CASE REPORT
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A Case of Successful Treatment of Refractory Synovitis Acne Pustulosis Hyperostosis Osteitis (SAPHO) Syndrome with Adalimumab

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Synovitis acne pustulosis hyperostosis osteitis (SAPHO) syndrome is a rare disease that involves the skin, bones and joints. It is thought to be caused by infection with low-toxicity bacteria and to be the result of reactive infectious osteitis. However, this hypothesis has not yet been clearly established. New SAPHO syndrome treatment methods are needed because the disease does not respond to treatment in many cases. In this paper, a case is reported of SAPHO syndrome with pain in the acromioclavicular joint and with squamous and pustular macules on the palms and soles. First, the patient was treated with aceclofenac, prednisolon and sulfasalazine for two weeks. However, the symptoms were not relieved, so methotrexate and pamidronate were added to the treatment. Since no improvement was seen after four weeks of treatment, adalimumab was prescribed. The skin lesions were relieved two weeks later, and the bone pain and arthralgia, four weeks later. No recurrence or adverse effects were observed at the 22-week follow-up.

Key Words: SAPHO syndrome, Treatment, Adalimumab

INTRODUCTION

Synovitis acne pustulosis hyperostosis osteitis (SAPHO) syndrome, which was first recognized by Kahn et al. in 1987, is characterized by synovitis acne pustulosis hyperostosis osteitis.[1] Its clinical manifestations are not specific but they are characterized by various forms of invasion of the bones and joints. Therefore, there is no established diagnostic criteria currently. Also, due to the low incidence rate of SAPHO syndrome, there are no randomized controlled clinical trials nor any adequate treatment guidelines. However, according to small case series and expert judgments, nonsteroidal anti-inflammatory drugs (NSAIDs), methotrexate, cyclosporine, sulfasalazine, and tumor necrosis factor (TNF)-α inhibitors can be used to treat SAPHO syndrome.[2]

A case of SAPHO syndrome treated with etanercept, a TNF-α inhibitor, was reported in 2012 in Korean literature; but there has been no report on a case treated with adalimumab, another TNF-α inhibitor, previously.

Therefore, we report a case of successful treatment of refractory SAPHO syndrome with adalimumab.

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CASE

Patient: A 39-year-old man

Chief complaints: Pain in the chest region with squamous and pustular macules on the palms and the soles

Present medical history: The patient had previously been in good health. He had visited a clinic approximately one year earlier due to pain in the chest and the acromioclavicular (AC) joint and the gradual development of squamous and pustular macules from pustular lesions on the palms and the soles. These lesions were diagnosed and treated with pom-

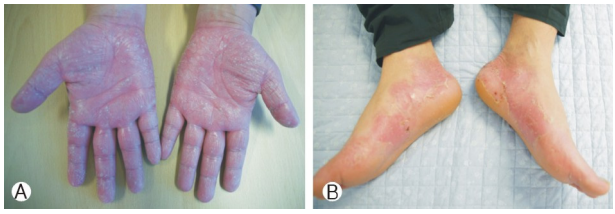

Fig. 1. Palmoplantar pustulosis was seen on his both hands (A) and feet (B).

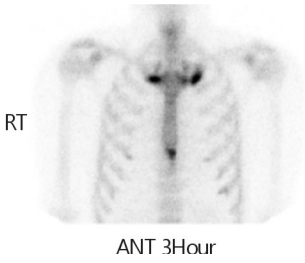

Fig. 2. Whole body bone scan shows increased uptake at bilateral sternoclavicular areas and distal end of sternum.

pholyx at the clinic, but the symptoms were not relieved. They were diagnosed as palmoplantar pustulosis at the department of dermatology of this hospital.

Past history: No past medical history note.

Physical findings: Mean blood pressure, heart rate, respiratory rate, and body temperature were normal. He had tenderness on AC joint, sternoclavicular joint, and sacroiliac joint (Schober's test: 4 cm), and squamous and pustular macules on the palms and the soles (Fig. 1).

Laboratory findings: In peripheral blood tests, white blood cells, hemoglobin, and platelets were within normal range at 9,110 cells/mm^3, 13.7 g/dL, and 325,000 cells/mm^3, respectively. Whereas C-reactive protein (CRP) the erythrocyte sedimentation rate (ESR) were increased: 1.37 mg/dL (normal value: 0-0.5 mg/dL) and 39 mm/hr (normal value: 0-17 mm/hr), respectively. In biochemical tests, aspartate transaminase (AST), alanine transaminase (ALT), and creatinine were normal: 22 IU/L, 34 IU/dL, and 1.1 mg/dL, respectively. Tests for fluorescent anti-nuclear antibody and rheumatoid factor were negative. In tumor marker tests, no special findings were observed, but HLA-B27 was positive.

Radiological findings: In whole body bone scan, increased uptake was observed in the sternoclavicular joint and at the end of the sternum (Fig. 2). Moderate subchondral sclerosis and cortical erosion was observed on computed tomography (CT) images of the sacroiliac joint (Fig. 3).

Clinical progress and treatment: The patient was diagnosed with SAPHO syndrome based on the results of the whole body bone scan and sacroiliac joint computed tomography and palmoplantar pustulosis.

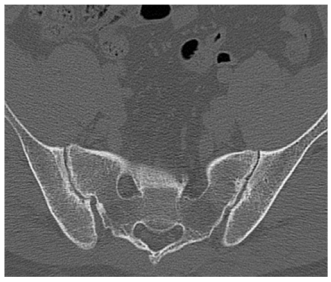

Fig. 3. CT scan shows moderate subchondral sclerosis and cortical erosion at the both sacroiliac joints.

Aceclofenac 100 mg bid, prednisolon 7.5 mg qd, and sulfasalazine 1,000 mg bid were administered for two weeks, but the symptoms were not relieved. The patient also newly complained of pain in the right sacroiliac joint. Therefore, methotrexate 7.5 mg/week and pamidronate 30 mg/week were used for four weeks. The addition of these drugs failed to relieve symptoms of the skin and joint. Therefore, the patient was diagnosed with refractory SAPHO syndrome, and treatment with adalimumab 40 mg/week was started for four weeks and reduced to 40 mg every other week. Two weeks after treatment with adalimumab, the skin lesions were relieved. After four weeks, there was marked remission of anterior chest and sacroiliac pain. The the visual analogue scale (VAS) score evaluated before beginning the treatment with adalimumab was 7.5/10, and the health assessment questionnaire (HAQ) score was 1.5. After six weeks of the treatment, the VAS score had decreased to 2.5/10, and the HAQ score had decreased to 0.6.

There were no adverse effects associated with adalimumab during the treatment, and there was no recurrence of clinical symptoms (arthralgia and palmoplantar pustulosis) for 22 weeks.

DISCUSSION

SAPHO syndrome is characterized by various forms of bone and joint invasion with chronic skin manifestations such as palmoplantar pustulosis or severe acne. Its prevalence rate is assumed to be lower than 1/10,000.[2] Although it is known to frequently occur in women in all age groups, data on actual onset indicate that it frequently occurs in children, young adults, and middle-aged people.[3]

Although its aetiology remains unclear, infection by *Propionibacterium acnes* is considered to be associated with the onset of disease. A recent study demonstrated positive micro-

biological cultures for *P. acnes* in 42-67% of bone biopsy in patients with SAPHO syndrome.[4,5] This supports the hypothesis that interleukin (IL)-1, IL-8, IL-18, and TNF-α are expressed in response to immunoreactions against low-toxic pathogenic bacteria (i.e., *P. acne*) and that the resultant reactive infectious osteitis causes SAPHO syndrome.[5]

SAPHO syndrome can be diagnosed based on clinical conditions and radiological findings. SAPHO syndrome should always be suspected if patients have inflammatory skin lesions and inflammatory bone and joint lesions. It should be diagnosed when the patient's conditions satisfy one of the diagnostic criteria for SAPHO syndrome of the European Spondyloarthropathy Study Group.[6] Among radiological diagnostic methods, simple radiography, bone scans (99-Tc), and CT are useful for diagnosis. This syndrome shows sclerosis (77.3%), erosions (44%), hyperostosis (41%), invades the sternoclavicular joint (72.7%), followed by the manubriosternal joint (34.1%), and the sacroiliac joint (20.5%) in CT scan.[7]

First-line therapy of SAPHO syndrome is based on NSAIDs and topical agent for skin lesion. If there is no response, disease modifying anti-rheumatic drugs (methotrexate, cyclosporine, and sulfasalazine), corticosteroid, bisphosphonate can be tried as second-line therapies. In refractory cases who do not respond any treatment, TNF-α antagonists are usually administrated as third-line therapy.[8] However, due to the low prevalence rate of this disease, neither randomized controlled clinical trials of the individual drugs nor treatment guidelines have been established yet.

Treatment with infliximab, etanercept, and adalimumab as TNF-α antagonists has been reported.[2,8] In patients treated with these agents, the symptoms subsided quickly in most cases after 1-4 infusions. When each TNF-α antagonists is not effective or when the agent causes side effects such as the aggravation of skin lesions, replacing it with another TNF-α antagonists was effective. Among the three agents, infliximab is frequently least effective on skin lesions and in some cases, it caused aggravation of skin lesions in some cases.[8]

Recently, a short-term study indicated that patients with refractory SAPHO syndrome showed relief of their symptoms and decrease in C-reactive protein values following treatment with anakinra, an IL-1 receptor antagonist.[9]

The present case suggests that TNF-α antagonists can be effective in refractory SAPHO syndrome which does not respond to treatment with NSAIDs, corticosteroids, methotrexate, and sulfasalazine and that adalimumab can be effective in patients with severe skin diseases, in particular.

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