Clinical Case Report

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Diagnostic value of ultrasonography in synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) syndrome

A case report

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Abstract

Rationale: Synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) syndrome is a rare condition that affects the skin, bones, and joints. Diagnosis of SAPHO syndrome is established based on clinical manifestations and imaging features on radiography or magnetic resonance imaging.

Patient concerns: We report a 44-year-old male with a 20-year history of pustulosis who presented with pain in the lower extremities. Plain radiography demonstrated hyperostosis with subperiosteal erosions in the right tibia. Magnetic resonance imaging and computed tomography showed inflammatory accumulation, whereas musculoskeletal ultrasonography clearly depicted a periosteal reaction, osteitis, and enthesitis with abnormal blood flow in the surface of the right tibia.

Diagnoses: A diagnosis of SAPHO syndrome was made.

Interventions: The patient was treated with combination therapy comprising prednisolone, methotrexate, and infliximab, which resulted in clinical improvement.

Outcomes: The elevated levels of C-reactive protein and matrix metalloproteinase-3 normalized, and the abnormal ultrasonographic findings disappeared.

Lessons: The present case report demonstrates that multiple imaging modalities are important for the definitive diagnosis of SAPHO syndrome. Ultrasonography might be a useful tool for evaluating local musculoskeletal inflammation in patients with SAPHO syndrome.

Abbreviations: CRMO = chronic recurrent multifocal osteomyelitis, CT = computed tomography, IL = interleukin, MMP-3 = matrix metalloproteinase-3, MRI = magnetic resonance imaging, SAPHO = synovitis-acne-pustulosis-hyperostosis-osteitis, TNF-α = tumor necrosis factor-α, US = ultrasonography.

Keywords: chronic recurrent multifocal osteomyelitis, power Doppler, SAPHO syndrome, ultrasonography

1. Introduction

Synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) syndrome is an intractable inflammatory disease that mainly causes skin rash, sternoclavicular/sacroiliac/peripheral arthritis, and enthesitis.[1] SAPHO syndrome has no serological or other specific biomarkers, and so radiographic imaging techniques such as bone scintigraphy, computed tomography (CT), or magnetic resonance imaging (MRI) are often used to assess disease activity.[2] However, these whole-body images can only roughly reveal localized inflammation, while it is difficult to assess local inflammation in detail. In recent years, musculoskeletal ultrasonography (US) has become useful for evaluating active synovitis in patients with rheumatoid arthritis. US or MRI are the modalities recommended by the American College of Rheumatology/European League Against Rheumatism for the evaluation of inflammatory joints.[3]

SAPHO syndrome is characterized by progressive hyperostosis, synovitis, and osteitis of multiple bones, including those in the lower extremities, as well as skin manifestations.[4] The term "chronic recurrent multifocal osteomyelitis (CRMO)" is used to describe an auto-inflammatory disorder characterized by painful

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The patient provided written informed consent for the publication of this case report.

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swelling of bones and joints, and many cases of CRMO in association with skin disorders have been reported.[5] CRMO is now widely considered to represent a subset of SAPHO syndrome.[6] Therefore, CRMO and SAPHO syndrome are now seen as different expressions of the same disease. The diagnosis of SAPHO syndrome remains challenging. The establishment of an early diagnosis of SAPHO syndrome may be aided by the evaluation of bone or articular abnormalities.[7]

In the present case, we used US to detect the periosteal reaction, osteitis, and enthesitis in a patient with SAPHO syndrome. Our study demonstrates that US can detect bone or articular abnormalities (including those associated with CRMO) in patients with SAPHO syndrome and suggests that US evaluation might be useful in the diagnosis of SAPHO syndrome.

2. Case report

A 44-year-old male was admitted to our department because of pain of the lower extremities. He had a 20-year history of pustulosis of the palms, soles, and toes. Three years before admission, he had been diagnosed with deep venous thrombosis because of pretibial edema of both legs; oral aspirin and diuretics had been administered, but the symptoms had not improved.

Physical examination revealed pustulosis on the chest, dermal detachment on the palms and soles, and enormous areas of scleroderma and pigmentation on both legs. The laboratory findings are summarized in Table 1. The white blood cell count was elevated. The red blood cell count and hemoglobin level were slightly low. Coagulation function, liver function, renal function, and electrolytes were normal. The erythrocyte sedimentation rate and the C-reactive protein level were elevated. Rheumatoid factor and anti-citrullinated peptide antibodies were normal. Matrix metalloproteinase-3 was elevated. Other autoimmune disease-specific antibodies were within normal ranges.

A radiograph of the lower extremities showed hyperostosis of the tibia (Fig. 1A). Bone scintigraphy showed substantial nuclide accumulation in the bilateral tibias, fibulas, and calcanei (Fig. 1B). Gadolinium-enhanced MRI showed extensive edema of the plantar flexor tendon (Fig. 2A, B), a contrast effect of the calcaneus, and edema of the retrocalcaneal bursa and plantar fascia (Fig. 2C). US assessment of the lower extremities was performed by a Japan College of Rheumatology-certified sonographer (T.A.). Representative US images revealed marked irregularities of the tibial surface (Fig. 3A), thickening of the tendon sheath of the tibialis anterior muscle with edema of the deep subcutaneous fat (Fig. 3B), effusion around the tibialis anterior tendon with synovial thickening of the ankle joint (Fig. 3C), low echoic enthesis of the Achilles tendon with a thickened retrocalcaneal bursa (Fig. 3D), synovial thickening of the metatarsophalangeal joints (Fig. 3E), and thickened plantar fascia (Fig. 3F). Substantially abnormal blood flow signals were seen at each of those sites in power Doppler mode. The patient was finally diagnosed with SAPHO syndrome based on Benhamou diagnostic criteria.[8]

The patient was treated with oral prednisolone and methotrexate, but this combination therapy did not alleviate his symptoms. Intravenous infliximab therapy (3 mg/kg every 8 weeks) was added to the treatment, which resulted in improvement of the leg pain. After 6 months, the arthritis had resolved, the cutaneous lesions had substantially improved, and the C-reactive protein level and erythrocyte sedimentation rate were within normal ranges. Follow-up US revealed that the tibial irregularity was markedly resolved, and the abnormal blood flow in each part of the lower extremities had completely disappeared (Fig. 4).

Table 1

Laboratory findings on admission.

Peripheral blood		
White blood cells	12,800/μL	(2800–8800)
Neutrophil	73%	(44–74)
Lymphocyte	15%	(20–50)
Red blood cells	4.02×10^6/μL	(3.66–4.78)
Hemoglobin	11.1 g/dL	(11.6–14.0)
Hematocrit	35.4%	(34.1–41.7)
Platelet	35.5×10^4/μL	(14.7–34.1)
Blood chemistry		
Total protein	6.8 g/dL	(6.7–8.3)
Albumin	3.4 g/dL	(3.9–4.9)
Total bilirubin	0.6 mg/dL	(0.2–1.2)
Aspartate transaminase	10 U/L	(13–33)
Alanine transaminase	8 U/L	(6–27)
Lactate dehydrogenase	156 U/L	(119–229)
Alkaline phosphatase	237 U/L	(115–359)
γ-Glutamyltranspeptidase	23 U/L	(10–47)
Creatine kinase	35 U/L	(45–163)
Blood urea nitrogen	18 mg/dL	(8–22)
Creatinine	0.58 mg/dL	(0.4–0.7)
Coagulation		
Prothrombin time	82%	(70–125)
Activated partial thromboplastin time	31.6 s	(23–38)
Fibrinogen	510 mg/dL	(181–398)
D-Dimer	0.5 μg/mL	(<0.9)
Lupus anticoagulant	1.00 ratio	(<1.19)
Serological tests		
C-reactive protein	7.0 mg/dL	(<0.30)
ESR (1 h)	39 mm	(3–15)
MMP-3	124 ng/mL	(17.3–59.7)
IgG	1441 mg/dL	(870–1700)
IgA	198 mg/dL	(110–410)
IgM	103 mg/dL	(35–220)
ASO	235 IU/mL	(<240)
ANA	<160 fold	(<159)
Rheumatoid factor	20 IU/mL	(<15)
Anti-CCP Ab	<0.5 U/mL	(<4.5)
Anti-CLβ2GP1 Ab	<1.2 U/mL	(<3.4)
MPO-ANCA	<1.0 EU	(<3.4)
PR3-ANCA	<1.0 EU	(<3.4)
SAA	249 μg/mL	(<8.0)
ACE	8 U/L	(7–25)
Cryoglobulin	(-)	
Infection		
HBs Ag	(-)	
HCV Ab	(-)	
Procalcitonin	<0.02 ng/mL	(<0.05)
β-D glucan	<6.0 pg/mL	(<11.0)
IGRA	(-)	
Anti-MAC ab	(-)	
Urinalysis		
Protein	(-)	
Blood	(-)	

ACE = angiotensin converting enzyme, ANA = anti-nuclear antibodies, Anti-CCP Ab = anti-cyclic citrullinated peptide antibodies, Anti-CLβ2GP1 Ab = anti-cardiolipin beta 2-glycoprotein 1 antibodies, Anti-MAC ab = anti-*Mycobacterium avium* complex antibodies, ASO = anti-streptolysin O, ESR = erythrocyte sedimentation rate, HBs Ag = hepatitis B virus surface antigen, HCV ab = anti-hepatitis C virus antibody, Ig = immunoglobulin, IGRA = interferon gamma release assay for *Mycobacterium tuberculosis*, MMP-3 = matrix metalloproteinase-3, MPO-ANCA = myeloperoxidase anti neutrophilic cytoplasmic antibodies, PR3-ANCA = proteinase 3 anti-neutrophilic cytoplasmic antibodies, SAA = serum amyloid A.

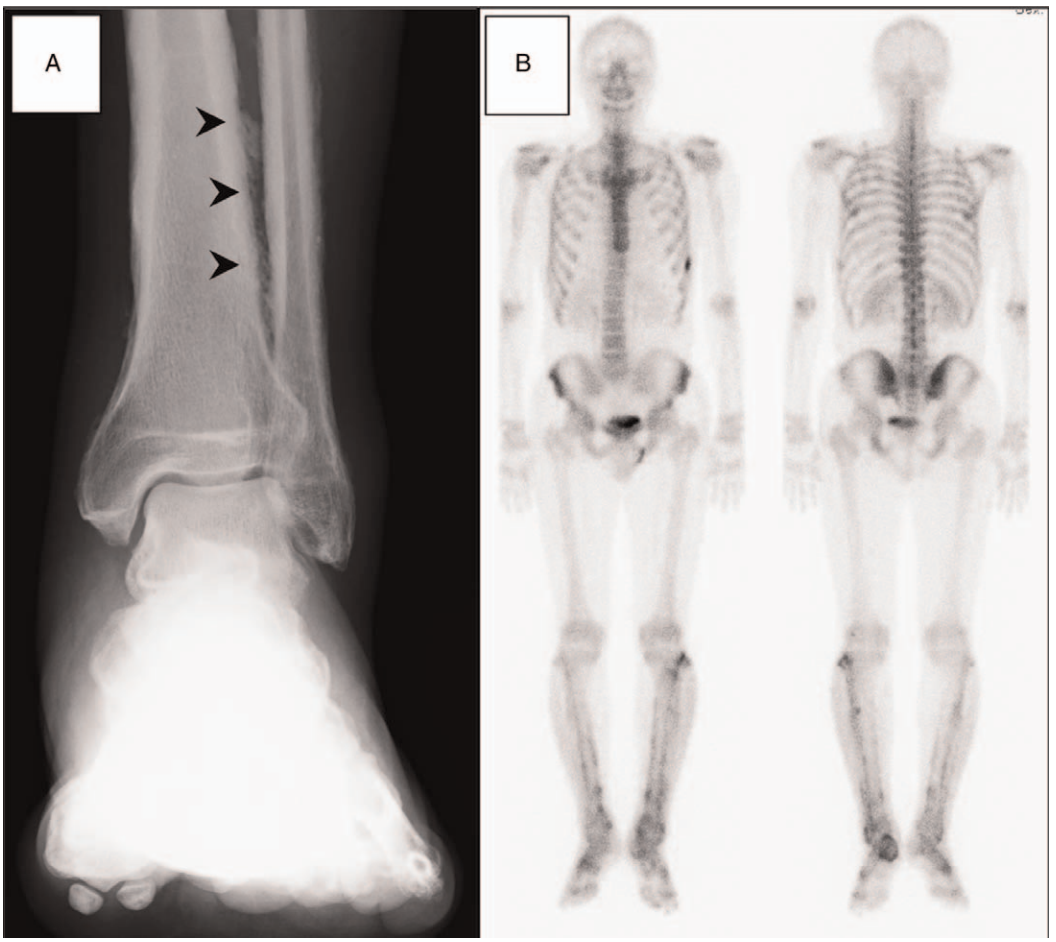

Figure 1. Radiograph and bone scintigraphy images. (A) Radiograph of the left lower limb showing slight hyperostosis of the tibial surface (arrowheads). (B) Whole-body bone scintigraphy showing substantial nuclide accumulation in the bilateral tibias, fibulas, and calcanei.

Figure 2. Gadolinium-enhanced magnetic resonance imaging. There is extensive edema around the plantar flexor tendon (A, B), a contrast effect of the calcaneus, edema around the retrocalcaneal bursa, and plantar fascia (C).

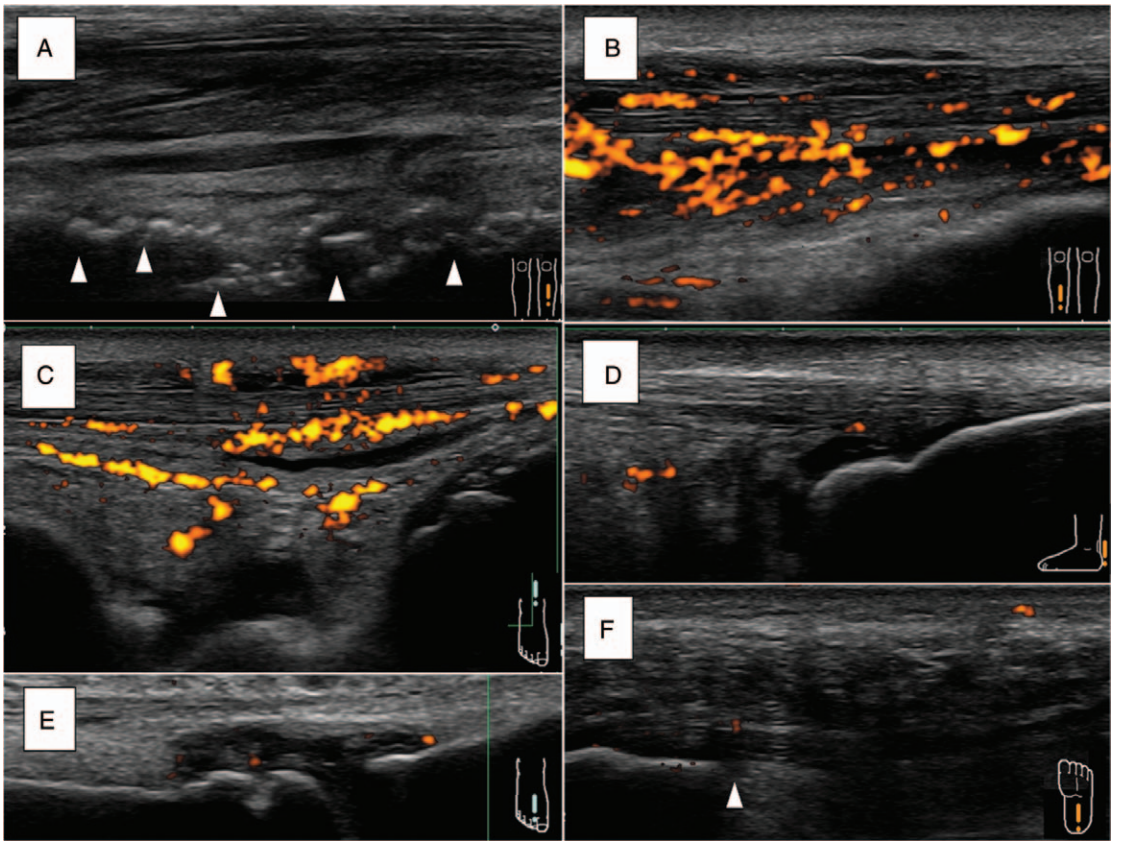

Figure 3. Musculoskeletal ultrasonographic images of the lower extremities. (A) Marked irregularities of the left tibial surface (arrowheads). (B) Thickened tendon sheath of the right tibialis anterior muscle with edema of the deep subcutaneous fat and a flame-like blood flow signal. (C) Effusion around the right tibialis anterior tendon with a beaded blood flow signal, and synovial thickening of the ankle joint. (D) Low echoic enthesis of the left Achilles tendon with thickened retrocalcaneal bursae, and a spot-like blood flow signal. (E) Synovial thickening of the metatarsophalangeal joints with a spot-like blood flow signal. (F) Thickened plantar fascia.

3. Discussion

SAPHO syndrome is a rare disease that is often under-recognized because of its peculiar and heterogeneous clinical presentation.[4] Osteoarticular manifestations are the hallmark of SAPHO syndrome. The most commonly involved area is the anterior chest wall, followed by the spine (particularly the thoracic bones).[9] The differential diagnoses for the osteoarticular manifestations of SAPHO syndrome include osteomyelitis, primary bone tumors, and granuloma.[10]

SAPHO syndrome is characterized by progressive hyperostosis, synovitis, enthesitis, and multiple bone lesions in various regions, including the lower extremities.[1] In addition to the assessment of skin manifestations, imaging modalities may aid the early diagnosis of SAPHO syndrome.[11] Multimodal imaging techniques such as conventional radiography, MRI, and bone scintigraphy play essential roles in the diagnosis of SAPHO syndrome.[12] In addition, US can detect osteoarticular inflammation with high sensitivity.[13] The present case report demonstrated that US can detect the bone or articular abnormalities in a patient with SAPHO syndrome. Hyperostosis, osteitis, and enthesitis were detected using power Doppler signals on US in the present patient. Therefore, US may be useful for the early diagnosis of SAPHO syndrome.

The osteoarticular manifestations of SAPHO syndrome are hyperostosis and osteitis, which are chronic inflammatory reactions involving the cortical and medullary bone.[14] Chronic bony lesions in patients with SAPHO syndrome are characterized by cortical thickening accompanied by enlargement of trabeculae.[14] CRMO is regarded as a subset of SAPHO syndrome.[6] The typical imaging findings of CRMO include lytic and sclerotic lesions in the metaphyses of long bones.[15] Because of the lack of diagnostic tests, CRMO remains a diagnosis of exclusion. Few reports have described the US findings in SAPHO syndrome, including CRMO.[16] Ikeda et al[17] reported a single US image report of a patient with SAPHO syndrome with severe synovial hypertrophy accompanied by markedly increased power Doppler signals in the sternoclavicular joint. Queiro et al[18] reported that US examination is useful for evaluating enthesitis in patients with SAPHO syndrome. The objective of the present case report was to describe the characteristic US findings of SAPHO syndrome, including CRMO. Although the anterior chest wall and sternoclavicular joints are the main regions predominately affected in patients with SAPHO syndrome,[19] the involvement of these regions is not pathognomonic. SAPHO syndrome also affects long bones, and bony involvement is highly distinctive as the mainstay of the diagnosis.[20] We consider that an US approach would increase the sensitivity for detecting hyperostosis and osteitis, despite the fact that these manifestations are predominantly found in the lower extremities, as seen in our patient with SAPHO syndrome.

Tumor necrosis factor-α (TNF-α) inhibitors show efficacy for bone, joint, and skin manifestations, and have been used in the management of SAPHO syndrome.[21] Consistent with previously

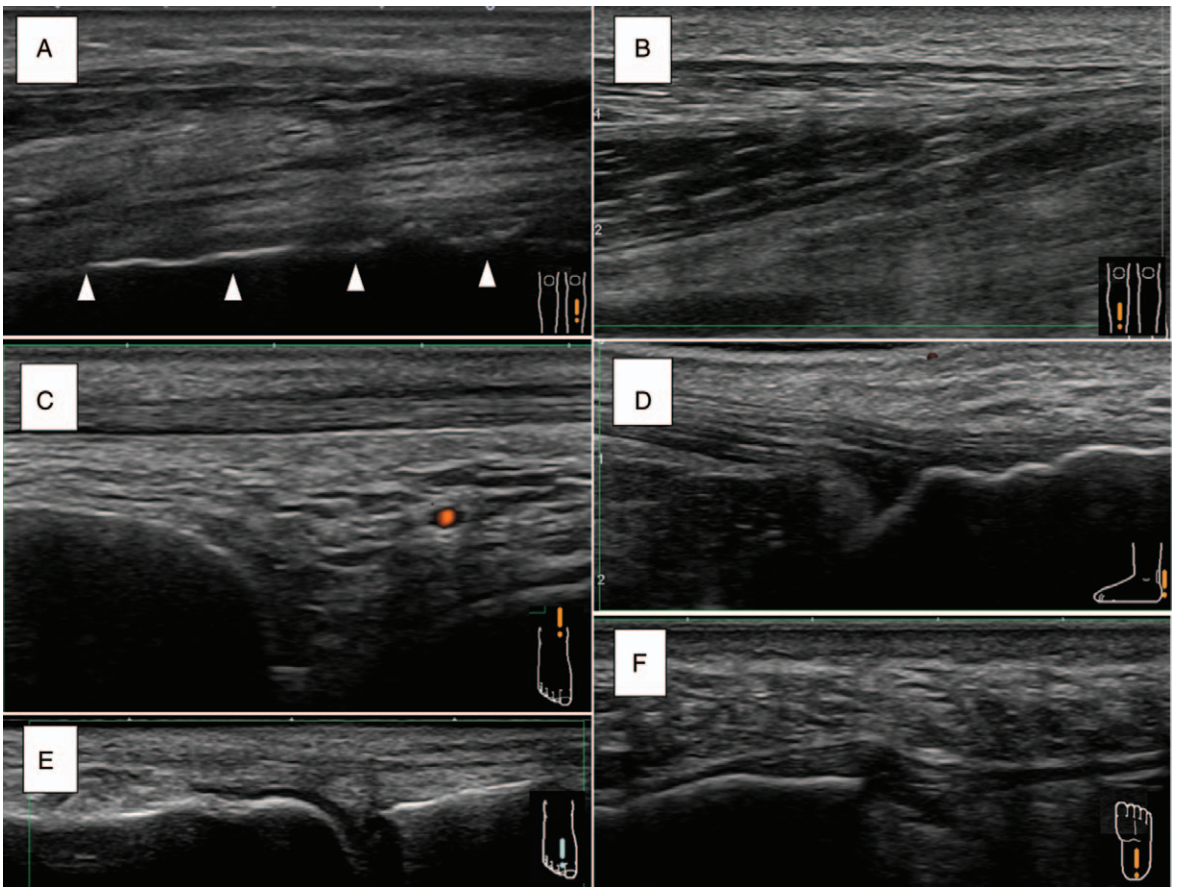

Figure 4. Follow-up musculoskeletal ultrasonographic images of the lower extremities after 6 months of treatment with oral prednisolone and methotrexate along with intravenous infliximab. (A) Reduced irregularity of the left tibia (arrowheads). (B) Right tibialis anterior muscle. (C) Right ankle joint. (D) Left Achilles tendon. (E) Right second metatarsophalangeal joint. (F) Left plantar fascia.

reported cases, infliximab administration in our patient with SAPHO syndrome was effective in alleviating the bone and joint manifestations. The rationale for the use of a TNF-α inhibitor is that TNF-α is a potent regulator of cytokines such as interleukin (IL)-1, IL-6, and IL-8, some of which are dysregulated in SAPHO syndrome.[22] Immunosuppressive drugs such as methotrexate, sulfasalazine, and cyclophosphamide are frequently administered in the treatment of SAPHO syndrome.[23] However, these treatments have shown only partial efficacy. Biologics, including TNF-α blockers, lead to sustained improvement of osteoarticular involvement of SAPHO syndrome.[24]

The present study has some limitations. It is a single case report, and there is no criterion for imaging diagnosis of SAPHO syndrome using US. We need to determine whether our US imaging report of SAPHO syndrome applies to other cases by increasing the number of US examinations performed in patients with SAPHO syndrome.

In conclusion, osteoarticular manifestations of SAPHO syndrome are characterized by hyperostosis and osteitis, which are chronic inflammatory reactions involving the long bones, including the tibial bone. The lesions are associated with sclerotic changes and are accompanied by periosteal reaction. US is an accurate and quick tool with which to assess the subperiosteal spread of osteitis and the periosteal reaction with a vascularized rim using the increased power Doppler signal. Therefore, US might be a very useful and versatile imaging modality that enables the early diagnosis of SAPHO syndrome. Further studies are needed to determine whether the US findings of hyperostosis or osteitis are common features in patients with SAPHO syndrome.

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