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ORIGINAL ARTICLE

Paradoxical skin lesions induced by anti-TNF-α agents in SAPHO syndrome

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Abstract

The objectives of the study were to characterize the clinical picture of paradoxical skin lesions in SAPHO patients treated with anti-TNF-α agents and to explore its pathogenesis. Patients treated with anti-TNF-α therapy were identified from a cohort of 164 SAPHO patients. The clinical data and skin biopsies were collected. The usage, efficacy, and side effects of anti-TNF-α therapy were recorded. Forty-one (25.0%) patients received anti-TNF-α therapy, of which seven (17.1%) developed paradoxical skin lesions after 1 to 14 infusions. Patients with such lesions were older at onset of skin lesions than those without ($p = 0.034$). Expression of TNF-α in palmoplantar pustulosis increased after anti-TNF-α therapy in the two examined patients with exacerbated skin lesions. Anti-TNF-α therapy induces paradoxical skin lesions in 17.1% SAPHO patients. Late onset of skin manifestations is associated with an increased risk of such lesions. The paradoxical elevation of TNF-α expression in lesions may contribute to this phenomenon.

Keywords Age of onset · Palmoplantar pustulosis · Psoriasiform lesions · SAPHO syndrome · Side effects · Tumor necrosis factor-α inhibitor

Introduction

Synovitis, acne, pustulosis, hyperostosis, and osteosis (SAPHO) syndrome encompasses a spectrum of osteoarticular and cutaneous manifestations, including sternocostoclavicular hyperostosis, sacroiliitis, ankylosing spinal hyperostosis, peripheral arthritis, palmoplantar pustulosis (PPP), severe acne, and hidradenitis suppurativa [1]. There is no standardized treatment for SAPHO syndrome. Current treatment strategies include non-steroidal anti-inflammatory drugs, analgesics, disease-modifying anti-rheumatic drugs, and antibiotics. These drugs show efficacy for some SAPHO patients, but the symptomatic relief of SAPHO syndrome is usually temporary [2–5]. In recent years, tumor necrosis factor (TNF)-α antagonists have gained widespread use in SAPHO syndrome and have shown promising results in relieving osteoarticular pain and cutaneous manifestations [6].

TNF-α is a pleiotropic proinflammatory cytokine that is primarily expressed on activated macrophages and lymphocytes; it plays a pivotal role in the pathogenesis of several immune-mediated inflammatory disease, such as inflammatory bowel disease (IBD), psoriasis, and SAPHO syndrome [7].

Chen Li, Xia Wu and Yihan Cao contributed equally to this work.

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However, it has been sporadically reported that SAPHO patients may exhibit worsening or even new onset of psoriasiform lesions as paradoxical side effects of TNF-α inhibitors [6, 8–10]. There are scarce data regarding the cutaneous side effects of TNF-α antagonist treatment for SAPHO syndrome. The incidence, characteristics, management, prognosis, and pathogenesis of these cutaneous side effects in SAPHO syndrome remain unclear [6].

The aim of this study was to assess the exacerbation of existing skin lesions and the incidence of new skin lesions associated with anti-TNF-α therapy in SAPHO syndrome in a large Chinese cohort and to evaluate their clinical characteristics, management, and outcomes. We also aimed to preliminarily explore the pathogenesis of these paradoxical side effects in SAPHO syndrome.

Methods

Study population

This was a cross-sectional observational study based on a Chinese cohort of 164 patients with SAPHO syndrome [11]. Patients fulfilling Kahn and Khan's criteria for SAPHO syndrome [12] were recruited in Peking Union Medical College Hospital from 2004 to 2015. At baseline, 41 (25%) patients had been treated with anti-TNF-α agents [11]. We retrospectively reviewed the baseline patient characteristics and recorded information regarding the anti-TNF-α therapy at baseline and during follow-up of the patients. The study was approved by the Ethics Committee of Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences (ethics documents number ZS-944). All individual participants provided written informed consent to participate in this cohort at the time of inclusion.

Data collection

Demographic and clinical information, including sex, age at diagnosis, age at onset of skin lesions and osteoarticular sypmtoms, and skin and osteoarticular manifestations, were collected at baseline. Laboratory results, including erythrocyte sedimentation rate (ESR), high sensitivity C-reactive protein (hs-CRP), anti-nuclear antibody (ANA), rheumatoid factor (RF), and human leukocyte antigen B27 (HLA-B27), were also retrieved at baseline. The regimen and course of treatment for anti-TNF-α therapy were recorded for every patient, taking into account the start and finalization time of each TNF-α antagonist treatment. Dermatological side effects (including exacerbation of previously existing skin lesions or the onset of new skin lesions), their management, and outcomes were documented retrospectively.

Measurement of tissue and serum TNF-α level

Among the patients whose lesions worsened or who developed new skin lesions after anti-TNF-α therapy, two had biopsies taken from their PPP lesions at the same position both before and after anti-TNF-α treatment. The four specimens (two for each patient) were examined for TNF-α expression by immunohistochemistry. Immunohistochemistry results were further evaluated by a semiquantitative approach used to assign a histochemistry score (H Score) using 3D Histech Pannoramic MIDI Slide Scanner [13]. The H Score of the epidermis, dermis, and the whole pathological tissue were calculated. In addition, serum TNF-α levels were measured before, during, and after anti-TNF-α therapy.

Statistical analysis

Categorical variables are presented as numbers (percentage), and quantitative data are presented as the mean value (SD) or median value (minimum to maximum). The chi-square test or Fisher's exact test was used to compare categorical variables between groups. Continuous variables were compared using a *t* test or a non-parametric test. Statistical significance was assumed for *P* values less than 0.05. All analysis was computed using SPSS statistics V.19.0.

Results

Clinical features

Of the 41 patients who had received anti-TNF-α therapies, seven (17.1%) developed new skin lesions during treatment. Meanwhile, none of the 123 patients who had not received any anti-TNF-α therapy developed the same kind of skin lesions. Demographic and clinical information for the seven patients with new skin lesions are listed in Table 1. Briefly, all seven patients presented with both osteoarticular and skin manifestations. The most pronounced osteoarticular phenotype was sternoclavicular hyperostosis, followed by sacroiliitis and peripheral arthritis. Axial and peripheral (ankle joints, shoulder joints, and metatarsal bones) skeleton involvement was demonstrated by bone scintigraphy or magnetic resonance imaging. Before anti-TNF-α therapy, all patients presented with PPP involving both hands and feet. One patient had co-existing psoriasis vulgaris, and another had severe acne. All the patients had received conventional treatment before anti-TNF-α therapy (Online Resource 1).

After one to two doses of infliximab or four to 12 doses of etanercept, these seven patients developed new psoriasiform skin lesions on the trunk and limbs where no skin manifestations were present prior to anti-TNF-α therapy. These newly developed lesions presented as pustular lesions (two patients,

Table 1 Demographic and clinical features of SAPHO patients with exacerbated or newly developed skin lesions

Patient	Age/sex	Clinical manifestation		Anti-TNF regimen (dose and infusion)	Duration of anti-TNF regimen before new skin lesions (weeks)	Treatment response	
		Osteoarticular	Cutaneous			Osteoarticular	Cutaneous
1	58/F	SCCH, sacroiliitis, peripheral arthritis	PPP	ETN 25 mg, × 12	6	Complete remission	New psoriasiform lesions on trunk and limbs; alopecia; PPP worsened
2	57/F	SCCH, peripheral arthritis	PPP, PV	ETN 25 mg, × 4	2	Partial remission	New psoriasiform lesions on lower legs; PPP and PV alleviated
3	36/M	SCCH, sacroiliitis	PPP	INF 5 mg/kg, × 2	3	Partial remission	New psoriasiform lesions on lower legs; alopecia; PPP worsened
4	52/F	SCCH, peripheral arthritis	PPP	ETN 25 mg, × 6	3	Complete remission	New pustular psoriasiform lesions on chest, abdomen, and back; PPP alleviated
5	33/F	SCCH, sacroiliitis	PPP, SA	ENT 25 mg, × 12; INF 5 mg/kg, × 2	10	Refractory to ENT, relieved after INF treatment	New pustular psoriasiform lesions on limbs and trunk; PPP and SA alleviated
6	58/F	SCCH	PPP	INF 5 mg/kg, × 1	1	Partial remission	New psoriasiform lesions on limbs and trunk; PPP alleviated
7	33/M	SCCH, sacroiliitis	PPP	ETN 25 mg, × 11	6	Partial remission	New psoriasiform lesions on limbs and trunk; PPP worsened

For osteoarticular response, complete remission was defined as a visual analog score (VAS) below 3; partial remission was defined as a VAS below 5

ENT etanercept, *INF* infliximab, *PPP* palmoplantar pustulosis, *PV* psoriasis vulgaris, *SA* severe acne, *SCCH* sternoclavicular hyperostosis, *TNF* tumor necrosis factor

28.6%) or psoriasiform scaly plaques (five patients, 71.4%) on the limbs and trunk, and they progressed rapidly (Figs. 1c and 2a, c). Moreover, two patients (28.6%) developed alopecia, and three patients (42.9%) experienced worsening of the initial PPP. Four (57.1%) patients showed an alleviation of initial skin lesions after receiving TNF-α antagonists (Fig. 1a, b).

TNF-α inhibitors were withdrawn after the onset of new skin lesions in all seven patients. Non-biological agents such as topical vitamin D analogs and disease-modifying anti-rheumatic drugs (DMARDs) were given in five patients (Online Resource 2). Most lesions resolved within 2 to 4 months (Figs. 1c, d and 2a, b), whereas some lesions on the lower legs required 1−2 years to disappear (Fig. 2c, d). The osteoarticular symptoms of all seven patients remained stable for at least 6 to 24 months after the discontinuation of anti-TNF-α therapy.

Possible risk factors

The clinical characteristics of the patients with and without newly developed skin lesions are summarized in Table 2. Patients with exacerbated or newly developed skin lesions were significantly older at onset of skin lesions than those without (46.0 ± 12.4 vs 35.1 ± 9.3 years, $p = 0.034$). No other significant differences were identified between the two groups for variables including sex, age at diagnosis, age at onset of symptoms, type of skin manifestations, ESR, hs-CRP, ANA, RF, and HLA-B27.

Tissue and serum TNF-α levels

The results of TNF-α expression in the four biopsies from the PPP lesions of the two patients with newly onset skin lesions are presented in Fig. 3. The H Score indicates substantially increased expression of TNF-α after anti-TNF-α treatment in the epidermis, dermis, and the whole pathological tissue in both patients (47.5, 56.9, and 38.4 versus 114.5, 93.5, and 120.7; 81.2, 84.7, and 85.4 versus 109.1, 131.6, and 138.6) (Fig. 3).

Serum TNF-α levels were measured in two patients (patient 1 and patient 3) with new skin lesions after discontinuing their anti-TNF-α therapy (Fig. 3). Notably, the serum TNF-α levels of patient 3 significantly increased to 775.0 pg/ml (< 8.1 pg/ml), whereas patient 1 had a moderately increased serum TNF-α level to 87.0 pg/ml. As time passed, the serum TNF-α levels in both patients gradually decreased to a nearly

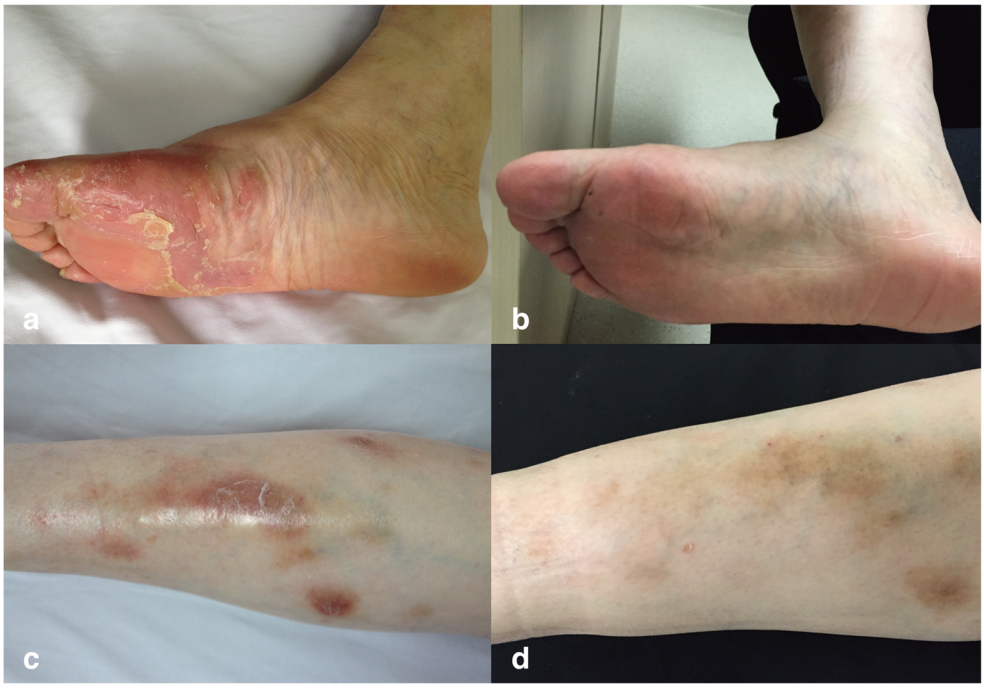

Fig. 1 **a** Palmoplantar pustulosis on right planta before anti-TNF-α treatment. **b** PPP resolved after anti-TNF-α treatment. **c** Newly developed psoriasiform scaly plaques on right lower leg during anti-TNF-α treatment. **d** Psoriasiform scaly plaques resolved 3 months after withdrawal of the TNF-α antagonist

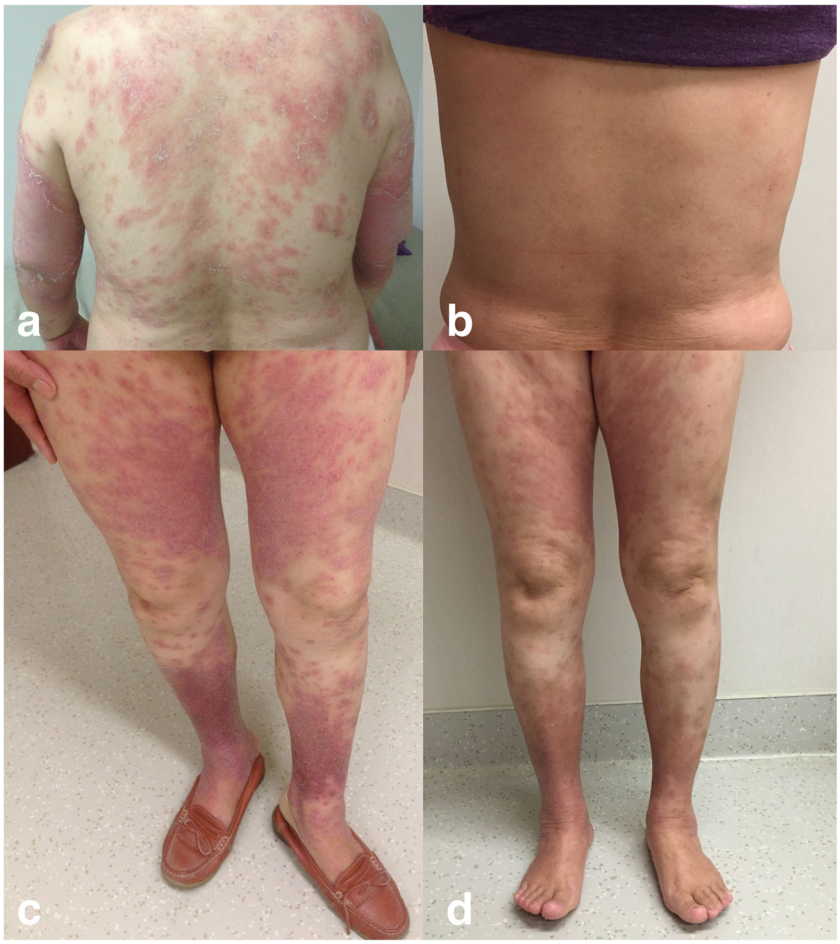

Fig. 2 **a**, **c** Psoriasiform lesions developed on dorsal trunk and legs during anti-TNF-α treatment. **b**, **d** Lesions resolved after withdrawal of TNF-α antagonists

Table 2 Baseline characteristics of patients with SAPHO syndrome with and without exacerbated or newly developed skin lesions

Characteristics	Patients with exacerbated or newly developed skin lesions ($n = 7$)	Patients without exacerbated or newly developed skin lesions ($n = 34$)	*P* value
Sex, female	5 (71.4)	26 (76.5)	1.000
Age at diagnosis (years)	46.4 ± 12.1	37.9 ± 8.8	0.171
Age at onset of skin lesions	46.0 ± 12.4	35.1 ± 9.3	0.034*
Age at onset of osteoarticular symptoms	45.9 ± 11.9	35.3 ± 9.8	0.074
Skin manifestations			
PPP	7 (100)	28 (93.3)	1.000
SA	1 (14.3)	3 (10.0)	1.000
PPP only	5 (71.4)	22 (73.3)	1.000
SA only	0 (0)	2 (6.7)	1.000
PV only	0 (0)	0 (0)	–
PPP and PV	1 (14.3)	5 (16.7)	1.000
PPP and SA	1 (14.3)	1 (3.3)	0.347
SA and PV	0 (0)	0 (0)	–
Laboratory tests			
ESR (mm/h))	25.6 ± 12.7	35.4 ± 18.2	0.121
hs-CRP (mg/l)	10.21 ± 8.45	20.01 ± 21.21	0.242
ANA, positive	1 (14.3)	3 (8.8)	0.542
RF, positive	0 (0)	0 (0)	–
HLA-B27, positive	2 (28.6)	2 (5.9)	0.129

Data are presented as number of patients with corresponding characteristics/total number of patients (%) or median (25th–75th percentiles)

ANA antinuclear antibody, *ESR* erythrocyte sedimentation rate, *HLA-B27* human leukocyte antigen B27, *hs-CRP* hypersensitive c-reactive protein, *PPP* palmoplantar pustulosis, *PV* psoriasis vulgaris, *RF* rheumatoid factor, *SA* severe acne

**P* values less than 0.05

normal range. In three of the patients without new skin lesions, serum TNF-α levels had also been measured before (two out of three patients) and after (all three patients) anti-TNF-α therapy. The serum TNF-α levels were slightly elevated (patient A, 7.6 pg/ml; patient C, 8.5 pg/ml) prior to anti-TNF-α therapy, and they increased (patient A 54.6 pg/ml; patient B, 87.4 pg/ml; patient C, 86.4 pg/ml) after the therapy.

Discussion

TNF-α inhibitors are used to treat many types of inflammatory disorders, such as rheumatoid arthritis, IBD, and psoriasis. TNF-α inhibitors are generally well tolerated, but they are linked to dermatologic complications, with psoriasiform lesions as the most common skin-related side effect [14–16]. It was reported that 8 out of 150 patients with rheumatoid arthritis and ankylosing spondylitis developed psoriasis-like lesions after receiving TNF-α inhibitors [9], whereas 21 out of 434 patients with IBD developed psoriasiform skin lesions [17]. In approximately 0.6 to 5.3% of psoriasis patients, symptoms worsened after anti-TNF-α treatments [18]. With increasing published studies reporting the development of cutaneous manifestations after anti-TNF-α therapy, it is widely accepted that the new onset of psoriasiform lesions and the flare-up of pre-existing psoriasis are paradoxical reactions caused by TNF-α antagonists.

However, these side effects have rarely been described in SAPHO syndrome; only four cases have been reported. Abdelghani KB et al. reported six patients with SAPHO syndrome treated with TNF-α antagonists, and two of these patients developed paradoxical psoriasis [6, 8]. To the best of our knowledge, we present here the largest group of patients with SAPHO syndrome who developed TNF-α inhibitor-induced psoriasiform lesions. The incidence of skin-related side effects from anti-TNF-α therapy in SAPHO syndrome was previously unclear due to the small patient population. However, in this retrospective study, we evaluated a relatively large cohort of patients and estimated that the incidence of new psoriasiform skin lesions in patients with SAPHO syndrome receiving TNF-α inhibitors is 17.1%. It is notable that the incidence of new lesions in SAPHO syndrome is higher than that reported in any other types of inflammatory disorders. Moreover, previous reports have linked infliximab with the development of

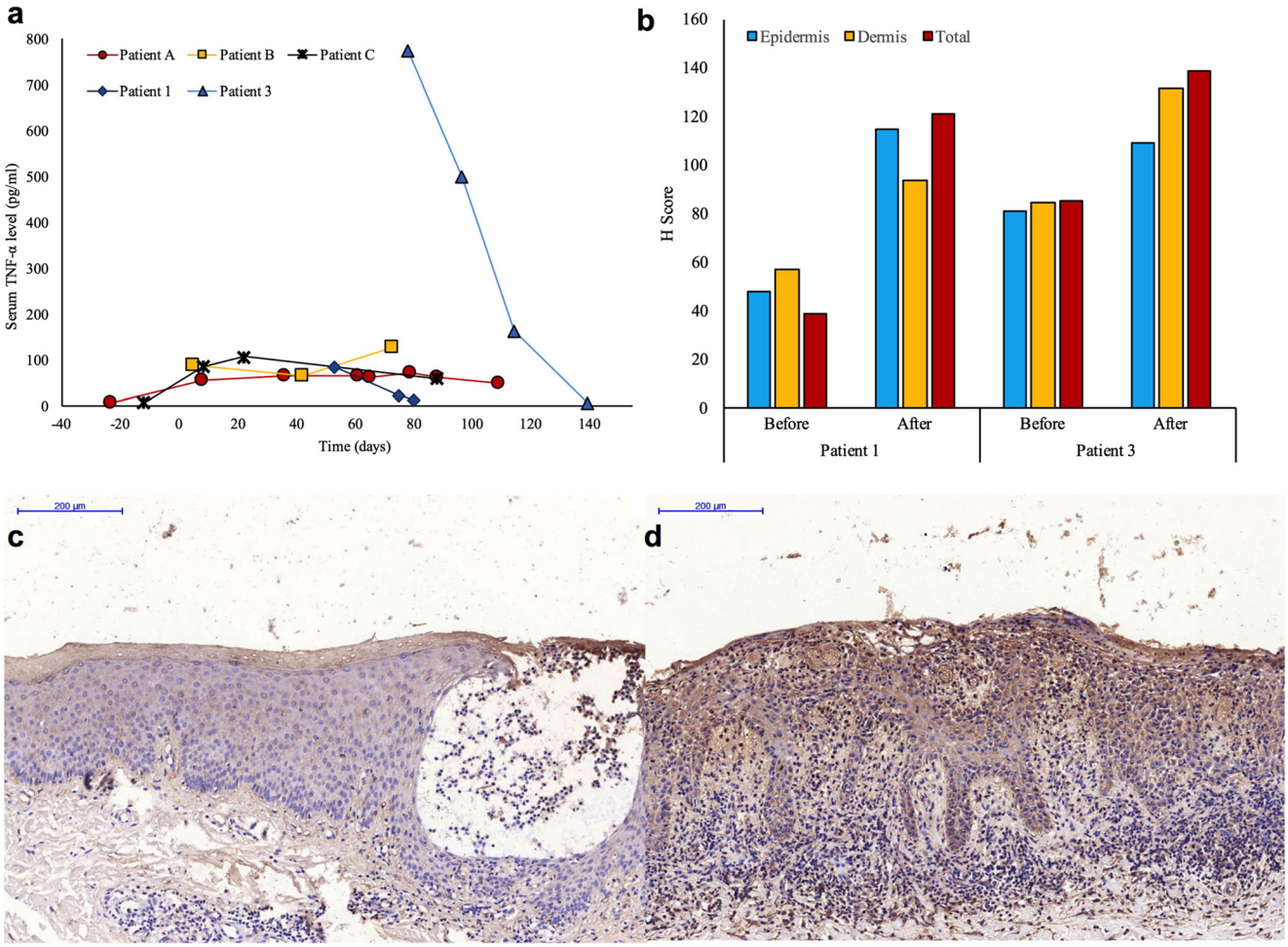

Fig. 3 **a** Serum TNF-α level before and after anti-TNF-α treatment. Day 0 is the day when the five patients started anti-TNF-α treatment. Patients A, B, and C had their osteoarticular pain relieved without any cutaneous adverse effects. All continued anti-TNF-α treatment during the period of testing for serum TNF-α levels. Patients 1 and 3 (indicated in Table 2) experienced the aggravation of initial PPP lesions and the development of new psoriasiform lesions after anti-TNF-α treatment. Patient 1 withdrew from etanercept at day 41; patient 3 withdrew from infliximab at day 16. **b** The H Score of TNF-α expression in biopsies from the PPPs of patients 1 and 3 before and after anti-TNF-α therapy. The H Score increased in the epidermis, the dermis, and the whole pathological tissue after anti-TNF-α therapy. **c**, **d** Immunohistochemical staining showing TNF-α expression in both dermis and epidermis. The expression of TNF-α increased after anti-TNF-α therapy

psoriasiform skin lesions in SAPHO patients [6, 8]. In this study, we found that etanercept could also induce psoriasiform lesions.

While sporadic psoriasis or psoriasiform dermatitis often develops on the extensor elbows, knees, and scalp, typical involved sites in patients with TNF-α inhibitor-induced psoriasis include soles (45.8%), extremities (45.4%), palms (44.9%), scalp (36.1%), and trunk (32.4%) [19]. In this study, we found that in patients with SAPHO syndrome, anti-TNF-α therapy-induced psoriasiform lesions developed mostly on the limbs (85.7%), trunk (71.4%), and scalp (28.6%). Meanwhile, pre-existing PPP might worsen during anti-TNF-α therapy. The morphological presentations of anti-TNF-α therapy-related psoriasiform lesions were variable as well. The most commonly observed types in SAPHO syndrome include psoriasiform scaly plaques (71.4%), worsened PPP (42.6%), pustular lesions (28.6%), and alopecia (28.6%). In our analysis, biopsy samples from TNF-α inhibitor-induced psoriasiform lesions were histologically indistinguishable from de novo psoriasis. In contrast to previous reports [20], no infiltration of eosinophils was observed in either exacerbated or newly developed skin lesions after anti-TNF-α therapy.

We found that the newly developed skin lesions would reduce upon the withdrawal of TNF-α inhibitors, consistent with previous results from patients with IBD [21]. It has been reported that TNF-α inhibitor-induced psoriasis can also be relieved upon switching to another different TNF-α inhibitor or continuing the same therapy, even though the resolution rate was much lower compared to the discontinuation of TNF-α inhibitors [19].

Consistent with previous reports, this study suggested that anti-TNF-α therapy is effective in reducing osteoarticular manifestations in patients with SAPHO syndrome. The

osteoarticular symptoms remained stably suppressed for a long period after TNF-α inhibitor discontinuation. Since osteoarticular pain has a substantial impact on quality of life in patients with SAPHO syndrome, anti-TNF-α agents are still recommended. However, frequent follow-up and monitoring of the cutaneous manifestations should be conducted to minimize the severity of these side effects by terminating TNF-α inhibitor therapy prematurely.

As both PPP and psoriasis are typical manifestations of SAPHO syndrome, an important issue is how to distinguish between a flare of the underlying disease and the paradoxical skin lesions induced by anti-TNF-α therapy. We used the following features to help identify such paradoxical skin lesions: First, the duration between the onset of new skin lesions and the initiation of anti-TNF-α therapy was relatively short (1–10 weeks, median 3 weeks), exhibiting a temporal correlation. Second, the new skin lesions exhibited a wider distribution in the limbs, trunk, and scalp (Table 1), which deviated significantly from the ordinary fluctuation of the primary lesions. Third, it only took days for paradoxical lesions to spread to an extended distribution, while such eruption of skin lesions was rarely seen in the clinical course of SAPHO syndrome. Fourth, the paradoxical skin lesions might develop while the osteoarticular symptoms alleviate. In contrast, skin lesions and osteoarticular symptoms of SAPHO syndrome often showed a parallel pattern of recurrence and remission in most cases. Fifth, the types of paradoxical skin lesions might be different from the existing ones; in patients with PPP, psoriasiform lesions may develop. Last, most of the paradoxical lesions resolved within 2 to 4 months after discontinuation of anti-TNF-α therapy, while the primary lesions of PPP remained and continued to fluctuate over time.

The clear mechanism underlying anti-TNF-α therapy-related psoriasiform skin lesions remains elusive. Several studies have postulated that an imbalance between Th1 and Th2 cytokine production and the subsequently increased production of interferon-α may play important roles. This imbalance leads to the migration of T cells to the skin after anti-TNF-α treatment [22, 23]. A positive feedback loop between IL-36γ or IL-17C and TNF-α may also contribute to this phenomenon [17, 24]. Tillack et al. [17] studied 21 IBD patients with anti-TNF-α therapy-induced psoriasiform skin lesions and discovered that their skin lesions were histologically infiltrated with IL-17A/IL-22-secreting Th17 cells, interferon-γ-secreting Th1 cells, and interferon-α-expressing cells. In addition, genetic studies found that three specific IL-23R polymorphisms are associated with anti-TNF-α therapy-induced psoriasis [17]. However, most of the pathogenic studies were performed in inflammatory diseases other than SAPHO syndrome. Whether similar changes occur in SAPHO syndrome remains unknown.

Interestingly, our study found that TNF-α expression in the biopsies of exacerbated PPP was strongly increased after anti-TNF-α therapy in SAPHO syndrome. Serum TNF-α levels increased transiently in SAPHO patients who did not have exacerbated or newly developed skin lesions after anti-TNF-α treatment, but the levels increased to a greater extent in patients who developed psoriasiform lesions after anti-TNF-α treatment. The pathogenic pathway that increased TNF-α could activate dendritic cells, which then induce the proliferation of T cells; keratinocytes are subsequently activated by proliferated T cells, which activate a positive proinflammatory feedback loop, including increased levels of TNF-α, IL-17C, IL-1α/β, IL-1F5, IL-1F9, IL-6, and IL-19 [25, 26]. This situation is distinct from previous reports indicating that the suppression of TNF-α expression and subsequently elevated interferon-α plays a role in the pathogenesis of anti-TNF-α therapy-induced psoriasis [22, 27]. Charles et al. found that in patients with RA, the serum TNF-α level dose-dependently increased after the infusion of infliximab but that the elevated serum TNF-α was not biologically active [28]. Based on preliminary evidence, Charles et al. suggested that an underlying mechanism for the elevated serum TNF-α may be the formation of a high molecular weight complex with infliximab [28]. The use of etanercept and infliximab may lead to the production of antibodies against the drugs [29]. Previous studies found that the presence of anti-infliximab antibodies (ATI) was correlated with a high serum TNF-α level, and the serum TNF-α level was higher in patients with active disease and could not be suppressed with the recommended dose of infliximab [30, 31]. Further studies are necessary to determine whether anti-drug antibodies contributed to the elevated TNF-α level in our study.

We discovered that late onset of skin manifestations of SAPHO syndrome was associated with exacerbated or newly developed skin lesions after anti-TNF-α treatment. Age at onset was discovered to be a key factor for stratification of genetic and clinical features of psoriatic disease [32–35]. Late-onset (≥ 40 years) psoriasis is associated with more sporadic pattern, less extensive skin disease, and less HLA-C06 positivity [33]. We hypothesized that the genetic heterogeneity among patients with different age at onset might be relevant to the development of paradoxical cutaneous lesions. Cabaleiro et al. identified five SNPs associated with paradoxical psoriasiform reactions [36], of which two (rs11209026 in IL23R and rs10782001 in FBXL19) have been reported to be related to age at onset in psoriatic disease [37, 38]. However, they were both associated with earlier onset. Given the differences in genetic features between psoriasis and SAPHO syndrome [39], further investigation is needed to uncover the underlying mechanism of such phenomenon. Previously, Guerra et al. reported that women and smokers had an increased risk of developing new skin lesions induced by TNF-α antagonists in patients with IBD [21]. However, we found no difference in the sex ratio between the two groups.

Important limitations of this study include the retrospective design and the small study population. Moreover, only in a

small number of patients (two out of seven), the tissue and serum TNF-α levels were determined. Future prospective studies including measurement of both tissue and serum TNF-α levels may help further unveil the pathogenesis of paradoxical skin lesions in SAPHO syndrome.

In summary, this study demonstrated that while effective for osteoarticular manifestations, anti-TNF-α therapy may induce severe psoriasiform lesions in 17.1% patients with SAPHO syndrome. Late onset of cutaneous manifestations is associated with increased risk of such paradoxical skin lesions. This phenomenon may be related to the paradoxically increased TNF-α expression in the pathological tissue.

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Compliance with ethical standards

The study was approved by the Ethics Committee of Peking Union Medical College Hospital, Peking Union Medical College, and Chinese Academy of Medical Sciences (ethics documents number ZS-944). All individual participants provided written informed consent to participate in this cohort at the time of inclusion.

Disclosures None.

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