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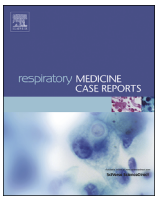

Case Report

A case of synovitis-acne-pustulosis-hyperostosis-osteitis syndrome with right pleural effusion

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ABSTRACT

A 79-year-old man presented with fatigue and right shoulder pain. Computed tomography revealed right pleural effusion and osteosclerosis of the sternoclavicular joint. There were no signs of malignancy or infection in the pleural fluid studies. His bone scintigraphy exhibited the "bull's head sign." Despite the absence of skin lesions, he was diagnosed with synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) syndrome. Remission was achieved after treatment with non-steroidal anti-inflammatory drugs and oral prednisolone.

SAPHO syndrome causes pleural effusion, even in patients without skin lesions. Bone scintigraphy should be considered in the workup for patients with unexplained pleural effusion.

1. Introduction

Synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) is a rare disease characterized by severe acne, palmoplantar pustulosis, and osteoarticular lesions [1]. Its prevalence was reportedly less than 1 in 10,000 [2]. The osteoarticular lesions are predominantly present in the sternoclavicular joint [1].

Herein, we present a case of SAPHO syndrome with unilateral pleural effusion, which was difficult to diagnose.

2. Case presentation

A 79-year-old man consulted his primary care doctor for a 2-week history of fatigue and pain in his right shoulder, right clavicle, and upper back. Chest radiography revealed a right pleural effusion and a right upper lung field mass (Fig. 1A). A malignancy was suspected, and he was referred to our hospital. The patient was a former smoker with a history of osteoporosis and cataracts. He presented at our hospital with a fever of 37.3 ˚C. His peripheral capillary oxygen saturation was 95% on room air, and he exhibited no signs of respiratory failure. Physical examination revealed decreased breath sounds on the right lower lung field. The right shoulder and sternoclavicular joints were swollen, warm, and tender. No abnormalities were observed in the palms or soles. Laboratory testing yielded an elevated C-reactive protein and matrix metalloprotease-3. All tumor markers were negative (Table 1A). A computed tomography scan was performed. The mass, detected on X-ray, was consistent with osteosclerosis of the sternoclavicular joints (Fig. 1B).

The cells in the pleural fluid had significantly more lymphocytes, and the ratio of total protein in the pleural fluid to total protein in the blood was 0.55, making it an exudative pleural fluid according to Light's criteria; however, the lactate dehydrogenase level in

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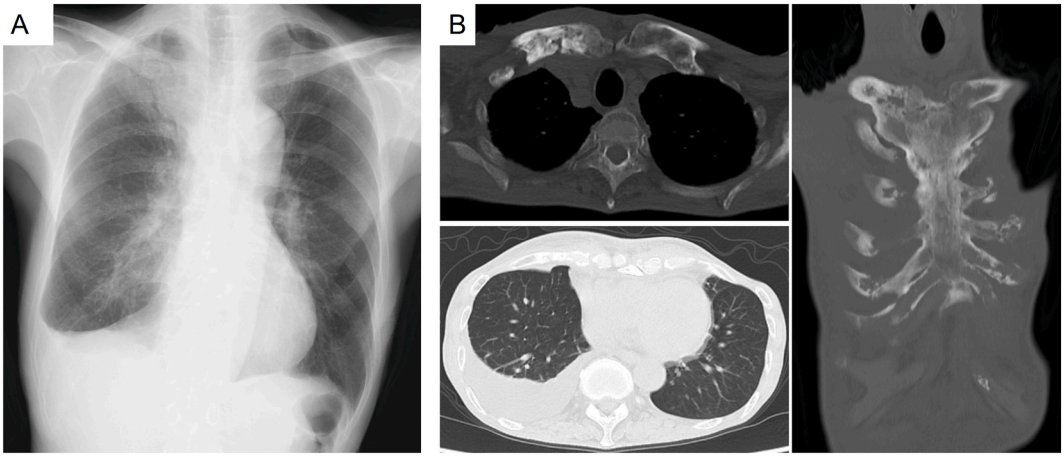

Fig. 1. A. The patient's chest radiograph was first interpreted by a primary care physician. Right pleural effusion and a right upper lung field mass, measuring 4.5 × 4.5 cm, near the right clavicle, were detected. B. Chest computed tomography was performed when he first visited our hospital. Chest radiography revealed right pleural effusion and sternoclavicular joint osteosclerosis. There were no noted pulmonary lesions.

Table 1

A. Patient's laboratory data on initial presentation to our hospital.

White blood cell	13,500	/μL
Neutrophils	89.1	%
hemoglobin	11.1	g/dL
total protein	7.1	g/dL
albumin	2.6	g/dL
lactate dehydrogenase	131	U/L
C-reactive protein	21.9	mg/dL
CEA	3.1	ng/mL
SCC	0.9	ng/mL
CYFRA	2.2	ng/mL
ProGRP	61	pg/mL
anti-Ro/SSA antibody	Negative	
Anti-La/SSB antibody	Negative	
Anti-Scl-70 antibody	Negative	
anti-Cyclic Citrullinated Peptide antibody	<0.6	U/mL
proteinase3-Anti-neutrophil Cytoplasmic Antibody	<1.0	U/mL
myeloperoxidase- Anti-neutrophil Cytoplasmic Antibody	<1.0	U/mL
antinuclear antibody	40	
Anti-double stranded-DNA IgG antibody	<10	IU/mL
rheumatoid factor	5	IU/mL
matrix metaroprotease-3	166	ng/mL

B. Pleural fluid analysis

Appearance	serofibrinous	
Laboratory data		
White blood cell	1250	/μL
Neutrophils	26.3	%
Lymphocytes	51.7	%
total protein	3.9	g/dL
lactate dehydrogenase	71	U/dL
adenosine deaminase	6.4	U/mL
hyaluronic acid	17400	ng/mL

the pleural fluid was as low as 71 U/dL. Bacteriological examination showed that both general bacteria and acid-fast bacilli in the pleural fluid were culture-negative, and the transcription reverse-transcription concerted reaction was also negative for *Mycobacterium tuberculosis* DNA. The cytological diagnosis revealed no malignancy (Table 1B). Although there were no typical dermatological findings, SAPHO syndrome was suspected based on the other findings. Moreover, bone scintigraphy exhibited the "bull's head sign," which was consistent with SAPHO syndrome (Fig. 2).

The patient was prescribed loxoprofen for pain control prior to diagnosis, so treatment was started with oral prednisolone (PSL) 15 mg/day, with the PSL dose tapered to 2.5 mg every 2 weeks. The pain resolved within a week of starting PSL, and the pleural effusion decreased significantly (Fig. 3). One year after starting PSL, there were no evidence of recurrence.

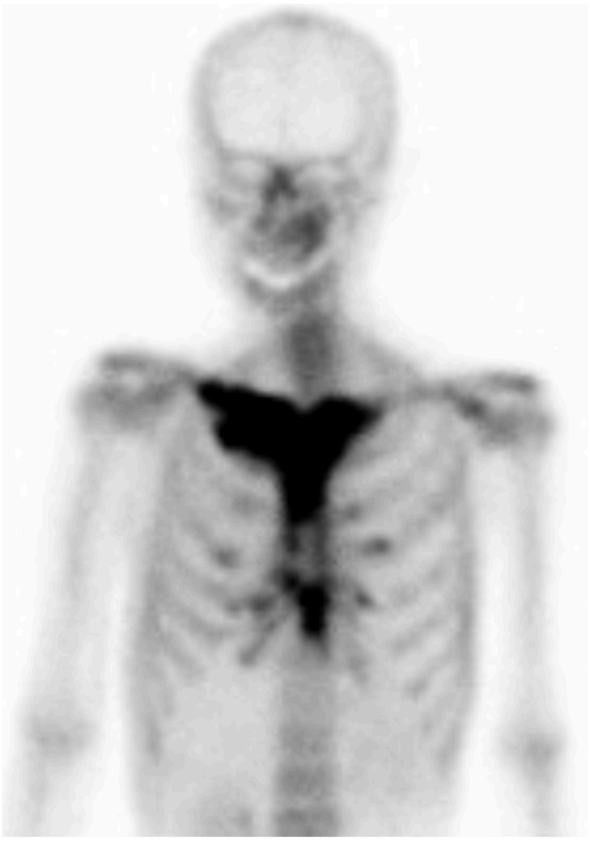

Fig. 2. Bone scintigraphy showed symmetric uptake in the sternoclavicular region. This represented a focal osteogenic reaction, called the "bull's head sign," a characteristic sign of SAPHO syndrome.

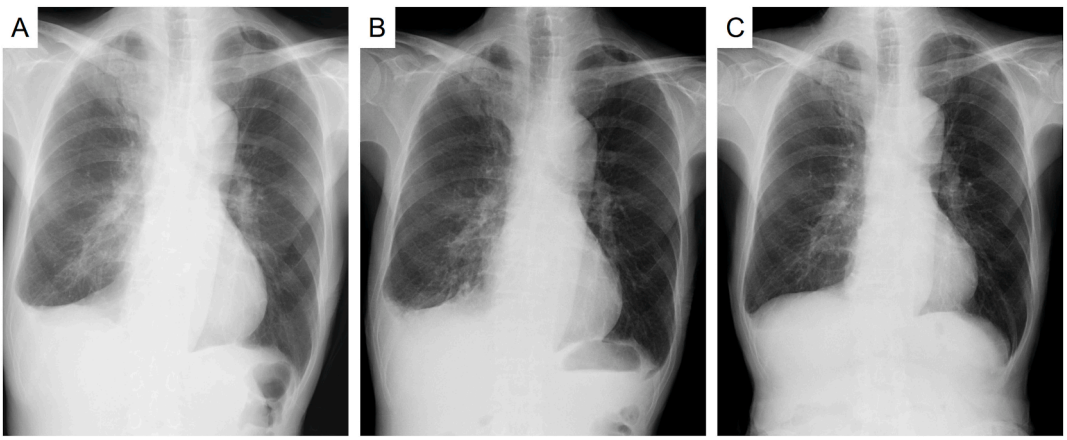

Fig. 3. Follow-up chest X-ray before and after the treatment. Day 0 corresponds to the initiation of oral prednisolone (PSL), and PSL was stopped on day 88. On day 15, the X-ray (when he visited his primary care doctor) showed right pleural effusion and osteosclerosis of the right sternoclavicular joint. On day 6 (when he was discharged), a similar amount of pleural effusion was detected, but the osteosclerosis was reduced (B). The right pleural effusion was gradually reduced, and almost no pleural effusion was observed on day 96 (C). The shadow of the right sternoclavicular joint persisted.

3. Discussion

SAPHO syndrome is a rare disease with various clinical presentations. Therefore, it is difficult to diagnose. The diagnosis of SAPHO syndrome is based on the criteria reported by Benhamou et al. [3] and Kahn et al. [4] (Table 2A, B). The most accurate diagnostic criteria have not been established [1,2]. Confirming the diagnosis is difficult because not all symptoms present simultaneously, and some symptoms are mild only (1). SAPHO syndrome presents with cutaneous symptoms, but these symptoms are not always accompanied by skeletal muscle symptoms. Skin and musculoskeletal involvement occur simultaneously in only 30% of patients. At

Table 2

A. Diagnostic criteria proposed by Benhamou for synovitis-acne-pustulosis-hyperostosis-osteitis syndrome.
Osteoarticular manifestations in severe acne
Osteoarticular manifestations in palmoplantar pustulosis
Hyperostosis with or without dermatosis and
Recurrent multifocal chronic osteomyelitis involving the axial or peripheral skeleton, with or without dermatosis
B. Diagnostic criteria proposed by Kahn for synovitis-acne-pustulosis-hyperostosis-osteitis syndrome were modified in 2003 (Kahn, American College of Rheumatology, 67th Annual Scientific Meeting, October 2003)
Inclusion
Bone-joint involvement associated with palmoplantar pustulosis and psoriasis vulgaris
Bone-joint involvement associated with severe acne
Isolated sterile[a] hyperostosis/osteitis (adults)
Chronic recurrent multifocal osteomyelitis (children)
Bone-joint involvement associated with chronic bowel diseases
Exclusion
Infectious osteitis
Tumoral conditions of the bone
Noninflammatory condensing lesions of the bone

(Benhamou CL et al. Clin Exp Rheumatol. 1998).
(Hayem G (2004) SAPHO syndrome: Rev Prat 54:1635–1636) (Iva Rukavina, 2015).
[a] Exception: growth of Propionibacterium acnes.

least 15% of adult cases and more than 70% of pediatric cases did not present with skin lesion [5]. As seen in the present case, SAPHO cannot be excluded in patients with only one lesion with no associated cutaneous manifestations.

The SAPHO syndrome is rarely associated with pleural effusion. A literature search was conducted in PubMed/MEDLINE using the keywords “SAPHO syndrome” and “pleural effusion”, and a further review of the citations identified a total of seven cases (Table 3). There were no trends in terms of age or sex. The pleural effusion may be unilateral or bilateral [2,6,7], and it usually consists of lymphocytic exudate. Like the patient in the present case, all patients from the previous studies complained of anterior chest pain [2,7]. The mechanism behind the development of pleural effusion in patients with SAPHO syndrome remains unclear. Chronic inflammation of the anterior thorax was suggested.

Radiological examinations, especially bone scintigraphy, are essential in establishing the diagnosis [8]. On bone scintigraphy, SAPHO syndrome exhibits a focal osteogenic reaction, known as the “bull's head sign,” which is a symmetric uptake in the sternoclavicular region. This finding helps confirm the diagnosis of SAPHO syndrome [1,6]. A bone biopsy also aids in distinguishing between a bone infection or an inflammatory state, such as in patients with SAPHO syndrome [9]. It is also important to exclude other entities, including infections, drug-induced pulmonary embolism, tumors, rheumatoid arthritis, postoperative complications, chylothorax, and uremic pleuritis [1,6]. Therefore, radiologic and histologic examinations are essential. However, the diagnosis is not solely based on these modalities [1].

SAPHO syndrome is difficult to diagnose because it is a rare disease with various clinical manifestations. Its vague symptoms make it difficult to recognize, and its true incidence may be higher than its reported incidence rate [2,10]. SAPHO syndrome, associated with pleural effusion, is rarer, and these cases are more likely to be missed and undiagnosed. The treatment of SAPHO syndrome in-

Table 3
List of SAPHO with pleural effusion.

Year	Author	Sex	Age (years)	Other symptoms	Pleural effusion unilateral/ bilateral	Pleural effusion characteristic	Treatment
1999	Dumorland A et al.	Female	16	Right sacroiliac joint and right knee pain	Left	Lymphocytic exudate	None
2001	Fernandez-Campillo J et al.	Male	61	Both shoulders and left hip pain, stiffness of the chest wall	Right	Eosinophilic exudate	NA
2014	Nukui Y et al.	Female	23	Anterior chest pain and swelling, and tenderness in the sternum and sternoclavicular joint	Bilateral	NA	Diclofenac
2017	Hasegawa S et al.	Female	66	Sternum, sternoclavicular, acromioclavicular, and sacroiliac joints pain, middle thoracic and lumbar vertebrae pain	Bilateral	Neutrophilic exudate	Acetaminophen Loxoprofen Tramadol Methotrexate
2018	Moran P et al.	Male	70	Proximal epiphysis of both clavicles and the sternochondral joints pain	Right (2013) Left (2017)	Lymphocytic exudate Lymphocytic exudate	Methotrexate (Continued before the onset of pleural effusion)
2021	Adachi-Katayama M et al.	Male	71	Sternum and both, sternoclavicular pain, lumbar vertebrae pain	Bilateral	Lymphocytic exudate	Loxoprofen, Prednisolone 30mg/day
2022	Present case	Male	79	Right sternoclavicular joint pain	Right	Lymphocytic exudate	Loxoprofen, Prednisolone 15 mg/day

volves non-steroidal anti-inflammatory drugs with cortisol. Therefore, it is crucial to establish the diagnosis. The present case showed that SAPHO syndrome should be considered in patients presenting with pleural effusion of unknown etiology, even with no noted cutaneous lesions. Bone scintigraphy or a bone biopsy is helpful in the diagnosis of this disease.

4. Conclusion

We reported a case of SAPHO syndrome with pleural effusion and sternoclavicular joint osteitis that needed to be differentiated from a malignant tumor. Cases of SAPHO syndrome with pleural effusion were rare, and these cases were difficult to diagnose. Sometimes, patients with SAPHO syndrome do not present with skin lesions, making its diagnosis more challenging. Bone scintigraphy was useful in the diagnosis of SAPHO syndrome. Among patients, who present with pleural effusion of unknown etiology, SAPHO syndrome should be considered, and a bone scintigraphy is recommended.

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Informed consent

Informed consent was obtained from the patient.

Declaration of competing interest

No conflict of interest.

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