

[CASE REPORT]

Synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) Syndrome with Significant Bilateral Pleural Effusions

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Abstract:

We herein report a rare case of a 66-year-old woman who had synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) syndrome with marked sternal osteitis and bilateral pleural effusions. SAPHO syndrome was diagnosed based on the characteristic features of a hyperostotic sternum and thoracic spine. The inflammatory changes of sternal osteitis and involvement of the adjacent soft tissue were assumed to be the cause of the pleural effusions. The effusions decreased during the natural course of the disease and resolved after methotrexate therapy. The pain dramatically decreased with oral tramadol. Physicians should consider the possibility of SAPHO syndrome in patients with anterior chest pain and pleural effusions.

Key words: SAPHO syndrome, anterior chest wall, sternum, osteitis, pleural effusion

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Introduction

Synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) syndrome is a disease characterized by pustular skin lesions and nonpyogenic osteoarticular lesions and was first described by Chamot et al. in 1987 (1). At present, SAPHO syndrome is regarded as a rare disease with an estimated prevalence of lesser than 1 in 10,000 (2). However, it may be under-diagnosed in routine medical practice because the diagnosis is difficult if skin disease is absent. As such, its prevalence may be much higher than previously reported.

We herein report a rare case of SAPHO syndrome accompanied by bilateral pleural effusions. Although this patient did not have a history of pustular skin lesions, such as palmoplantar pustulosis (PPP), she presented with osteitis of the sternum and spine, which is characteristic of the disease. The osteitis was presumed to be sterile based on the negative culture results as well as her clinical presentation. In this report, we describe our case and review the pertinent literature.

Case Report

A 66-year-old woman developed chronic anterior chest pain after being hit in the chest with her grandchild's head 6 months prior to admission. She gradually developed chronic low back pain and habitually rolled over while lying down to ease her pain. Three months before admission, she received a medical checkup at a nearby clinic. Her chest radiography revealed normal lung fields and costophrenic angles (CPAs), but osteosclerotic changes were seen in the proximal right clavicle (Fig. 1A). Two months before admission, she visited the same clinic, as the chest pain had become increasingly severe. Repeated chest radiograph revealed proximal clavicular osteitis and a small amount of pleural effusion (Fig. 1B). Thus, loxoprofen sodium hydrate and acetaminophen were prescribed. However, she developed a skin rash on both legs. The skin rash gradually subsided after the cessation of both drugs. Her rash was erythematous and had been suspected to be drug-induced by the previous clinic. One and a half months before admission, her blood tests showed an elevated C-reactive protein (CRP) level of 13

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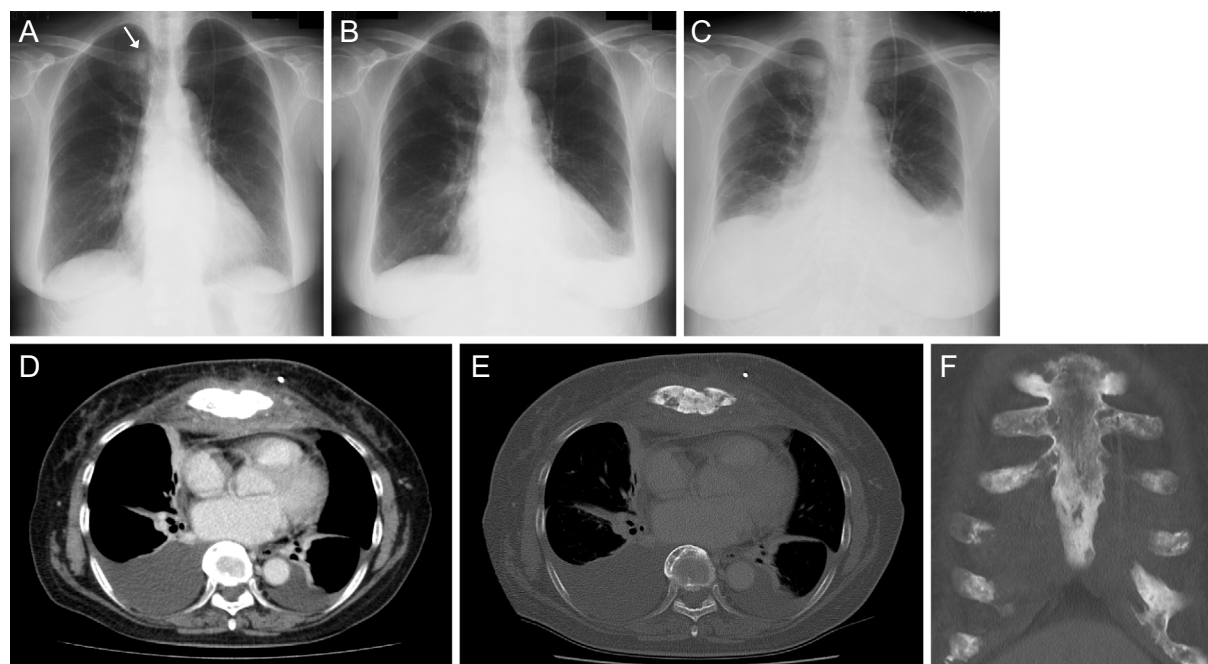


Figure 1. Radiographs and CT images taken prior to admission. (A) Chest radiograph taken three months before admission shows normal lung fields and costophrenic angles, but osteosclerotic changes are seen in the proximal right clavicle (arrow). (B) Chest radiograph taken two months before admission shows proximal clavicular osteitis and a small amount of pleural effusion. (C) Repeat chest radiograph taken one and a half months before admission shows marked bilateral pleural effusions. (D) Contrast-enhanced chest CT taken one month prior to admission shows significant bilateral pleural effusions as well as thickened and weakly enhanced soft tissue around the sternum. (E) Chest CT reveals hyperostosis, osteosclerotic changes, and bony erosions of the sternum. (F) A coronal view of the chest CT scan shows hyperostosis of the inferior sternum.

mg/dL, and repeat chest radiography revealed marked bilateral pleural effusions (Fig. 1C). She was then referred to our hospital. At the initial visit, she was pyrexial (37.6°C), but her blood culture results were negative. She complained of dyspnea when lying down, but her peripheral capillary oxygen saturation (SpO₂) was 97% on room air. Diagnostic thoracentesis showed exudative pleural effusions, and culture of the pleural fluid was negative. Contrast-enhanced computed tomography (CT) performed one month prior to admission had shown bilateral pleural effusions, marked sternal hyperostosis, and swelling of the soft tissue around the sternum (Fig. 1D-F). She was referred to our rheumatology clinic for suspected SAPHO syndrome. Since her severe chest pain continued unabated, she was soon unable to perform her usual activities. Therefore, she was admitted to our hospital for further investigations and treatment.

On admission, the patient complained of severe chest and back pain. A physical examination revealed tenderness over the sternoclavicular joints, sternum, acromioclavicular joints, and sacroiliac joints. Percussion pain at the middle thoracic vertebrae and lower lumbar vertebrae was recognized.

The patient's medical history included subarachnoid hemorrhaging (SAH) at 60 years of age and post-SAH hydrocephalus for which she received ventriculoperitoneal shunting at 61 years of age. She had no personal history of PPP or a family history of rheumatic diseases.

Laboratory findings

The white blood cell (WBC) count was 8,120/μL, hemoglobin (Hb) 9.0 g/dL, total protein 7.3 g/dL, albumin 2.8 g/dL, lactate dehydrogenase (LD) 123 U/L, alkaline phosphatase 236 U/L, CRP 4.24 mg/dL, erythrocyte sedimentation rate (ESR) 138 mm/h, antinuclear antibody (ANA) 40x, rheumatoid factor <10 U/mL, and anti-cyclic citrullinated peptide (CCP) antibody <0.6 U/mL.

Pleural fluid examination

The specific gravity was 1.032, LD 173 U/L, adenosine deaminase 8.2 IU/L, and cell count 1,340/μL (neutrophils 41%, eosinophils 0.2%, lymphocytes 22%). She had negative pleural fluid cultures and no malignant cells on cytology.

Imaging findings

Chest X-ray on admission revealed bilateral blunt CPA, but the pleural effusion shadow showed improvement (Fig. 2A). Thoracolumbar spine X-ray revealed non-marginal spinal syndesmophytes of the right side of the thoracic spine as well as vertebral body osteosclerosis of the middle and lower thoracic spine (Fig. 2B). Lateral sternum X-ray showed hyperostosis of the lower sternum (Fig. 2C). Bone scintigraphy revealed 'hot' lesions at the lower ster-

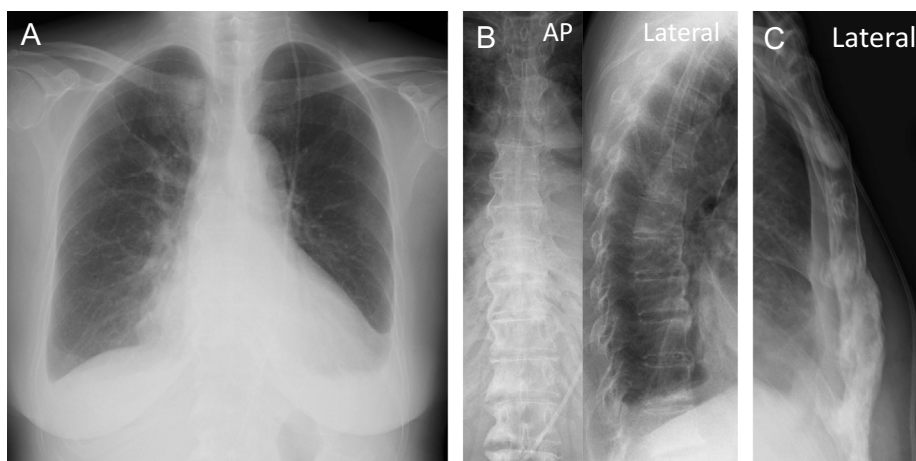


Figure 2. Radiographs taken on admission. (A) Chest X-ray on admission shows bilateral blunt CPA, but the pleural effusion shadow shows improvement. (B) Frontal thoracolumbar spine radiograph shows non-marginal syndesmophytes of the right side of the thoracic spine, and vertebral body osteosclerosis is recognized in the lower thoracic spine. In the lateral view, marginal and non-marginal syndesmophytes are seen on the anterior side of the thoracic spine. (C) Lateral sternum radiograph shows hyperostosis of the lower sternum.

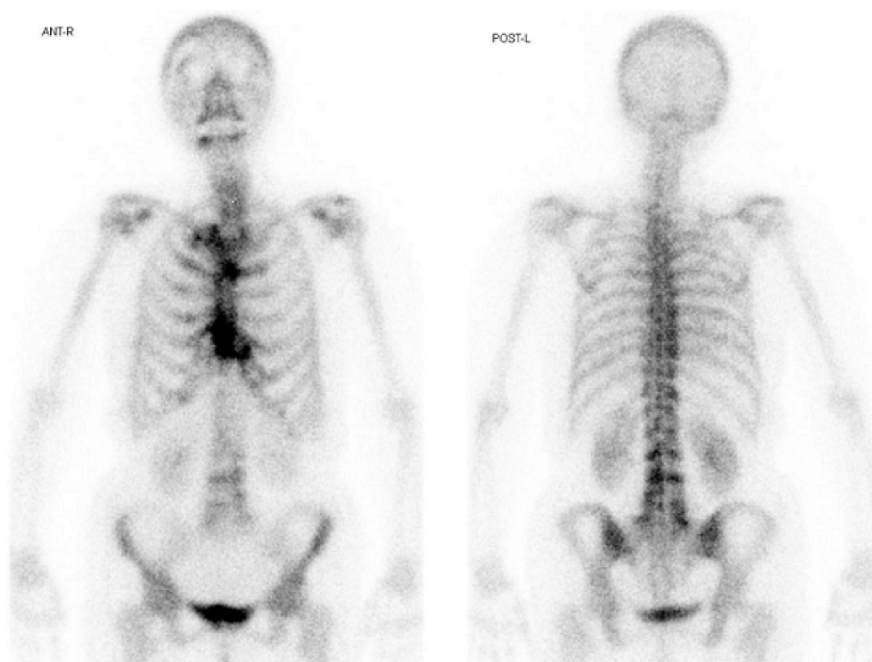


Figure 3. Bone scintigraphy shows 'hot' lesions at the lower sternum, the right side of sternoclavicular joint, the lower thoracic spine, and the lumbar vertebrae.

num, the right side of sternoclavicular joint, and the lower thoracic spine and lumbar vertebrae (Fig. 3).

Clinical course

Infectious disease was unlikely since her body temperature and inflammatory markers normalized without antibiotic treatment, and subsequent cultures of her blood and pleural fluid were negative. Primary and metastatic bone tumors were ruled out because no mass lesions were detected on her CT scans. Rheumatoid arthritis (RA) and ankylosing spondylitis were unlikely because RA-specific antibodies

were not present, and her human leukocyte antigen (HLA) test was negative for HLA-B27. However, she had the sternal and thoracic spine osteitis characteristics of SAPHO syndrome, and the diagnostic criteria confirmed this diagnosis (3).

Since she had a positive drug lymphocyte stimulation test (DLST) for loxoprofen sodium hydrate and acetaminophen, we suspected drug allergy and prescribed tramadol to relieve her severe chest and back pain on hospital day (HD) 1 instead. Her pain improved from a numerical rating scale (NRS) of 5.4 on admission to 1 at HD 3. The bilateral pleu-

ral effusions gradually decreased in size, but there was no immediate improvement in her CRP levels.

We commenced treatment with methotrexate (MTX) on HD 15 because tramadol is known not to have anti-inflammatory effects. On HD 20, she was discharged from the hospital. One month after discharge, pleural effusion disappeared on X-ray. Six months after discharge, there was no exacerbation of the pain or pleural effusions. Her CRP had also improved to near-normal levels.

Discussion

SAPHO syndrome is a rare but clinically important disease that is characterized by pustular skin lesions and non-pyogenic osteoarticular lesions. The anterior chest wall is most commonly affected, especially the clavicles, first ribs, sternum, and sternoclavicular joints. The diagnostic criteria for SAPHO syndrome are based on the exclusion of infectious arthritis and osteitis and the presence of at least 1 of the following 4 inclusion criteria: osteoarticular manifestations of severe acne; osteoarticular manifestations of PPP; hyperostosis with or without dermatosis; and chronic recurrent multifocal osteomyelitis with or without dermatosis (3).

Our case was unique because of the presence of bilateral pleural effusions. Malignant tumors, infectious diseases or other autoimmune diseases are common causes of exudative pleural effusions. In our case, the cytological and microbiological findings ruled out malignancies and infectious diseases. Autoimmune diseases, such as systemic lupus erythematosus (SLE) and rheumatoid vasculitis, which are often accompanied by pleurisy, were also unlikely because of the absence of ANA, disease-specific antibodies, peripheral arthritis, characteristic skin rashes, and weight loss. The likelihood of a drug allergy was also low, because pleural effusions appeared before starting any drugs, and no previous reports of loxoprofen sodium hydrate- or acetaminophen-induced pleurisy exist.

We hypothesized that the pleural effusions were caused by the sternal osteitis of SAPHO syndrome, as no other causes were found and the exacerbation of osteitis occurred almost concurrently with the pleural effusions. The pleural effusions resolved without antibiotic therapy in tandem with the reduction in CRP levels, which was indicative of sterile inflammation as the underlying cause.

The etiology of SAPHO syndrome is still unclear, but neutrophil activation is suggested to contribute to the pathophysiology of this disease (2). In the acute stage of SAPHO syndrome, bone histology shows prominent acute inflammation and edema with infiltration of polymorphonuclear leukocytes (2, 4). A case of SAPHO syndrome characterized by an inflamed synovium with abundant neutrophils and lymphocytes was reported (5). In our case, the predominant neutrophils and lymphocytes in the pleural fluid were deemed to be consistent with the effects of severe osteitis in SAPHO syndrome. Given the finding of soft tissue swelling surrounding the sternum on CT scans, we speculated that

the inflammation of sternal osteitis had spread to the soft tissue and pleura.

We performed a search for English- or Japanese-language articles on the subject and found two previous case reports of pleural effusion in patients with SAPHO syndrome (6, 7). Fernandez-Campillo et al. presented the case of a 61-year-old man who had scalp psoriasis, pubic osteitis, pain and stiffness of the anterior chest wall, and right exudative pleural effusion (6). Nukui et al. described the case of a 23-year-old Japanese woman who had SAPHO syndrome with pleural effusion. She presented with a high body temperature of up to 38°C as well as an elevated CRP (9 mg/dL) level. CT also revealed the increased density of fatty tissue anterior to the sternal osteitis (7). Similarly, our patient presented with anterior chest pain, a fever, and highly elevated inflammatory markers; these findings may be common in cases of SAPHO syndrome with pleural effusion. In addition, our patient had a considerable amount of soft tissue swelling around the sternum and a large amount of exudative pleural effusion, which may have been influenced by the inflammation caused by the severe anterior chest wall osteitis. However, decreased pleural effusion was observed on admission. Given that the CRP level was also decreased, it seems more likely that the inflammation had been ameliorated as part of the natural course of the disease.

Loxoprofen sodium hydrate and acetaminophen could not be prescribed for our patient because of a possible allergy to these drugs. Therefore, we prescribed tramadol, and her skeletal pain dramatically decreased after two days. SAPHO syndrome is not fatal and does not lead to a debilitating condition (8). According to previous research, the mean visual analog scale (VAS) for pain score and mean impairment in activities of daily living were reported to exceed the threshold generally considered acceptable for other diseases, such as ankylosing spondylitis (9). In SAPHO syndrome, diagnostic delays reportedly span 3.8-9.1 years (5, 8, 9), which leads to persistent pain and a diminished quality of life. Therefore, it is clear that an earlier diagnosis and therapeutic interventions are needed.

Anti-inflammatory therapy using oral nonsteroidal anti-inflammatory drugs (NSAIDs) is regarded as the first-line treatment for SAPHO syndrome (10). For patients who have an insufficient response to NSAIDs, glucocorticoids, bisphosphonates, and disease-modifying anti-rheumatic drugs (DMARDs), such as MTX and sulfasalazine, can be added (5, 10). In the case of refractory disease, biologics, such as tumor necrosis factor (TNF) inhibitors, may also be used (10, 11).

In our case, the patient's CRP levels did not improve immediately after starting tramadol, but relieving the pain improved her satisfaction levels and quality of life. As the patient had severe osteitis and tramadol is known to have minimal anti-inflammatory effects, we considered the application of TNF inhibitors, including adalimumab. The use of MTX reportedly reduces antidrug antibodies, such as anti-adalimumab antibodies, in psoriatic arthritis and RA (12).

Therefore, in our patient, we preliminarily administered MTX. After MTX therapy, pleural effusion was diminished, and the CRP levels gradually decreased further without pain recurrence. Aljuhani et al. reported that MTX was effective in half of patients with SAPHO syndrome (13). In RA therapy, MTX is known to suppress the inflammatory functions via adenosine release (14). In our case, we cannot rule out the possibility that MTX exerted an anti-inflammatory effect and reduced the osteitis activity of SAPHO syndrome.

Colina et al. reported that about half of patients with SAPHO syndrome had a chronic course characterized by fluctuating intermittent periods of exacerbation and short bouts of improvement (15). In the follow-up of our patient, special attention should be paid to the possibility of the reagravation of osteitis and the recurrence of pleural effusion.

The patient experienced an event of minor trauma at the onset of chronic osteitis. A preceding traumatic event has been reported in a few cases of chronic recurrent multifocal osteomyelitis (CRMO) which is the pediatric presentation of SAPHO syndrome (16, 17). Recently, Van Mechelen et al. suggested that biomechanical factors may play a role in the onset and progression of spondyloarthritis in interaction with the immune system (18). A possible link between SAPHO syndrome and spondyloarthritis has been suggested based on the high prevalence of axial involvement, including sacroiliitis (2). In our case, minor trauma might have functioned as a trigger for chronic osteitis. In spondyloarthritis, appropriate exercise and physical therapy are recommended (18), which may also benefit our case.

This case has two important points of note: First, SAPHO syndrome with severe anterior chest wall osteitis may be associated with pleural effusions. Second, good pain management is particularly important in patients with SAPHO syndrome. Therefore, when encountering a case with anterior chest pain and pleural effusion, we should consider the possibility of SAPHO syndrome and investigate the presence of osteosclerosis and hyperostosis of the anterior chest wall with imaging studies, such as X-ray and CT.

The authors state that they have no Conflict of Interest (COI).

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