesions and exacerbations of primary cutaneous lesions. A diagnosis of SAPHO syndrome was established based on the patient's osteoarticular pain, characteristic bone scintigraphy findings, and palmoplantar pustulosis. TwHF monotherapy was then administered, which reversed paradoxical skin lesions rapidly during early treatment; it also improved the patient's clinical symptoms of SAPHO syndrome.

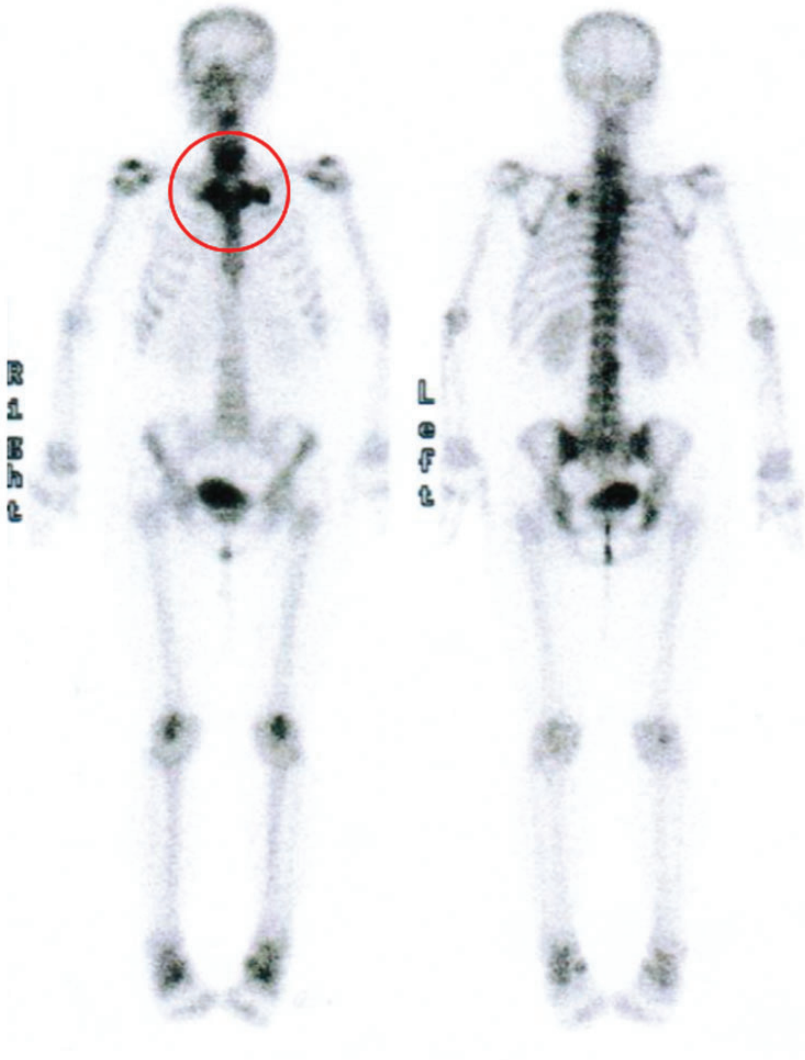

Figure 3. Typical "bull's head" sign (red circle) detected in the anterior chest wall upon ^{99m}Tc-methylenediphosphonate whole-body bone scintigraphy examination.

TNF-α antagonists are commonly used for various types of inflammatory disorders with largely good tolerance; however, dermatologic complications such as new-onset psoriasiform lesions and worsening of primary skin diseases have been reported.[9,10] Recently, TNF-α antagonists have been used for treatment of SAPHO in patients with disease that is unresponsive or refractory to conventional drugs.[11] Similar side effects of TNF-α antagonist therapy were observed in a cohort of 164 patients with SAPHO; among these patients, seven of 41 (17.1%) who had been treated with etanercept or infliximab eventually developed psoriasiform lesions.[3] The pathophysiology underlying the paradoxical skin lesions remains poorly understood,

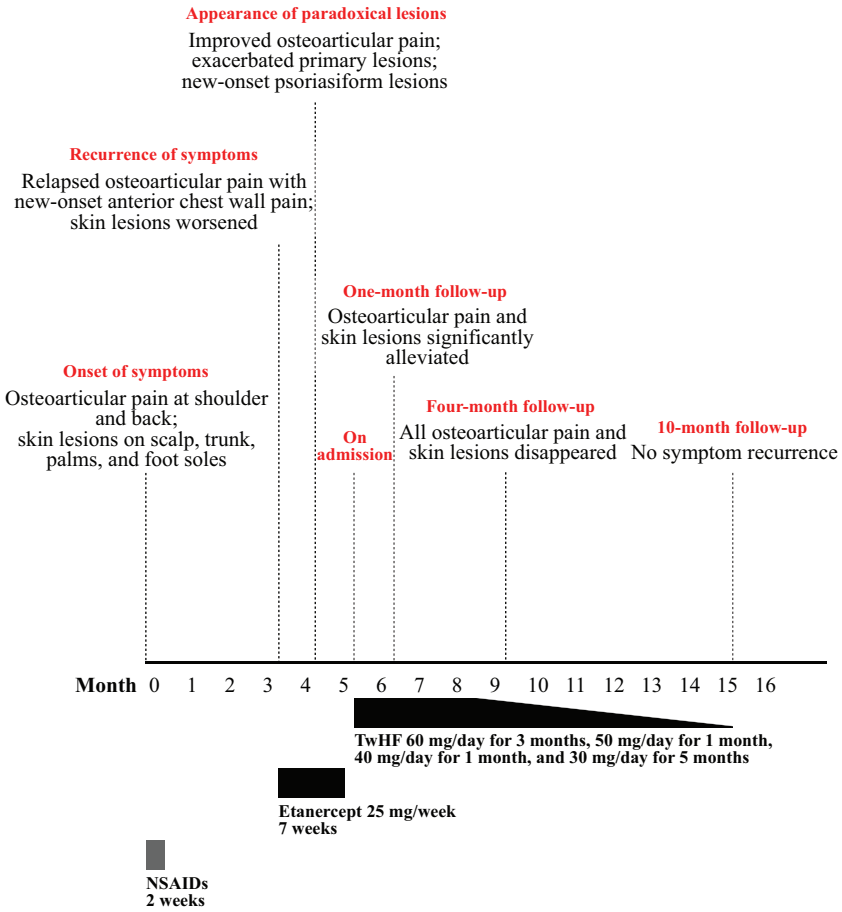

Figure 4. Timeline of changes in clinical symptoms (SAPHO and paradoxical skin lesions) and treatments (NSAIDs, etanercept, and TwHF).
Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; SAPHO, synovitis, acne, pustulosis, hyperostosis, and osteitis; TwHF, *Tripterygium wilfordii* hook F.

although several hypothetical mechanisms have been postulated. First, previous studies demonstrated strong interferon (IFN)-γ activation within TNF-α antagonist-induced lesions. High levels of IFN-γ are mainly produced by T helper (Th) 1 lymphocytes, in response to the abundant production of IFN-α by plasmacytoid dendritic cells activated by TNF blockade.[12,13] Furthermore, other cytokines have been identified as potential triggers in the pathogenesis of paradoxical skin lesions; these cytokines include interleukin (IL)-17A and IL-22 released from Th17 cells.[10,13]

A recent literature review[14] revealed that there are currently no guidelines for the treatment of paradoxical cutaneous lesions induced by TNF-α antagonists. Therefore, various therapeutic approaches have been used to treat patients with paradoxical skin lesions. A treatment algorithm has been proposed by Collamer and Battafarano.[10] For patients with paradoxical cutaneous lesions occupying less than

5% of the body surface, topical treatments (e.g., corticosteroids, keratolytics, and vitamin D analogs) are recommended. For patients with skin lesions occupying more than 5% of the body surface, or patients with pustular psoriasis, recommended therapy comprises topical treatments, ultraviolet light therapy, and systemic treatments (e.g., methotrexate, retinoids, and cyclosporine). If patients do not respond well to these therapies, discontinuation of TNF-α antagonist treatment or use of an alternative TNF-α antagonist should be considered. However, there have been few published reports of paradoxical skin lesions in patients with SAPHO syndrome; current clinical experience related to paradoxical skin lesions is primarily based on findings in patients with rheumatoid arthritis, seronegative spondyloarthropathy, and inflammatory bowel disease.[10,14]

To the best of our knowledge, there remains no standard treatment for SAPHO syndrome due to the lack of relevant clinical trials. Nonsteroidal anti-inflammatory drugs are commonly regarded as first-line therapy, but SAPHO in many patients does not respond to these drugs.[1] Alternative treatments include antibiotics, corticosteroids, immunosuppressive drugs (e.g., colchicine, sulfasalazine, and methotrexate), and bisphosphonates.[15] In recent years, biological agents have been used in treatment of patients with SAPHO refractory to conventional therapy. Infliximab, etanercept, and adalimumab are the most commonly used TNF-α antagonists; however, patients with SAPHO who exhibit cutaneous manifestations do not respond well to these common therapies.[1,16] Recently developed cytokine-directed antibodies (e.g., anakinra, ustekinumab, secukinumab, and tocilizumab) have shown promising efficacy in some case reports and case series.[16] In addition, successful treatment of refractory SAPHO syndrome was achieved in one patient by using the JAK inhibitor tofacitinib[17] and in another patient by using apremilast (a specific phosphodiesterase-4 inhibitor);[18] those findings suggest the availability of further therapeutic options for the management of SAPHO syndrome. In 2017, we described a patient with SAPHO who achieved a remarkable degree of remission following TwHF treatment.[7] Furthermore, a clinical trial conducted by our research group demonstrated that 12 weeks of TwHF treatment should be considered for the treatment of SAPHO syndrome because of significant efficacy, reliable safety, and high socioeconomic value (unpublished data, Chinese Clinical Trial Registry number, ChiCTR1900025912).

The anti-inflammatory and immunosuppressive effects of TwHF are related to the regulation of inflammatory cytokines and the activities of T cells and dendritic cells.[19] Specifically, TwHF exhibits a clear suppressive effect on Th17 cells, which leads to defects in mRNA expression of IL-17A, IL-22, and TNF-α; it also reduces the expression levels of IL-1, IL-6, IL-8, and TNF-α through inhibition of nuclear factor (NF)-κB.[6,19,20] In addition, TwHF has been demonstrated to block IFN-γ-induced inflammation.[6,21] Therefore, based on a potential connection between the pharmacological mechanism of TwHF and the pathophysiology underlying paradoxical skin reactions, as well as the previously demonstrated efficacy of TwHF treatment for SAPHO syndrome,[7] we selected TwHF for management of etanercept-induced paradoxical skin lesions and treatment of SAPHO syndrome in our patient.

The findings in this case suggest that TwHF may be a good choice for treatment of SAPHO in patients who exhibit adverse cutaneous reactions to TNF-α antagonists. However, our previous research revealed that paradoxical skin lesions can resolve spontaneously within 2 to 4 months,

following discontinuation of TNF-α antagonist therapy; notably, primary lesions of palmoplantar pustulosis persist after discontinuation of treatment.[3] Therefore, additional case reports or clinical trials are needed to determine whether TwHF could shorten the course of paradoxical skin lesions.

Conclusions

We have described a patient with SAPHO syndrome who exhibited TNF-α antagonist-induced paradoxical skin lesions and benefitted from treatment with TwHF. Following TwHF treatment, the patient's paradoxical skin lesions resolved rapidly and exhibited durable remission; her osteoarticular pain was also substantially improved. Thus, TwHF may be a suitable treatment for patients with SAPHO who exhibit TNF-α antagonist-induced cutaneous lesions.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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ORCID iD

Xinlu Zhang https://orcid.org/0000-0001-7435-2701

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