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CASE REPORT

Successful Treatment of Refractory Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis (SAPHO) Syndrome with Baricitinib, a Janus Kinase Inhibitor

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Abstract: Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome, a rare immune-mediated inflammatory disease, poses diagnostic and therapeutic challenges owing to its multi-system involvement, high heterogeneity, and lack of specific laboratory tests. Additionally, lacking evidence-based treatment recommendations, with the primary approach focusing on symptomatic relief. Herein, we report the case of a 32-year-old Chinese woman who presented with recurrent, generalized multiple osteoarticular pain lasting over one year and skin erythema pustulosis for 11 months. Traditional treatments, including non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease-modifying antirheumatic drugs (DMARDs), and other traditional approaches, yielded no significant effects. Despite the prior use of adalimumab and acitretin capsules, the treatment remained unsatisfying, especially regarding the skin lesions. Considering the complex pathogenesis of SAPHO syndrome, the patient was orally administered baricitinib (2 mg), a Janus kinase (JAK) inhibitor, twice daily. A notable improvement in both skin lesions and osteoarticular pain was observed within two weeks of treatment initiation. Subsequently, the dosage of baricitinib was halved and continued for an additional three months, during which regular follow-ups revealed neither disease recurrence nor adverse effects. Collectively, the successful treatment of refractory SAPHO syndrome with baricitinib presents a promising implication for addressing the therapeutic challenges of this rare autoimmune condition, offering a potential breakthrough in managing its complex manifestations.

Keywords: SAPHO syndrome, autoinflammatory conditions, therapeutic challenges, baricitinib

Introduction

Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome is a rare autoimmune disease and can be considered as an autoinflammatory condition.[1] This syndrome is primarily characterized by chronic aseptic inflammation affecting the skin, bones, and joints, presenting clinical rarity with no precise data on its prevalence, especially among different ethnic groups.[2] Although previous studies explored the genetic susceptibility, infection, and immune dysfunction associated with SAPHO, the exact etiology and pathogenesis of this disease remain incompletely elucidated.[1,3–5] Whole exome sequencing(WES) and Variant Enrichment Analysis(VEA) have been used to investigate the complex pathogenic landscape of SAPHO syndrome and other related autoinflammatory syndromes. WES was used to identify polygenic variants in patients with overlapping pyoderma gangrenosum, acne, and hidradenitis suppurativa (PASH)/SAPHO, and VEA was used to explore molecular mechanisms and etiopathogenic pathways involved in its onset. This approach revealed impaired macroautophagy pathways in patients with PASH/SAPHO. Autophagy deficiency in endothelial cells (EC) results in unregulated leukocyte transendothelial migration, increasing neutrophil infiltration and tissue damage. Moreover, enriched exclusive pathways (eEP) are associated with extracellular matrix organization in SAPHO patients.[6,7] Due to the involvement of multiple systems, high heterogeneity, and a lack of specificity in laboratory tests, diagnosing and treating this disease pose significant challenges. Currently, standardized treatment guidelines for SAPHO syndrome are lacking, and the primary therapeutic strategy involves

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symptomatic relief to alleviate pain, control inflammation, and enhance the overall quality of life of patients.[8,9] In recent years, the therapeutic strategies consisting of a combination of biologics and small molecules have brought new promising options for patients.

In this study, we present a case of SAPHO syndrome unresponsive to conventional therapy that was effectively treated with an oral Janus kinase (JAK) inhibitor, baricitinib.

Case Report

A 32-year-old woman presented with sternal pain one year ago, followed by pain in the left articulatio humeri, spine, and right ankle with limited activity. A month later, erythema and pustules appeared on the surfaces of the soles, and the lesions gradually expanded. Diffuse psoriasis-like lesions appeared on the trunk and limbs, accompanied by rice grain-sized pustules on the anterior chest, causing mild itching. Imaging examinations, including computed tomography (CT) and magnetic resonance imaging (MRI), were conducted at the local hospital to establish a definite diagnosis. All tests revealed an abnormal signal in the sternum. Positron emission tomography (PET)/CT indicated bone destruction, osteogenic changes, and bone marrow edema. Partial sternotomy and bone histopathology were subsequently performed, which revealed a large number of neutrophil-dominated inflammatory infiltrates and fibrous tissue hyperplasia. After treatment with non-steroidal anti-inflammatory drugs (NSAIDs), high-dose corticosteroids, and disease-modifying anti-rheumatic drugs (DMARDs), the osteoarticular pain improved slightly; however, the treatments were insufficient to control the disease. Notably, the skin lesions exhibited no observable improvement.

The patient was admitted to our hospital for diagnostic and therapeutic purposes. Physical examination revealed swelling, tenderness, and limited range of motion in the sternum, left articulatio humeri, and right ankle; reduced lumbar motion; tenderness between the 4–5 lumbar vertebrae and sacral vertebrae (+); and percussion pain (+). The visual analog scale (VAS) indicated a severity score of 9. Dermatology examination revealed erythema and scales of varying sizes scattered on the trunk and limbs, multiple red papules accompanied by pustules ranging from needle tip-to-rice grain size visible on the anterior chest. Both soles exhibited diffuse erythema with lamellar peeling and with needle tip-to-rice grain-sized pustules (Figure 1a-d). Laboratory results revealed a C-reactive protein (CRP) level of 57.82 mg/L (normal range: 0–10 mg/L) and an erythrocyte sedimentation rate (ESR) level of 39 mm/h (normal range: < 20 mm/h). The serum leukocyte count was within the normal range. Tests for serum autoantibody, antinuclear antibody (ANA), rheumatoid factor (RF), human leukocyte antigen B27 (HLA-B27), CMV-DNA, EBV-DNA, HBV-DNA, tuberculosis infection T cell, HIV antibody, streptococcus pneumoniae antigen, and cytokine detection [including interleukin (IL)-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, tumor necrosis factor (TNF)-α, interferon (IFN), IL-17], and microorganism cultivation from the pustular secretion of the soles, were all negative. Skin biopsy pathology of the sole revealed mild hyperkeratosis accompanied by parakeratosis and infiltration of neutrophils and lymphocytes in the superficial and intermediate dermis (Figure 1e and f).

The patient initially presented with pustules on the soles and psoriasis-like lesions on her trunk and limbs. No signs of acne were observed. The patient experienced recurrent pain and swelling in the affected osteoarticular areas, including the sternum, spine, and limbs, which was consistent with the diagnostic criteria for SAPHO syndrome, as proposed by Kahn and Khan.[10] Considering the extensive skin lesions, osteoarthrosis, and inadequate response to previous medical treatment, adalimumab was subcutaneously injected at 40 mg once weekly. After five weeks, her joint symptoms improved. The skin lesions showed no improvement. The patient voluntarily requested discontinuation of adalimumab therapy. Subsequently, acitretin capsules (10 mg twice daily) were introduced; however, the skin lesions still did not improve significantly after four weeks, leading to the discontinuation of acitretin. Ultimately, we recommended oral JAK inhibitors; baricitinib (2 mg twice daily) was prescribed. Two weeks after initiation, the skin lesions disappeared across the entire body, and the symptoms of osteoarticular pain were significantly relieved. Laboratory review indices returned to normal, with the VAS of pain decreasing from 9 to 2. Following discharge, the dose of baricitinib was halved and continued for three months, with no recurrence or adverse effects observed during the follow-up period (Figure 2a-d).

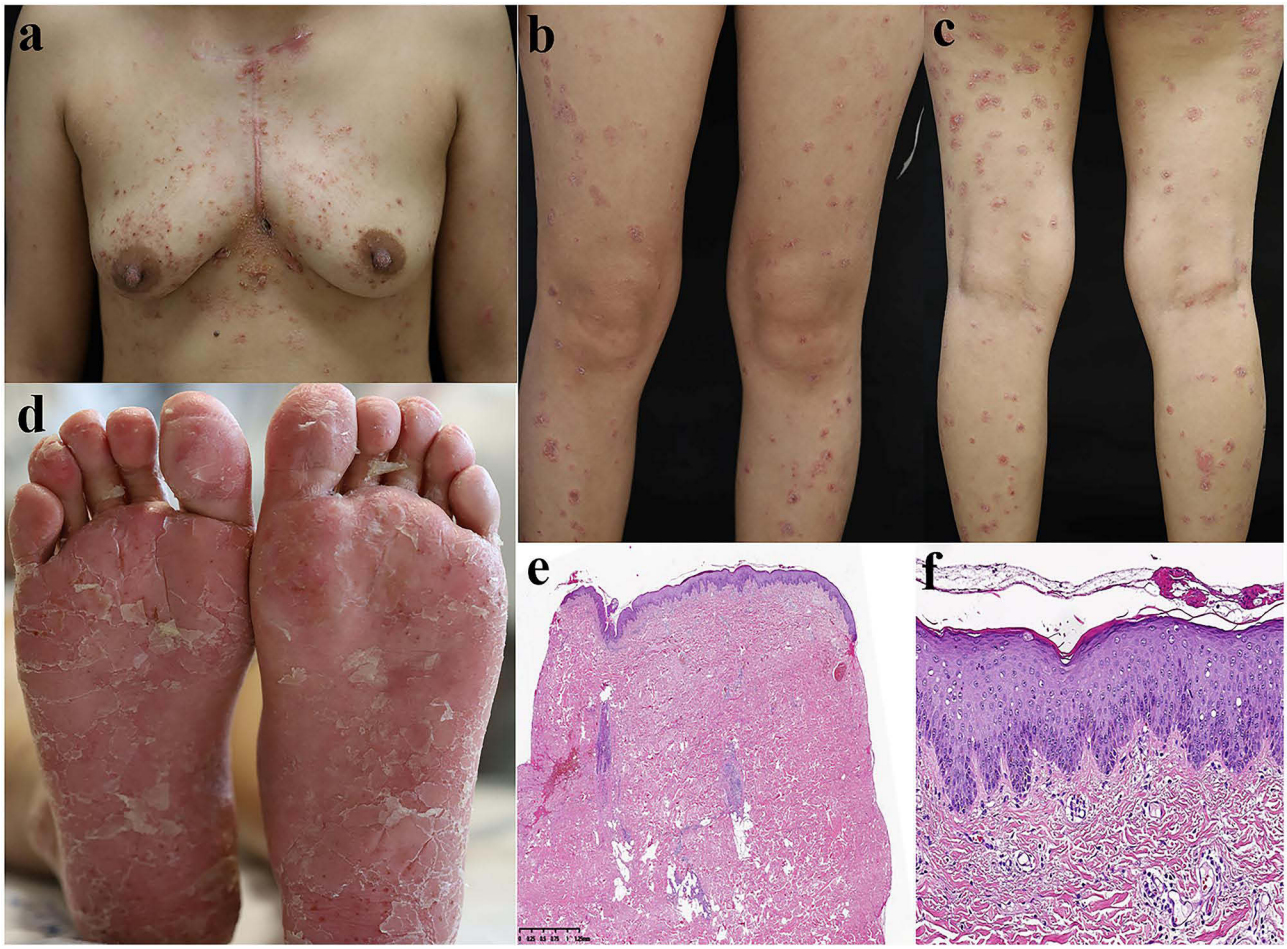

Figure 1 SAPHO syndrome patient with pre-treatment cutaneous manifestation. (**a**) Scaly erythema, papules, accompanied by pustules ranging from needle tip-to-rice grain size visible in the anterior chest. The postoperative red linear hypertrophic scar was about 10 cm long, and the bean grain size hypertrophic scar was scattered below. (**b** and **c**) Scattered red papules, plaques, and scales of varying sizes in both lower extremities. (**d**) Sole diffuse erythema with lamellar peeling and with needle-tip-to-rice-grain-sized pustules. (**e** and **f**) Histopathological examination of a SAPHO syndrome lesion from sole (stained with haematoxylin and eosin; magnifications: (**e**) ×40, (**f**) ×200), revealed mild hyperkeratosis accompanied by parakeratosis and infiltration of neutrophils and lymphocytes in the superficial and intermediate dermis.

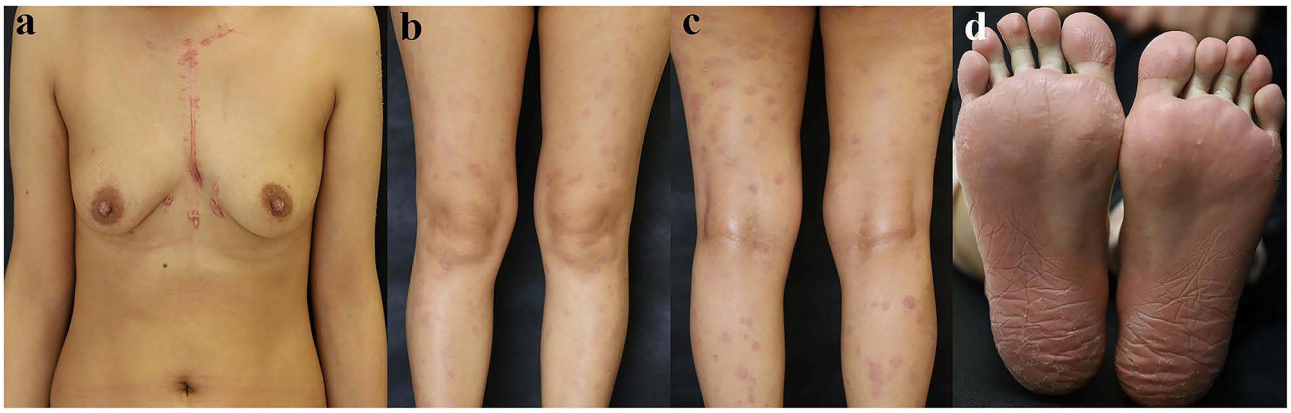

Figure 2 SAPHO syndrome patient with after-treatment skin lesions. (**a-d**) Erythema, papules, and pustules gradually subsided, leaving slight pigmentation.

Discussion

SAPHO syndrome is a heterogeneous disease characterized by chronic inflammation affecting osteoarticular and cutaneous manifestations, presenting with a broad spectrum of clinical features and a highly diverse combination. The disease can manifest at all ages, with the most common occurrence between 30–50 years, showing a slightly higher

prevalence in women than in men.[11] The main skin lesions consist of multiple sterile pustulosis in the palmoplantar region, accompanied by keratosis and scaling. Severe pustulosis may extend to the chest, back, or even the entire body. Subsequently, acne and psoriasis-like lesions may develop.[12] Hidradenitis suppurativa is also considered a dermatological manifestation of SAPHO syndrome; however, data from the literature remain controversial.[13] Women are reportedly more likely than men to exhibit pustulosis, whereas men are more prone to develop acne than women, with varying degrees of skin damage.[14] The location of osteoarticular damage is usually related to age; in adults, it primarily occurs in the anterior chest wall, especially at the sternal end of the sternoclavicular joint and the front end of the ribs of the upper chest wall. It then extends to the spine, sacroiliac joint, and limb joints, showcasing chronic inflammatory changes such as bone destruction, hyperostosis, sclerosis, and osteogenic changes. The later the age of onset, the more likely the initial symptom of osteoarthrosis is to manifest. Laboratory tests lack specificity, with approximately 50% of patients exhibiting elevated ESR and CRP levels, and 20% of patients exhibiting elevated cytokine levels during the active stage of the disease.[15,16] Imaging examination can help identify the lesion site, osteolysis, osteitis, hyperplasia, osteosclerosis, and bone marrow edema.[17] In this patient, the age of onset, skin and osteoarticular damage, and laboratory tests were consistent with the characteristics of the disease.

NSAIDs, intra-articular injection, or systemic use of corticosteroids, DMARDs, and bisphosphonates continue to serve as the main methods of traditional treatment.[18,19] However, NSAIDs, often prove insufficient in controlling the widespread involvement observed in patients with SAPHO when used as an initial treatment strategy.[11] Corticosteroids, generally requiring large doses for effectiveness, are not recommended for long-term use owing to potential side effects. The efficacy of conventional DMARDs and bisphosphonates in treating skin lesions remains unsatisfactory.[20,21] In our case, the disease did not control well after undergoing various conventional treatments, especially the skin lesions. In recent years, biologics (including TNF-α antagonists such as adalimumab, infliximab, and etanercept; IL-1, IL-17, IL-12/IL-23 receptor antagonists, such as anakinra, secukinumab, ustekinumab) and small-molecule targeted drugs have garnered interest as an alternative approach when traditional drug therapy exhibits partial effectiveness or is ineffective. These options provide more diverse programs for disease management.[22] The combination of biologics and conventional treatments as valid therapeutic option.[23] In a systematic review of cases from 2019, the response rates of TNF-α inhibitors for osteoarthritis and skin lesions were 93.3% and 72.4%, respectively, demonstrating positive therapeutic effects.[24] Furthermore, the TNF-α antagonist adalimumab is the most widely used; therefore, we initially considered the use of adalimumab. However, while biologics have proven effective in treating some patients, they have also demonstrated ineffectiveness in others and may even cause new rashes or aggravate existing ones. Additionally, adverse reactions may occur, potentially leading to treatment discontinuation.[24,25] This patient was treated with adalimumab for five weeks, which improved the bone and joint pain; however, the rash did not subside, and the patient refused to continue adalimumab treatment. Subsequently, the patient was treated with acretin capsules to alleviate pustules and psoriasis-like lesions; however, the skin lesions did not respond well after four weeks of treatment. Additionally, there have been reports suggesting that retinoids could act as a trigger for osteoarthritis, leading to its discontinuation.[26] This indicates the refractory of this patient.

The use of the phosphodiesterase-4 inhibitor apremilast and the JAK inhibitors opens a new era for pan-cytokines and cells.[27] JAK inhibitors are key targets in signaling pathways for inflammatory diseases, effectively blocking the upstream components of various cytokines and their pathway effects. These inhibitors exhibit more significant anti-inflammatory activity compared with that of biologics that target a single cytokine.[28] Simultaneously, they contribute to regulating the expression of inflammatory factors, proving beneficial for autoimmune diseases. Additionally, baricitinib inhibits osteoclast-mediated structural damage in arthritis by blocking the receptor activator for the nuclear factor kB ligand (RANKL) pathway. Based on these findings, we decided to administer baricitinib, a JAK inhibitor. Currently, there are over 10 reported cases worldwide of SAPHO syndrome treated with JAK inhibitors (Table 1). In these patients, the time required to improve osteoarticular pain symptoms and cutaneous damage is typically around three months, whereas the duration needed for bone marrow edema to subside was longer. Among these reports, tofacitinib was more frequently used, with only two cases involving baricitinib. In one case series with five patients, four exhibited varying degrees of remission in clinical symptoms and laboratory indices after 12 weeks of treatment, whereas one patient showed no significant improvement.[29–32] Our patient experienced a significant and rapid response after two weeks of oral

Table 1 A Summary of Cases with SAPHO Syndrome That Were Treated Using JAK Inhibitor

#	Reference/ Publication (yr)	Age (yr)	Sex	Osteoarticular Manifestations	Skin Manifestations	Other Systems	JAK Inhibitors	Time and Effect of Treatment	Adverse Event
1	Yang et al 2018[29]	44	F	Right wrist arthralgia, hot, swollen, tenderness, and limited movement	PPP	None	Tofacitinib (5mg, twice daily)	4 weeks: symptoms improved, VAS score decreased, and serum inflammatory parameters decreased to normal; 12 weeks: MRI amelioration	None
2	Liu et al 2019[33]	26	F	Polyarthralgia and elevated serum inflammatory parameters	Unknown	LAM	Tofacitinib (5mg, twice daily)	3 weeks: symptoms improved, and inflammatory markers decreased to nearly normal ranges; 16 weeks: bone marrow edema amelioration	None
3	Li et al 2020[30]	62	F	Sternoclavicular joints, back and right knee pain, swollen	PPP	None	Tofacitinib (5mg, twice daily)	3 days: pain remarkably relieved; 4 weeks: cutaneous lesions healed; 6 months: vertebral damage improved and serum inflammatory parameters decreased to normal	None
4	Li et al 2020[34]	39.42±10.29	F	Multiple osteoarticular damage	PPP, nail lesions	None	Tofacitinib (5mg, twice daily)	Pain and rash alleviated, systemic inflammation reduced and MRI remitted	None
5	Li et al 2021[31]	34.62±12.78	F	Anterior chest wall and multiple joint lesions	PPP, PV, nail lesions	None	Tofacitinib (5mg, twice daily)	8 weeks: VAS score decreased; 12 weeks: nail lesions and PPP remitted, inflammatory markers improved	None
6	Yuan et al 2022[35]	36	M	Bilateral gluteal region, lumbosacral area, and chest and back pain	PPP, hidradenitis suppurativa	AS	Tofacitinib (5mg, twice daily)	1 month: rash subsided, chest and back pain relieved	None
7	Wuriliga et al 2022[32]	41	F	Back pain, right lower limb claudication, bone marrow edema	PPP	None	Baricitinib (2mg, daily)	Back pain and claudication significant improvement; 1 year: bone marrow edema resolution	None
8	Baisya et al 2023[36]	18	M	Bilateral forearms pain and swelling, polyarthritis of both knees, ankles, and sternoclavicular joints, bone marrow edema	Scattered throughout the body in acneiform and pustular lesions.	Uveitis	Tofacitinib (5mg, twice daily)	3 months: symptoms achieved resolutions, then discontinued	None

(*Continued*)

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Table 1 (Continued).

#	Reference/ Publication (yr)	Age (yr)	Sex	Osteoarticular Manifestations	Skin Manifestations	Other Systems	JAK Inhibitors	Time and Effect of Treatment	Adverse Event
9	Ma et al 2023[37]	27	F	Anterior chest wall and low back pain, bone erosion and marrow edema	PPP	None	Upadacitinib (15mg, daily)	3 months: bone pain and pustules all relieved; 6 months: followed up the symptoms did not recur	None
10	Liu et al 2023[38]	43.20 ±17.70	F/M	Anterior chest wall and other joint pain	PPP, nail lesions, and acne	None	Baricitinib (2mg, daily)	12 weeks: inflammatory markers declined, cutaneous manifestation improved, osteoarticular pain relieved, and function improved	None
11	Ru et al 2023[39]	36	M	Sternoclavicular joint pain	PPP	TAK	Tofacitinib (5mg, twice daily)	2 months: skin symptoms relieved, and sternal pain and pain in the right neck near the jaw significantly reduced; 6 months: carotid artery thickness became thinner	None
12	Cao et al 2023[40]	28	M	Mandibular and auricles swelling, and pain	Recurrent facial acne	RP	Tofacitinib (5mg, daily)	Acne, swelling, jaw and ears and pain effectively alleviated	None
13	Wang et al 2023[41]	25	F	Left clavicle and the sternoclavicular joint pain	PPP and maculopapular rash, ulcer	HSP	Tofacitinib (5mg, twice daily)	2 months: ulcer completely healed, palmoplantar psoriasis improved, and pain relieved	None
14	Liu et al 2023[42]	22	F	Mandible and left wrist swell and pain	None	None	Tofacitinib (5mg, twice daily)	3 months: systemic inflammation status and peripheral osteoarticular symptoms remission	None
15	Luan et al 2023[43]	42	M	Left sternoclavicular joint and left sacroiliac joint pain, swollen	PPP	None	Tofacitinib (5mg, twice daily)	1 month: rash subsided, and sternoclavicular joints and sacroiliac joint pain also improved; 4 months: all skin lesions resolved, the sternoclavicular joints and sacroiliac joint pain disappeared	None

Abbreviation: PPP, Palmoplantar pustulosis; LAM, Lymphangioleiomyomatosis; PV, Psoriasis vulgaris; AS, Ankylosing spondylitis; TAK, Takayasu arteritis; RP, Relapsing polychondritis; HSP, Henoch–Schönlein Purpura.

administration of baricitinib, a selective JAK inhibitor targeting JAK1 and JAK2. Common adverse reactions, including infection, anemia, platelet elevation, leukopenia, and cholesterol elevation, were considered during the course of use.[30] The relevant indicators were closely monitored, and regular follow-up was conducted. No disease recurrence, abnormalities in serological indicators, or adverse effects were observed. This suggests that baricitinib may be a beneficial treatment for patients with refractory SAPHO syndrome; however, individual differences exist in treatment, and our findings from a single case cannot be extrapolated to the entire patient population. Thereby, further investigations on a larger scale are warranted to validate and generalize these findings. Our findings hold the potential for reshaping the paradigm for treating similar inflammatory diseases with JAK inhibitors. Additionally, the patient had a short follow-up period and would be reevaluated at six months and one year, highlighting the need for validating the optimal treatment duration and indications for drug withdrawal.

Conclusion

Our findings suggest that JAK inhibitors hold great breakthrough promise as a therapeutic approach for SAPHO syndrome, particularly for treating inflammatory diseases, and exhibit favorable efficacy with minimal side effects. When conventional drugs or biologics are not well tolerated or fail to produce adequate results, JAK inhibitors offer a viable alternative. These insights not only open avenues for personalized treatment but also prompt a reevaluation of the conventional therapeutic landscape for this challenging condition.

Ethics statement

The Ethics Committee at Dushu Lake Hospital Affiliated with Soochow University approved the study. This study complied with the Declaration of Helsinki. The participant provided her written informed consent to participate in this study and was allowed to publish images and clinical details.

Consent for publication

The authors certify that they have obtained the consent of the patient for publication.

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Disclosure

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

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