

Failure of tocilizumab in treating two patients with refractory SAPHO syndrome: a case report

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Abstract

Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome is a rare autoinflammatory disease with no standard treatment. Interleukin (IL)-6 inhibitors represent a novel therapeutic option for rheumatoid arthritis and some autoinflammatory diseases. However, the clinical utility of IL-6 inhibitors in treating SAPHO syndrome has been poorly investigated. In the present report, we describe two patients with SAPHO syndrome that was unresponsive to conventional treatment. Tocilizumab, an anti-IL-6 receptor monoclonal antibody, was putatively administered according to positive IL-6 immunohistochemical staining in biopsied bone tissues. However, the disease continued to progress, and new-onset or worsening skin lesions were noted with transient neutropenia. These cases demonstrate that tocilizumab may not be an ideal option for treating SAPHO syndrome.

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Keywords

SAPHO syndrome, tocilizumab, interleukin-6, failure, neutropenia, immunohistochemistry, disease progression

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Introduction

Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome is a rare autoinflammatory disease with an enigmatic pathogenesis characterized by both osteoarticular manifestations and cutaneous lesions.¹ No standard treatment has yet been established. Nonsteroidal anti-inflammatory drugs (NSAIDs) are generally insufficient to control the disease, and no definite effect of disease-modifying anti-rheumatic drugs (DMARDs) has been proven.¹ Some recent evidence suggests the clinical utility of bisphosphonates and biological agents, especially tumor necrosis factor (TNF) inhibitors.^{2,3} However, physicians may encounter intractable cases and patients with contraindications for these drugs in clinical practice, indicating the need to develop novel therapeutic targets.

As a proinflammatory cytokine, interleukin (IL)-6 may play a pivotal role in the pathogenesis of rheumatoid arthritis (RA) and some autoinflammatory diseases; it has thus attracted significant attention as a prominent therapeutic target in these disorders.⁴ To date, the efficacy and safety of IL-6 inhibitors in the treatment of SAPHO syndrome or adult-onset chronic recurrent multifocal osteomyelitis has only been explored in two case reports, and opposite outcomes were observed.^{5,6} We herein report two cases of SAPHO syndrome with disease progression and unexpected neutropenia after treatment with tocilizumab (TCZ), an anti-IL-6 receptor monoclonal antibody.

Case report

Written informed consent was obtained from both patients for publication of this case report, and the study was approved by the Ethics Committee of Peking Union Medical College Hospital and Chinese Academy of Medical Sciences.

Case 1

A 53-year-old woman noted palmoplantar pustulosis after eating seafood with spontaneous remission in 2008. Thereafter, she developed gradual swelling and moderate pain in the bilateral sternoclavicular joints with a marked elevation of her erythrocyte sedimentation rate (ESR). Whole-body bone scintigraphy (WBBS) revealed tracer concentration in the superior margin of the sternum. Pathological examination following a sternal biopsy suggested aseptic chronic osteomyelitis. After treatment with antibiotics, her symptoms were temporarily relieved. In 2011, the patient presented with pain in the anterior chest wall (ACW), thoracic and lumbar vertebrae, and left hip. Magnetic resonance images of the spine obtained with various sequences indicated vertebral compression and multiple lesions with abnormal signals, which were suggestive of bone marrow edema and deposition of fat. A biopsy of the right sternoclavicular joint indicated pathological changes in accordance with chronic inflammation. The patient was therefore diagnosed with SAPHO syndrome according to the criteria proposed in 1988.⁷ A 1-month treatment

regimen involving administration of NSAIDs and DMARDs was accordingly initiated, resulting in moderate improvement of her osteoarticular symptoms and a significant decrease in her ESR. However, the cutaneous abnormalities did not improve. In 2013, painful swelling of the ACW, vertebrae, and left hip relapsed with stiffness and limitation of activity in the cervical and lumbar regions. The ESR was also notably elevated. Various types of DMARDs were tentatively administered in sequence. Nevertheless, her symptoms were not resolved, and the bone lesions persisted as shown by further magnetic resonance imaging and WBBS examinations (Figure 1(a)). In 2015, bisphosphonate treatment was started, resulting in rapid remission of both her symptoms and inflammatory markers (Figure 1(b)). Nevertheless, the palmoplantar pustulosis and painful swelling of the axial skeleton reappeared and became progressively aggravated in 2017 (Figure 1(c)). Consequently, the patient was admitted to our hospital. She had undergone a thyroidectomy due to papillary thyroid carcinoma

in 2014, but no family history of similar symptoms was reported.

On admission, the patient had a significantly elevated ESR, serum IL-6 level, and serum TNF- α level. The WBBS results showed multifocal osteoarticular lesions in the ACW, vertebrae, and left sacroiliac joint with a typical “bull’s head” sign, indicating more progressive involvement of the osteoarticular system when compared with the findings in the last WBBS. Considering that the patient was not responding to conventional treatment with NSAIDs, DMARDs, and bisphosphonate, we intended to use biological agents. We performed a puncture biopsy of the T9 vertebra, and the tissue was immunohistochemically positive for both IL-6 and TNF- α . Although most of the currently available evidence suggests no association between TNF inhibitor therapy and overall cancer risk, some conflicting evidence suggests the contrary.⁸ However, according to the current literature, patients with RA treated with an IL-6 antagonist do not have a statistically increased risk of malignancies.⁹ Because our patient had a history of thyroid carcinoma,

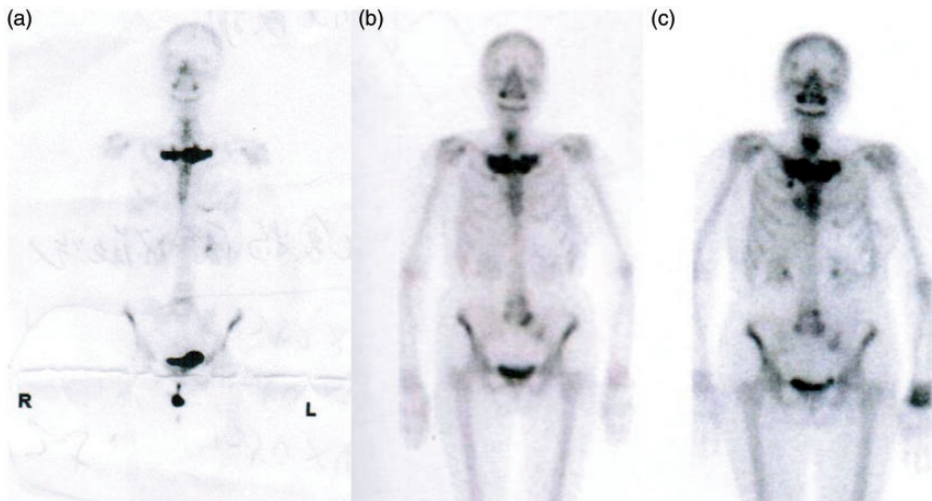


Figure 1. Imaging examinations of the first patient. Whole-body bone scintigraphy in (a) 2010, (b) 2015, and (c) 2017 showed persisting lesions. R, right; L, left

we discussed with her the potential risk of tumor recurrence, and she finally decided to take TCZ instead. After obtaining written informed consent, TCZ was tentatively administered at a dose of 8 mg/kg body weight. Despite a rapid decrease in the ESR, her existing osteoarticular and cutaneous manifestations became aggravated and a new-onset painful swelling of the left wrist appeared. With limited choices, corticosteroid treatment was initiated despite the fact that it had been previously avoided due to the risk of exacerbation of vertebral compression. The patient's condition was then partially improved. Additionally, the patient developed transient severe neutropenia with a neutrophil count of $380/\mu\text{L}$ on the second day after the introduction of TCZ. Consequently, TCZ therapy was stopped and the neutropenia resolved spontaneously in 10 days with no indication of infection during this period.

Case 2

A 29-year-old woman developed progressively severe pain in the bilateral sternoclavicular joints, shoulders, and posterior neck in May 2016. She also noted swelling of the left clavicle and motion restriction of the shoulders. Four months later, she presented with pain in the right mandible after tooth extraction and recovered after NSAID treatment. Thereafter, relapses of osteoarticular pain after NSAID withdrawal were reported with an elevation of inflammatory markers (serum IL-6 and serum TNF- α). Chest computed tomography (CT) demonstrated osteolysis and osteosclerosis in the sternum and left clavicle and swelling of the surrounding tissue. WBBS revealed multifocal lesions with abnormal tracer uptake in the bilateral sternoclavicular joints, first anterior rib, maxilla, and mandible. Histological examination following a sternal biopsy suggested chronic inflammation. Based on the patient's osteoarticular

manifestations, typical imaging findings, and pathological changes, the diagnosis of SAPHO syndrome was established. Because the patient responded well to NSAIDs, no DMARDs or biological agents were prescribed. In February 2017, her symptoms relapsed again and she was admitted to our hospital. No family history of similar symptoms was reported.

On admission, the patient's ACW was diffusely tender and her ESR, serum IL-6 level, and TNF- α level were elevated. Extensive osteolytic lesions in the mandible were demonstrated by three-dimensional CT reconstruction (Figure 2(a)). Although NSAIDs temporarily relieved the pain, they did not prevent disease progression as evidenced by the gradual aggravation of symptoms and imaging findings. Considering the patient's high demand for fertility preservation, DMARDs would have had to be used with caution. Accordingly, biological agents were recommended. Immunohistochemical assays of the sternal biopsy specimen indicated IL-6 positivity (Figure 3(a)) and TNF- α negativity (Figure 3(b)), suggesting possible ineffectiveness of anti-TNF- α agents and a potential benefit of TCZ therapy. After obtaining written informed consent from the patient, TCZ therapy was begun at a dose of 8 mg/kg. After the first administration, the pain in the affected joints rapidly resolved and the abnormally high levels of inflammatory markers decreased to the reference ranges. Nevertheless, the patient complained of painful swelling of the left mandible and reduced mouth opening 1 month later (Figure 2(b)). Additionally, she experienced worsening of the pain in the ACW, neck, and shoulders with new-onset scattered pustular rashes on the upper and lower limbs. Although the inflammatory markers remained normal, radiography demonstrated significant progression of the osteolytic damage in the mandible. Bisphosphonate and minocycline

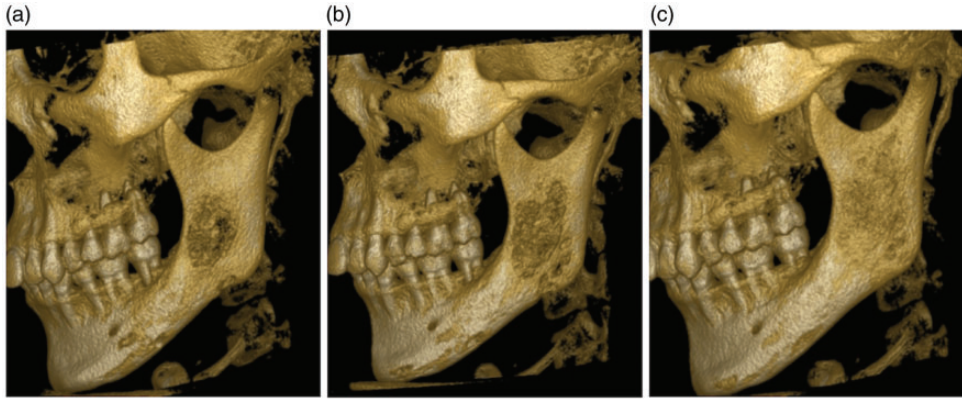


Figure 2. Three-dimensional computed tomography (CT) reconstruction in Patient 2 before and after tocilizumab treatment. (a) Extensive osteolytic lesions in the mandible were demonstrated by three-dimensional CT reconstruction on admission. (b) Aggravation of the mandibular lesions was revealed 1 month after tocilizumab treatment (c) Improvement of the mandibular lesions was shown by CT scans 3 months after treatment

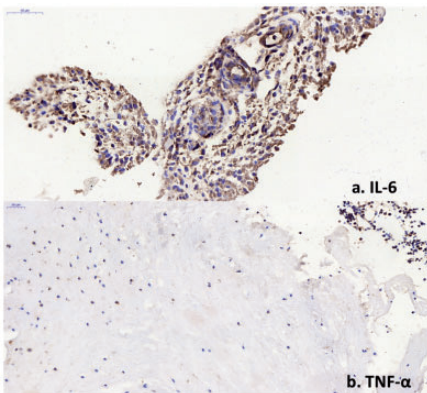


Figure 3. Immunohistochemical staining of the sternal bone in Patient 2. IL-6 assays of the sternal biopsy specimen indicated (a) IL-6 positivity and (b) TNF- α negativity, suggesting the potential benefit of tocilizumab therapy. IL-6, interleukin-6; TNF- α , tumor necrosis factor- α

were then prescribed and seemed to effectively relieve the pain and rashes. Improvement of the mandibular lesions was also illustrated by CT scans performed 3 months later (Figure 2(c)). Severe neutropenia was noted after the administration of

TCZ. However, the neutrophil count spontaneously returned to the normal range approximately 1 week later, and no infection developed.

Discussion

We have herein described two patients with SAPHO syndrome who achieved unsatisfactory remission after TCZ treatment. No evidence suggesting a potential contribution of IL-6 to the underlining pathology of SAPHO syndrome is currently available. We tentatively prescribed TCZ treatment exclusively based on the positive immunohistochemical result of IL-6 in the biopsy tissues. However, new-onset arthritis in the peripheral joints and/or exacerbation of existing osteoarticular involvement was noted, implying that the histopathological findings were not sufficient to justify IL-6 direct intervention. Additionally, we speculate that IL-6 is not an ideal target for clinical intervention in patients with SAPHO syndrome, or at least during certain periods of the disease course. Accordingly, as mentioned by Trotta et al.,¹⁰ clarifying the

pathogenesis is the greatest challenge to optimize the treatment of SAPHO syndrome.

In previous studies, TCZ has reportedly induced or worsened psoriatic skin lesions in patients with RA.^{11,12} One possible explanation is that suppression of the IL-6 pathway results in compensatory proinflammatory effects by other cytokines, ultimately exacerbating psoriatic inflammation.¹¹ Similar dermatological adverse effects were also observed during treatment with other biological agents, especially anti-TNF- α agents, in patients with other chronic immune-mediated disorders.¹² In line with these findings, progression or new onset of cutaneous manifestations was noted in both of our patients after TCZ treatment. However, these two patients developed pustular rashes instead of psoriatic lesions. The precise mechanism remains unclear, but this phenomenon should raise concerns about the use of TCZ and other biological agents.

In both of our patients, the neutrophil count markedly decreased rapidly after TCZ treatment. However, spontaneous recovery after TCZ withdrawal was observed without accompanying infection during this period. In prior studies, a higher incidence of neutropenia was noted in patients with RA undergoing TCZ treatment, which may be associated with inhibition of the effect of IL-6 on recruiting neutrophils into the peripheral blood.¹³ In a pooled analysis of data from clinical trials, neutropenia induced by TCZ was usually transient and not linked to an increased risk of serious infection.¹⁴ Therefore, TCZ may be a safe treatment despite the fact that neutropenia sometimes appears.

Conclusion

In our cases, TCZ showed a limited therapeutic effect and may have induced worsening of the patients' osteoarticular and cutaneous manifestations and development of transient

severe neutropenia in the treatment of refractory SAPHO syndrome. Therefore, we do not recommend the use of TCZ in patients with SAPHO syndrome regardless of IL-6 positivity in the biopsy tissue.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Authors' contributions

X. Sun, S. Liu, W. Hao, and C. Li conceptualized the manuscript. S. Zhang and X. Shi interpreted the immunohistochemical staining. M. Wang performed the mandible evaluation. W. Zhang provided guidance in the treatment. X. Sun and S. Liu prepared the manuscript. All authors approved the final version of the manuscript.

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