

CASE REPORT

SAPHO syndrome in which certolizumab pegol was effective: A case report

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ABSTRACT

A 45-year-old male suffered from persistent swelling and redness, with pain in his left lower leg and ankle. Pathological findings isolated from the ankle joint by arthroscopic synovectomy showed mild synovitis. Initially, this case was diagnosed as chronic mild arthritis and later treated as phlegmon because of the persistent redness and swelling inflammatory findings in his left lower leg. A systemic survey was performed. Based on the findings—such as chronic ankle arthritis with ipsilateral plantar pustulosis, chronic recurrent multifocal osteomyelitis in left distal tibia with magnetic resonance imaging (MRI), calcaneal osteitis with computed tomography, and pathological findings that neither malignant tumor nor infection was detected—this case reached the definitive diagnosis of SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome. The hot spots detected in the bilateral sternoclavicular and costosternal joints with bone scintigraphy and their arthritic change detected by computed tomography also supported the diagnosis of SAPHO syndrome. This case was refractory to nonsteroidal antiinflammatory drugs (NSAIDs); therefore, the TNF inhibitor certolizumab pegol was tried. This agent rapidly improved not only the chief complaints but also the objective symptoms and laboratory findings at most six weeks after its administration.

Keywords: SAPHO syndrome; certolizumab pegol; plantar pustulosis; sternoclavicular arthritis; chronic recurrent multifocal osteomyelitis

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Introduction

SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome is a condition that was proposed by Chamot *et al.* in 1987^[1] and characterized by aseptic osteoarticular lesions complicating pustular skin lesions. We report a patient with SAPHO syndrome who showed a prominent effect of the tumor necrosis factor (TNF) inhibitor certolizumab pegol.

It is difficult to acquire the definitive diagnosis of SAPHO syndrome because of insufficient findings. Initially, this case was diagnosed as chronic mild arthritis and later treated as phlegmon because of the persistent redness and swelling of left lower leg with inflammatory findings. A systemic survey including computed tomography, bone scintigraphy, magnetic resonance imaging (MRI), and biopsy enabled us to acquire the definitive diagnosis of SAPHO syndrome. This case was refractory to nonsteroidal antiinflammatory drugs (NSAIDs); thus, TNF inhibitor certolizumab pegol was tried. This agent rapidly improved not only the chief complaint but also the objective symptoms and laboratory findings six weeks after its administration.

Case presentation

A 45-year-old male had been suffering from persistent redness and diffuse swelling and eruption in his left lower leg and ankle joint since 2013. His history included alcoholic chronic pancreatitis, and partial pancreatectomy was performed in 2010. In addition, his condition was complicated with pancreatic diabetes mellitus (DM) and was treated with insulin. In 2014, he was diagnosed with neutrophilic dermatitis by a dermatologist. In 2015, his

left ankle joint was remarkably swollen; hence, he consulted our facility. No swelling was detected in any other joints. Arthroscopic ankle synovectomy was performed, and pathological examination demonstrated nonspecific mild synovitis (**Figure 1A and B**). Bone marrow punctation was performed in January 2015 to detect any bone-marrow-associated diseases and showed normocellular marrow. At this stage, this case did not reach a definitive diagnosis. Eventually, contracture occurred in his left ankle joint and metatarsophalangeal joints. In November 2016, the redness, local heat, and swelling worsened in his left calf and ankle joint (**Figure 2A and C**). Apart from these findings,

he felt chronic pain. Plain radiograph images demonstrated slightly narrow talocrural joint space (**Figure 3A**), enthesopathy in the insertions of the calcaneal tendon, and plantar aponeurosis (**Figure 3B**). Blood test revealed elevated inflammatory parameters, including C-reactive protein (CRP) at 11.4 mg/dL and erythrocyte sedimentation rate (ESR) at 97 mm/h; IgG (2369 mg/dL; reference range; 861–1747 mg/dL) and IgA (612 mg/dL; reference range; 93–393 mg/dL) were also upregulated, but were otherwise unremarkable. The rheumatoid factor was less than 5 IU/mL, antinuclear antibody was 12.0 times, serum MMP-3 was 59.8 ng/mL (within normal), and neither myeloperoxidase-anti-

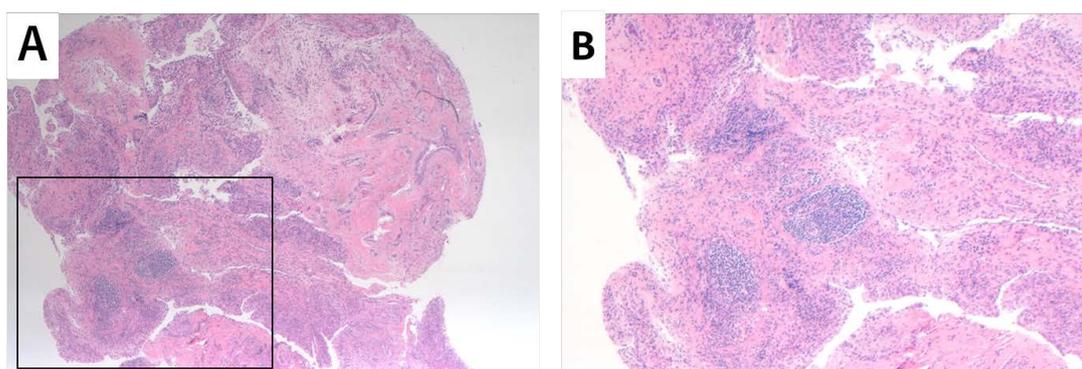


Figure 1. Microscopic findings isolated from synovium (hematoxylin and eosin staining). (**A**): Nonspecific and very mild synovitis is detected; magnification 20 \times . Rectangle area of (**A**) shows (**B**) lymphoid follicle formation is sparsely observed; magnification 40 \times .



Figure 2. Macroscopic findings of the left lower leg and foot before and after certolizumab use. Before certolizumab use, left lower leg showed swelling and redness especially around the ankle joint (**A and C**). Pustulosis was detected in medial plantar skin (**C**). After treatment of certolizumab for six weeks, swelling and redness remarkably improved and pustulosis disappeared (**B and D**).

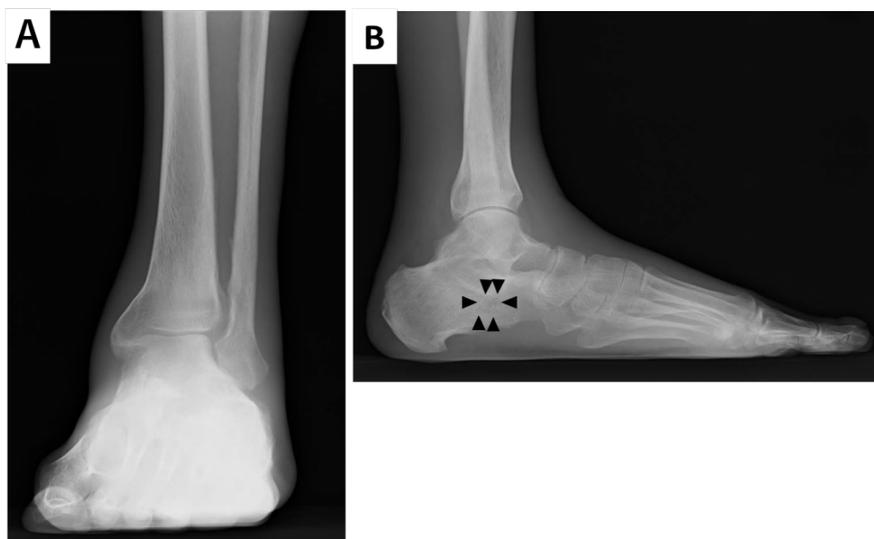


Figure 3. Plain radiograph of the left ankle and foot. Talocrural joint space is narrow in A–P view (A). In lateral view, cystic lesion in calcaneus body (arrow heads) is shown. Enthesitis in the insertions of calcaneal tendon and plantar tendinous membrane is also detected (B).

neutrophil cytoplasmic antibody (MPO-ANCA) nor proteinase 3 (PR3)-ANCA were more sensitive. He was initially diagnosed with phlegmon of the left lower leg and ankle and was treated with antibiotics such as levofloxacin, cephazolin, clindamycin, and meropenem for two months. However, no improvement occurred with antibiotic therapy. In addition, plain radiographs showed a 1-cm sized cystic lesion in the calcaneal body (**Figure 3B**, black arrowheads). Subsequently, systemic computed tomography and bone scintigraphy were performed, and a lower leg MRI was further evaluated. Bone scintigram detected hot spots in the left lower leg and ankle joint and bilateral sternoclavicular and costosternal joints (**Figure 4A**). In computed tomography, bilateral sternoclavicular joints were destructive (**Figure 4B**, black arrowheads) and costosternal joints were also destructive and changed (**Figure 4C**, black arrow heads) in accordance with hot spots in bone scintigram. MRI of bilateral lower legs showed intensity change (T1 low intensity and T2 high intensity) in bone marrow of the left distal tibia, and diffuse swelling and intensity change in the soft tissue of the left lower leg (**Figure 5**), suggesting chronic recurrent multifocal osteomyelitis (CRMO). Biopsy from the bone cystic lesion and calf muscle was performed in January 2017. Neither malignant nor bacterial infections were detected in microscopic findings of bone and skin tissues (**Figure 6A–C**).

Laboratory findings demonstrated that anti-CCP antibody and rheumatoid factor were less than the reference value, and in ACR/EULAR criteria (2010), the arthritic score was 2. So, rheumatoid arthritis

was ruled out. Antinuclear antibody and other auto-antibodies such as PR3-ANCA and MPO-ANCA were negative, so other collagen diseases were ruled out. Serum ferritin was 61 ng/mL (reference range: 13–277 ng/mL), so adult onset Still disease was ruled out.

Based on the findings of chronic arthritis in the left ankle associated with left plantar pustulosis, CRMO in left distal tibia, bilateral sternoclavicular and costosternal arthritis, and considering that the biopsy from bone marrow and muscle ruled out malignancy and infectious disease, he was finally diagnosed with SAPHO syndrome.

He refused oral drug so we did not induce methotrexate but biologics. He selected certolizumab pegol (CZP) as the sole treatment of his SAPHO syndrome because his symptoms did not improve with NSAIDs alone. CZP was his choice among the TNF inhibitors, as a subcutaneous injection with an administration interval fit for him. The amount and dosing schedule of CZP were exactly same as those used in the treatment of rheumatoid arthritis.

Just before the treatment with CZP, CRP was 5.71 mg/dL and ESR was 88 mm/hr. CZP downregulated CRP to 0.71 mg/dL and ESR to 25 mm/hr immediately after the loading treatment. In addition, the left calf swelling remarkably improved and plantar pustulosis disappeared (**Figure 2B** and **D**). The left ankle joint's range of motion improved by 10° both in dorsiflexion as well as in plantar flexion. His chief complaint (visual analogue scale) prominently

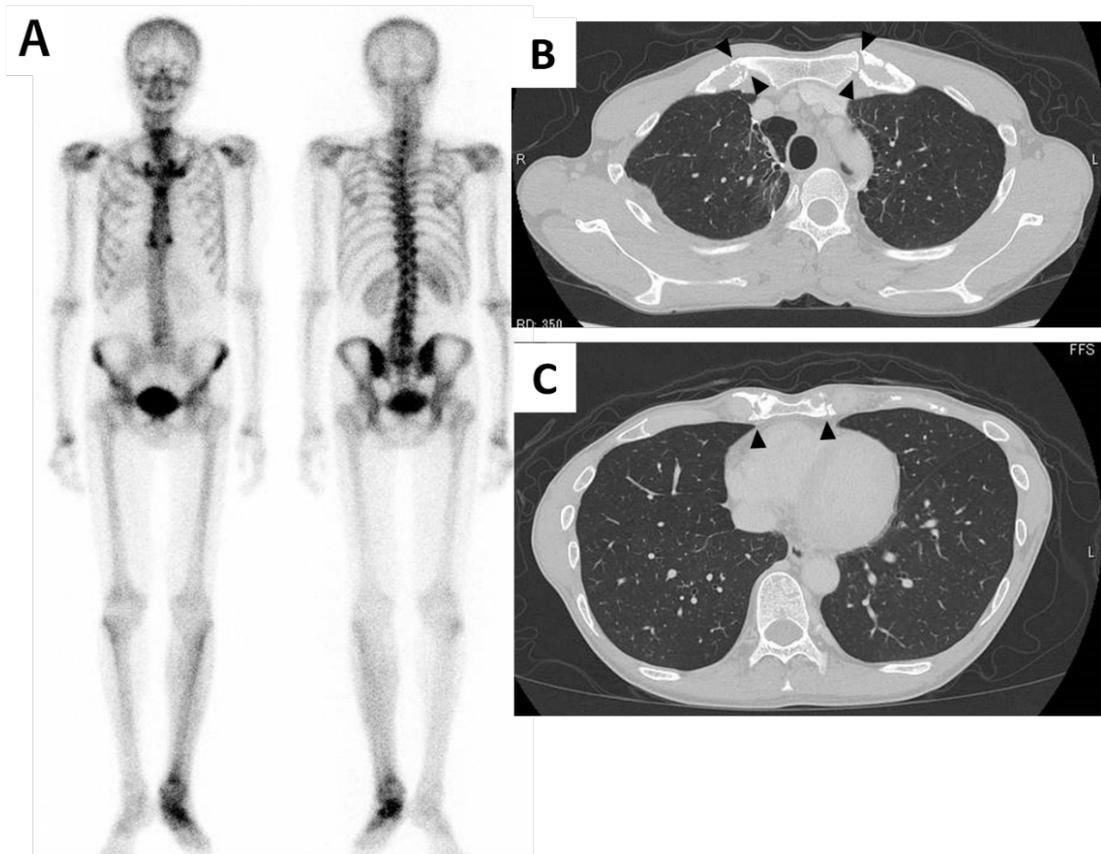


Figure 4. Bone scintigram of 99m technetium–MDP of the whole body. Hot spots were detected in the left ankle and distal tibia, bilateral sternoclavicular joints, and costosternal joints (A). Computed tomography demonstrates that bilateral sternoclavicular joints were destructive (B, black arrow heads) and costosternal joints were also destructive and changed in accordance with hot spots in bone scintigram (C, black arrow heads).

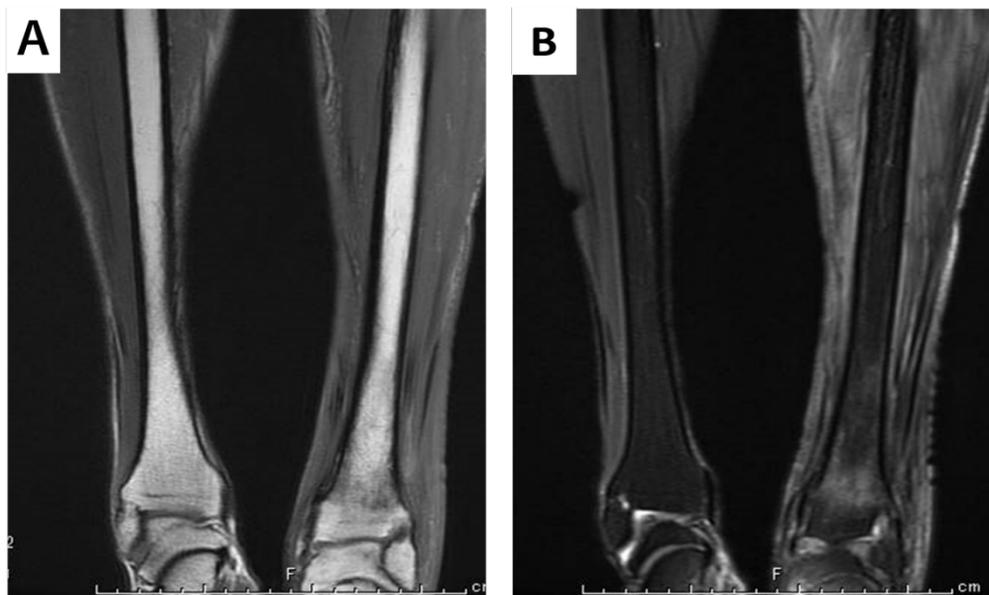


Figure 5. Plain MRI view of the left lower leg. T1-enhanced view (A) shows low intensity and T2-enhanced view (B) shows higher intensity region in left distal tibia (coronal view). Furthermore, soft tissue adjacent to the left distal tibia was more swollen than that in right distal tibia.

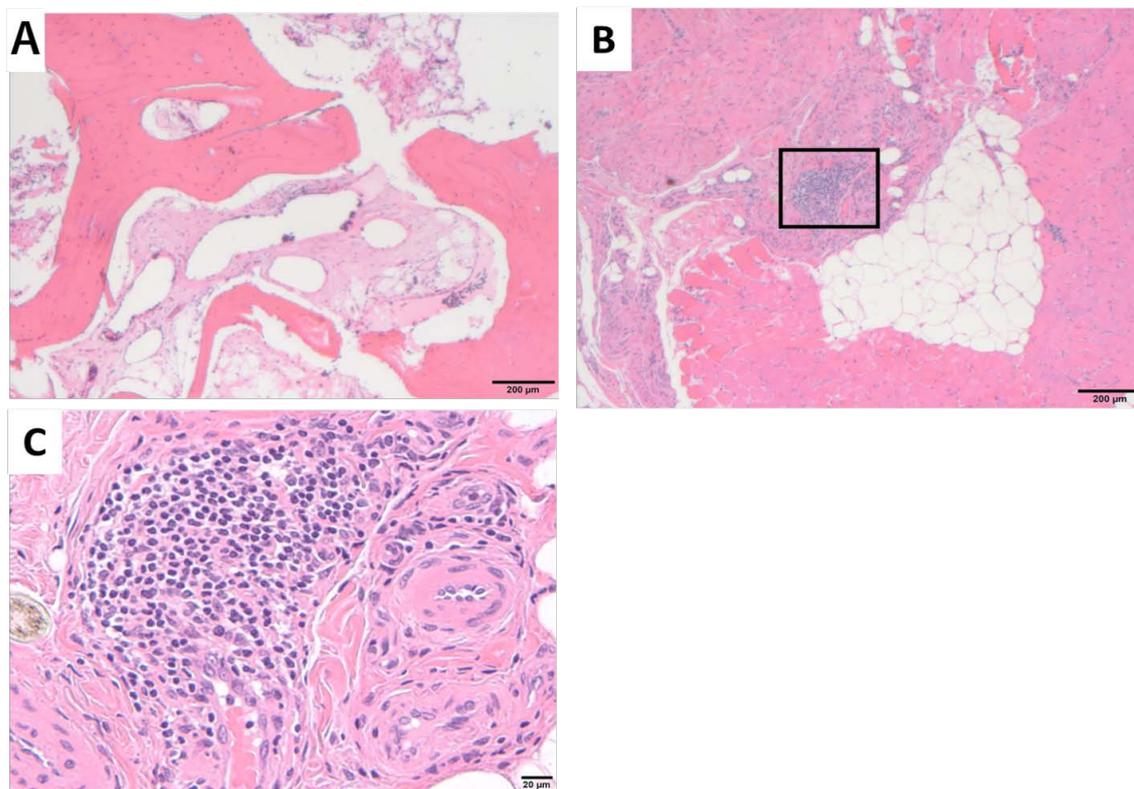


Figure 6. Microscopic findings from bone and muscle biopsy. Bone tissue demonstrates that no osteoid formation was detected, and no atypical plasma cells were detected in bone marrow, suggesting no malignancy (A); original magnification: 40×. In the skin tissue, the infiltration of lymphocytes (B, black rectangle frame) is detected between fat and muscle layers, suggesting chronic inflammation; original magnification: 40×. (C): Enlargement findings of (B) (skin tissue); original magnification: 200×.

improved from 100 to 30 at the time point just after the loading treatment (six weeks) of CZP. He had no adverse event with CZP therapy.

Discussion

This case was difficult to diagnose as SAPHO syndrome, and it took four years to determine this diagnosis.

Positive findings were CRMO in the left distal tibia with ipsilateral plantar pustulosis, chronic ankle arthritis of left ankle joint, and left calcaneal osteitis (cystic change) associated with ipsilateral pustulosis. The findings of hot spots in bilateral sternoclavicular and costosternal joints with technetium-99m bone scintigraphy supported the definitive diagnosis. In addition, malignant tumor and infectious diseases were ruled out with bone and skin biopsies. Although this case did not show axial spondyloarthritis, enthesopathies in the insertions of calcaneal tendon and plantar aponeurosis suggested peripheral spondyloarthritis.

We finally verified that this case fulfilled the diagnostic criteria proposed by Kahn *et al.*^[2] and also excluded infectious osteitis, tumoral conditions of the bone, and noninflammatory condensing lesions of the bone^[2,3] and then confirmed the diagnosis of SAPHO syndrome. In this case, bone marrow change was considered as CRMO. This case was atypical in that the CRMO lesion was detected despite of an adult case (not a child).

Concerning the laboratory test, elevated inflammatory response is usually observed in patients with SAPHO syndrome. In addition, IgA upregulation has been previously reported in a cohort of 29 SAPHO patients^[4,5]. In our report, IgA was also upregulated; hence, it could be useful for the definitive diagnosis of SAPHO syndrome.

The treatment of SAPHO syndrome has not been estimated. The first-line treatment of SAPHO syndrome involves the use of NSAIDs^[6]. Other treatment options are colchicine, glucocorticoid, bisphosphonates, and disease-modifying agents such as methotrexate, sulfasalazine, and anti-TNF- α therapy^[4]. The effectiveness of infliximab^[7],

etanercept^[8], and adalimumab^[9] have been previously reported for SAPHO syndrome. Only one report of CZP has been acquired, as far as we know^[10].

In this case, CZP demonstrated very rapid and positive effects for symptoms and laboratory findings, which was in agreement with Kamata *et al.*'s report^[10]. However, the long-term effects of CZP remain unknown. That is the limitation of our case report.

Conclusion

We reported a case with refractory SAPHO syndrome in which the definitive diagnosis was difficult. Certolizumab pegol showed rapid and definite efficacy in the treatment of this case.

Conflict of interests

All authors declare no conflict of interest with respect to the research, authorship, and/or publication of this article.

Informed consent

Written informed consent was obtained for the case before the study.

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