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Case Report

The value of multi-modality imaging in establishing the diagnosis of Adolescent SAPHO☆

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ABSTRACT

SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis and osteitis) is a rare chronic autoinflammatory disorder of unknown etiology. Radiological investigation, including the use of magnetic resonance imaging and nuclear medicine is pivotal to the diagnosis of SAPHO syndrome. We present a case of a 15-year-old male diagnosed with SAPHO syndrome displaying the classic diagnostic findings of this condition on bone scan and magnetic resonance imaging.

Introduction

SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis and osteitis) is a rare autoinflammatory condition that may have cutaneous, osseus and articular manifestations. SAPHO is thought to exist on a spectrum of autoinflammatory disorders given the overlapping clinical features shared with conditions such as chronic recurrent multifocal osteitis (CRMO) and other spondyloarthritides. The disease can present at any age and has a highly variable clinical picture [1]. Given the lack of a diagnostic test for SAPHO syndrome, the diagnosis of this disease relies on clinical and radiological features.

A wide variety of radiological investigations can offer valuable insight into the evaluation of SAPHO syndrome, including bone scintigraphy to identify inflammatory foci, local-

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ized magnetic resonance imaging (MRI) investigations to identify and further characterize inflammatory changes within affected bones and joints, computed tomography (CT) to show joint deformities and in some cases even plain radiographs may pick up articular deformities [2].

Of these investigations, MRI is considered the most sensitive in detecting osteitis in SAPHO syndrome, with reported sensitivity of 98% [3].

Herein, we present a case that highlights the plethora of radiological signs in SAPHO syndrome and the utility of radiological examination in attaining an early and accurate diagnosis of this rare condition.

Case

A 15-year-old male presented to the emergency department with a 6-week history of sub-acute lower back pain. The pain started in the left costophrenic angle and the ipsilateral hip and groin. This was associated with unintentional weight loss of 6 kgs and lethargy. Past medical history revealed a self-limiting episode of macroscopic hematuria as a child, investigated with a renal tract ultrasound that showed no focal abnormalities. He had no family history of immune mediated or neoplastic conditions and was previously a healthy and active teenager.

A review of his medical record showed that he had previously presented to the same hospital 2 years prior, when he suffered anterior chest wall tenderness after a fall which was assumed to be related to the fall, and he was discharged on a short course of NSAIDs.

During the current ED presentation, examination revealed a pale, thin, tired boy, obviously limping due to his pain. Multiple acne scars were noted. He had midline lumbar spinal tenderness and an enlarged (2 cm, soft, non-tender) left inguinal lymph node. The examining clinician also noted a palpable liver edge. An erect chest radiograph was obtained at this time point and, retrospectively, it was noted to reveal right sternoclavicular joint irregularity, as a new finding compared to a chest radiograph from 2 years prior (Fig. 1).

At the time of his presentation, blood workup showed microcytic anemia, thrombocytosis, delayed prothrombin time and an INR of 1.5. He had a CRP of 51.2 mg/L, an ESR of 101 mm/hr and subsequent iron studies showed a chronic inflammatory picture with raised ferritin and decreased serum iron.

At this point the initial differential diagnoses to consider included septic arthritis or possible hematological, renal, or hepatic malignancy given the unexplained weight loss, and signs on examination as well as a deranged coagulation panel. However, there were no pathological findings on the hepatic and renal ultrasound examinations that were subsequently performed. A hematological malignancy was considered less likely due to normal blood film examination and subsequent imaging findings.

A computed tomography (CT) scan of the abdomen and pelvis was performed (Fig. 2) given the patient was still experiencing pain in the lower back, and this scan showed mild stranding around the sacroiliac joints, particularly on the left side. The CT bone window images (Fig. 3) demonstrate the presence of subtle erosions with associated joint space widening asymmetrically involving the left SI joint. These features are consistent with sacroiliitis.

A bone scan was performed, showing increased tracer uptake in the sacroiliac joints, especially on the left side (Fig. 3) (Fig. 5). Increased uptake was also noted on the anterior chest wall in the anterior sixth rib and within the right ankle (Fig. 4). A negative gallium scan made infection very unlikely (Fig. 6), supported by negative blood cultures.

The polyarticular nature of the patient's biochemical and imaging findings in combination with the lack of evidence to suggest disseminated infection, suggested an inflammatory etiology, such as spondyloarthropathy or SAPHO syndrome to be more likely. Chronic recurrent multifocal osteomyelitis (CRMO) was also considered as a possible diagnosis, however it was considered less likely due to the presence of dermatological manifestations (severe acne) in the patient.

Given the increased radiotracer uptake in the sacroiliac joints, a lumbar spine MRI was included to assess for features of inflammatory spondyloarthropathy. This showed an asymmetrical sacroiliitis that was then further assessed with a sacroiliac joint MRI revealing mild articular erosion in the left SIJ and periarticular osseus oedema with enhancement of the periarticular bone (Figs. 7 and 8). An infectious etiology was not considered likely due to the bilateral joint involvement.

At this point the provisional diagnosis was SAPHO syndrome, given the imaging findings so far. Further dedicated MRI of the right ankle was performed to evaluate for radiological features of SAPHO given the focal uptake seen on bone scan (Figs. 9 and 10). Patchy marrow oedema was identified on this scan, within the tibia, fibula, talus navicular and calcaneus suggesting a non-infectious osteitis that reaffirmed the provisional diagnosis of SAPHO syndrome.

During his hospital stay and diagnostic workup, the patient was treated with a short course of low dose oral prednisone (10 mg daily for 1 week), was discharged on non steroidal anti inflammatory drugs (NSAIDs) (Naproxen 250 mg 8 hourly) and multivitamins. The patient's pain persisted in follow up visits (1, 2 weeks post discharge) and he was started on methotrexate (10 mg weekly, later increased to 20 mg weekly). Subsequently, an improvement of symptoms was noted, but they were not adequate as the patient still experienced flares of severe pain. The decision was made to conduct baseline investigations and start the patient on adalimumab.

At the time of publication, the patient has been free from painful flares for a year since starting adalimumab but confirms persistence of acne.

Discussion

SAPHO is a rare clinical entity with an estimated prevalence of 1 in 10000 among Caucasian males [4] and 0.00144 in 100000 in the Japanese population [5], however the difficulty in diagnosing the condition suggests that these figures underestimate the prevalence of SAPHO. Overall, SAPHO appears to affect females more often and the first presentation of disease tends to occur more commonly in middle aged adults [3,6]. In compar-

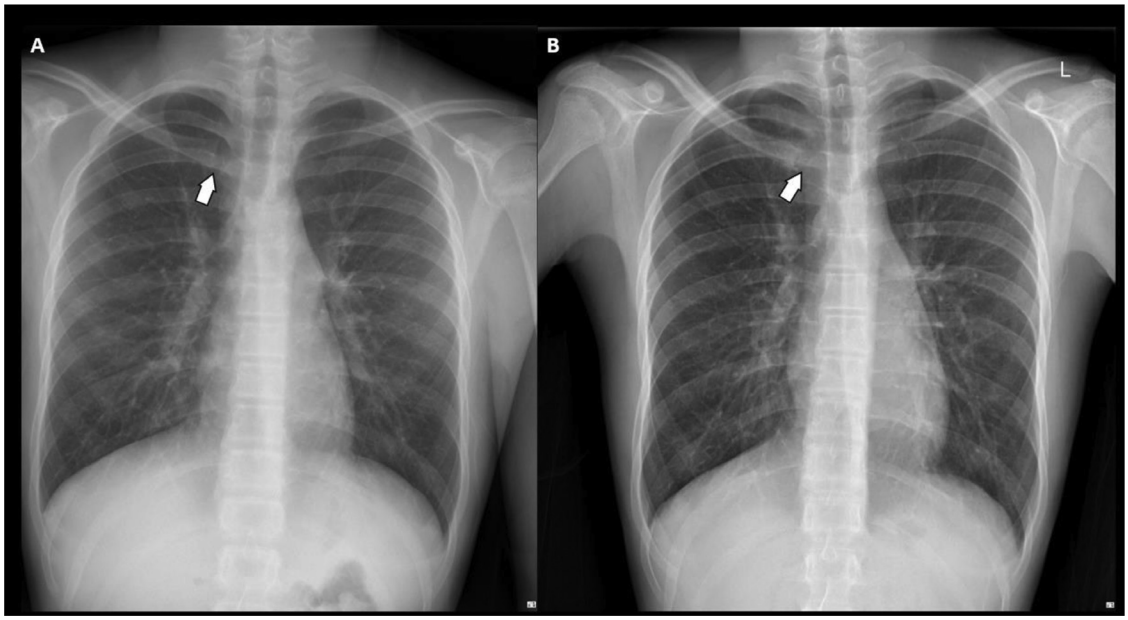

Fig. 1 – Comparison between chest X-rays taken on the day of patient's presentation (B) and 2 years prior (A), showing subtle irregularity along the right sternoclavicular joint margins compared to the earlier X-ray.

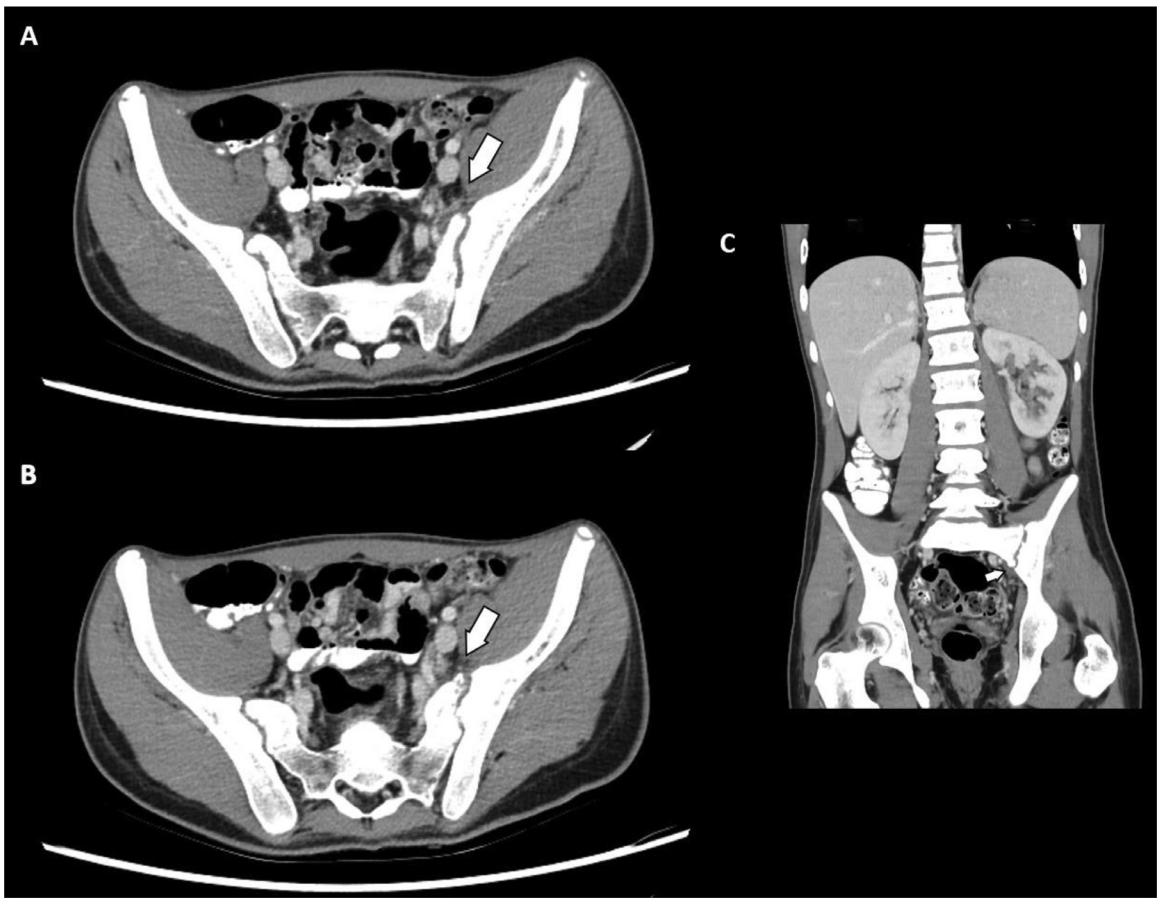

Fig. 2 – Computed tomography (CT) scan of abdomen and pelvis performed with intravenous contrast. Subtle asymmetric fat stranding and para-articular inflammation around the left sacroiliac joint seen on the axial (A, B) and coronal (C) views.

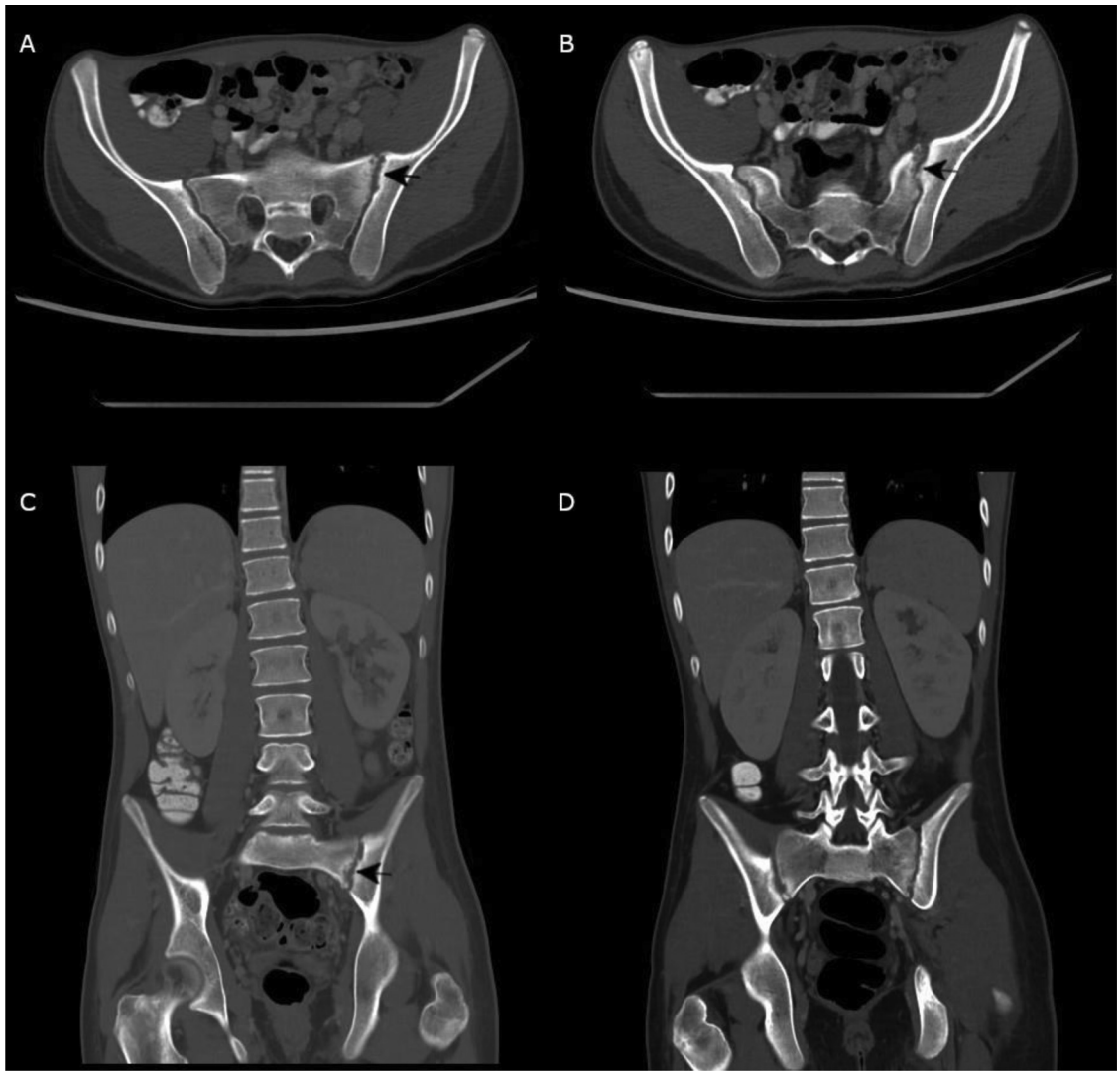

Fig. 3 – Computed tomography (CT) scan of abdomen and pelvis (bone windowed) showing subtle asymmetrical bony erosions and joint space widening at the left sacroiliac joint on the axial (A, B) and coronal (C, D) views.

ison, while CRMO presents with symptoms similar to those seen SAPHO syndrome, CRMO is more common in children, while SAPHO is more common in adolescents and adults [7].

While the precise pathogenesis of SAPHO syndrome is unclear, it is understood that immune dysfunction, infections and genetic susceptibilities may contribute to its development [1]. Studies on the inflammatory response in patients have shown involvement of IL-1, 8, 17, 18 and tumor necrosis factor – α [8]. Although the osseus inflammation in SAPHO syndrome is considered to be sterile, there have been multiple studies where organisms (often *Cutibacterium acnes*) have been isolated from osseus lesions in patients diagnosed with SAPHO [9], suggesting an infection precipitating the inflammation. The importance of genetic predisposition is yet unclear, however several family clusters of SAPHO have been reported [10,11].

There are at least three sets of diagnostic criteria for SAPHO syndrome, however none have been clinically validated for use (Table 1). The diagnosis ultimately depends on identification of characteristic osseus (sterile osteitis, hyperostosis on radiological investigation) and articular lesions (inflammatory synovitis) with or without cutaneous lesions (palmar plantar pustulosis, acne vulgaris). Importantly, the diagnosis of SAPHO can only be made on the exclusion of infectious osteitis, osseus tumors and non-inflammatory condensing lesions of the bone [15].

Clinically, many findings in SAPHO syndrome closely overlap with other spondyloarthritides, especially CRMO. CRMO generally occurs in children and is also characterized by sterile multifocal bone lesions. There is debate as to whether SAPHO syndrome and CRMO represent the same clinical entity, and many consider CRMO as the pediatric presentation of SAPHO syndrome. However, the presence of associated skin manifestations can differentiate between these conditions. Acne is more characteristic of SAPHO than CRMO, which is more commonly associated with other skin manifestations such as palmoplantar pustulosis or pyoderma gangrenosum [16].

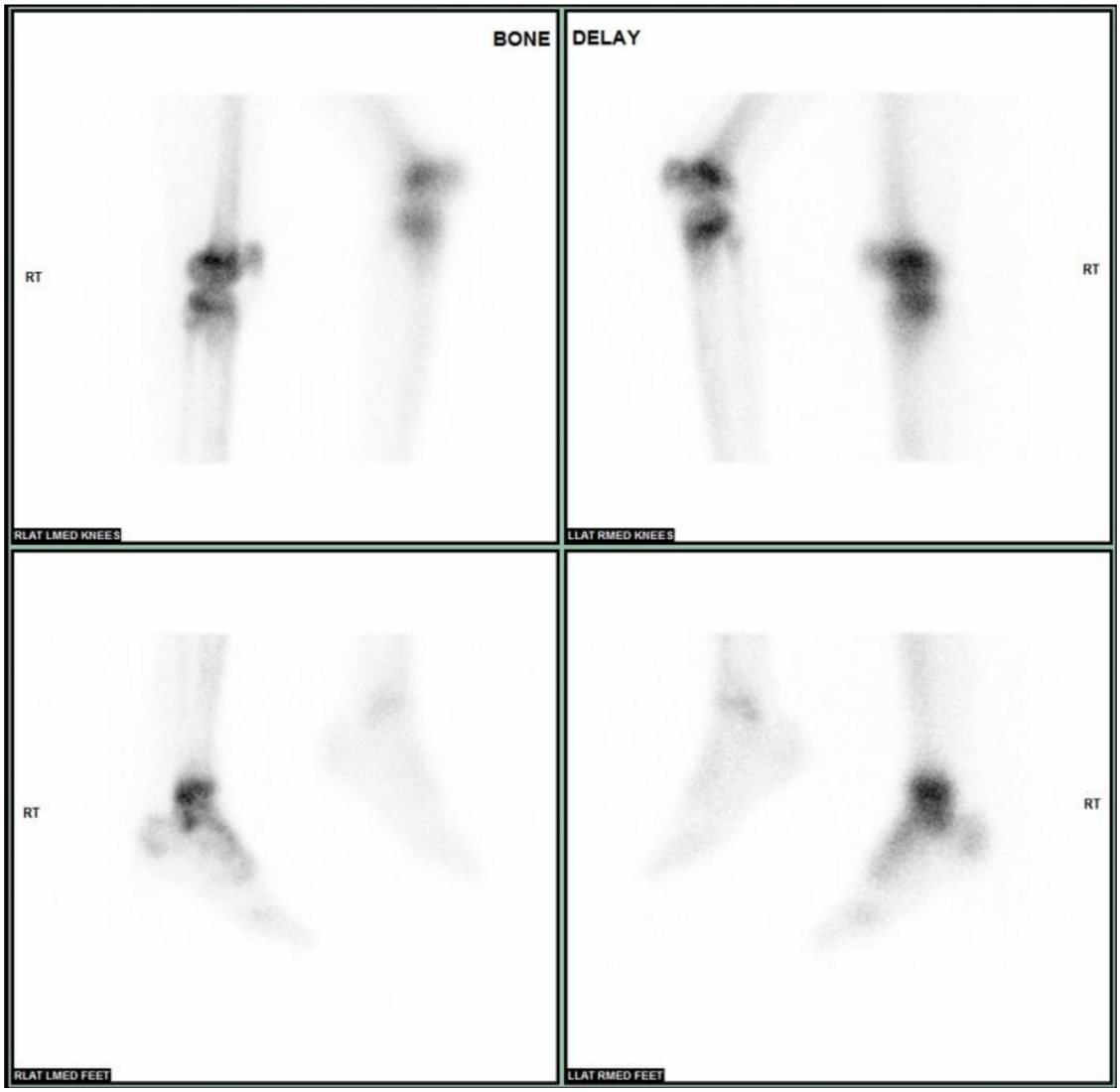

Fig. 4 – Bone scan delayed phase images showing increased tracer uptake in the right ankle compared to the left.

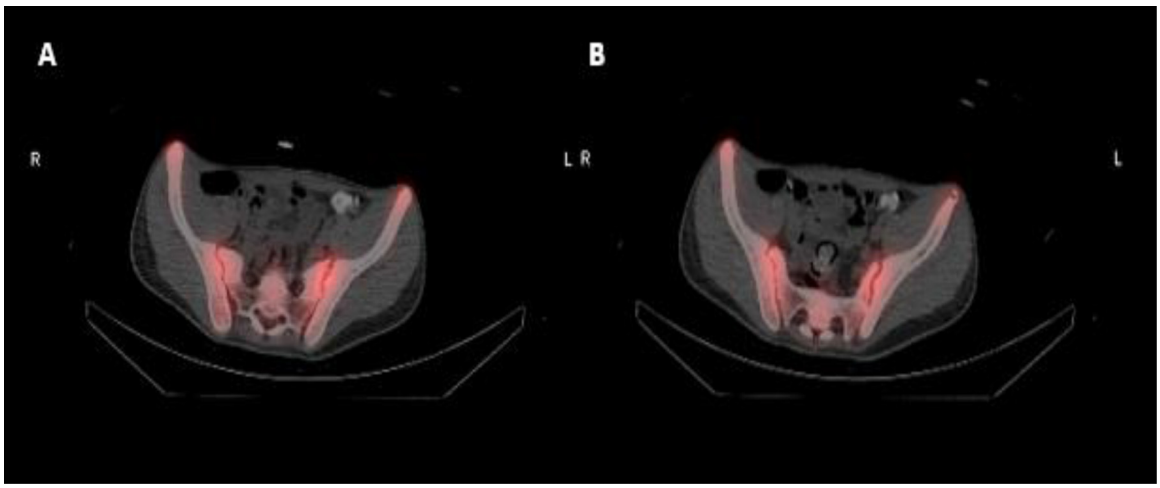

Fig. 5 – Single-photon emission computed tomography (SPECT) bone scan showing asymmetrical tracer uptake in the sacroiliac joints, slightly greater on the left side.

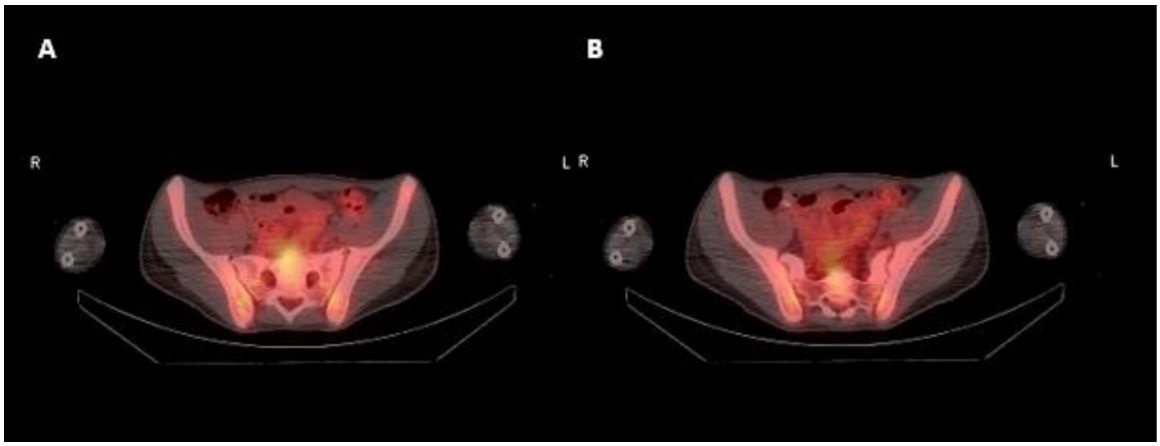

Fig. 6 – Gallium injection image showing no asymmetrical tracer uptake at sacroiliac joints.

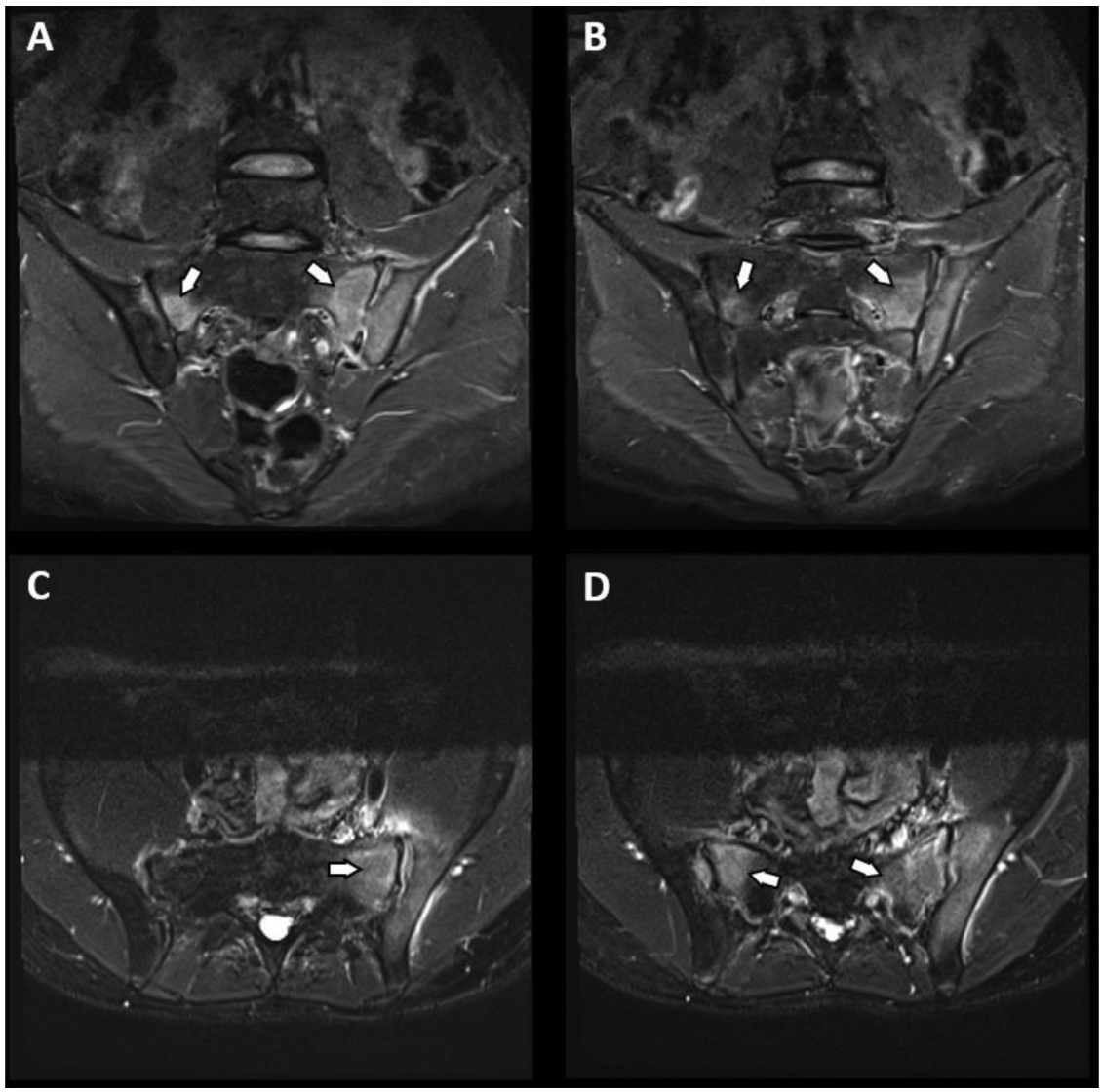

Fig. 7 – A, B - Coronal STIR sacroiliac MRI. C, D Axial T2 fat saturated sacroiliac joint MRI. Asymmetric osteitis with bilateral bone marrow oedema, more intense at the left sacroiliac joint. MRI, magnetic resonance imaging; STIR, short time inversion recovery.

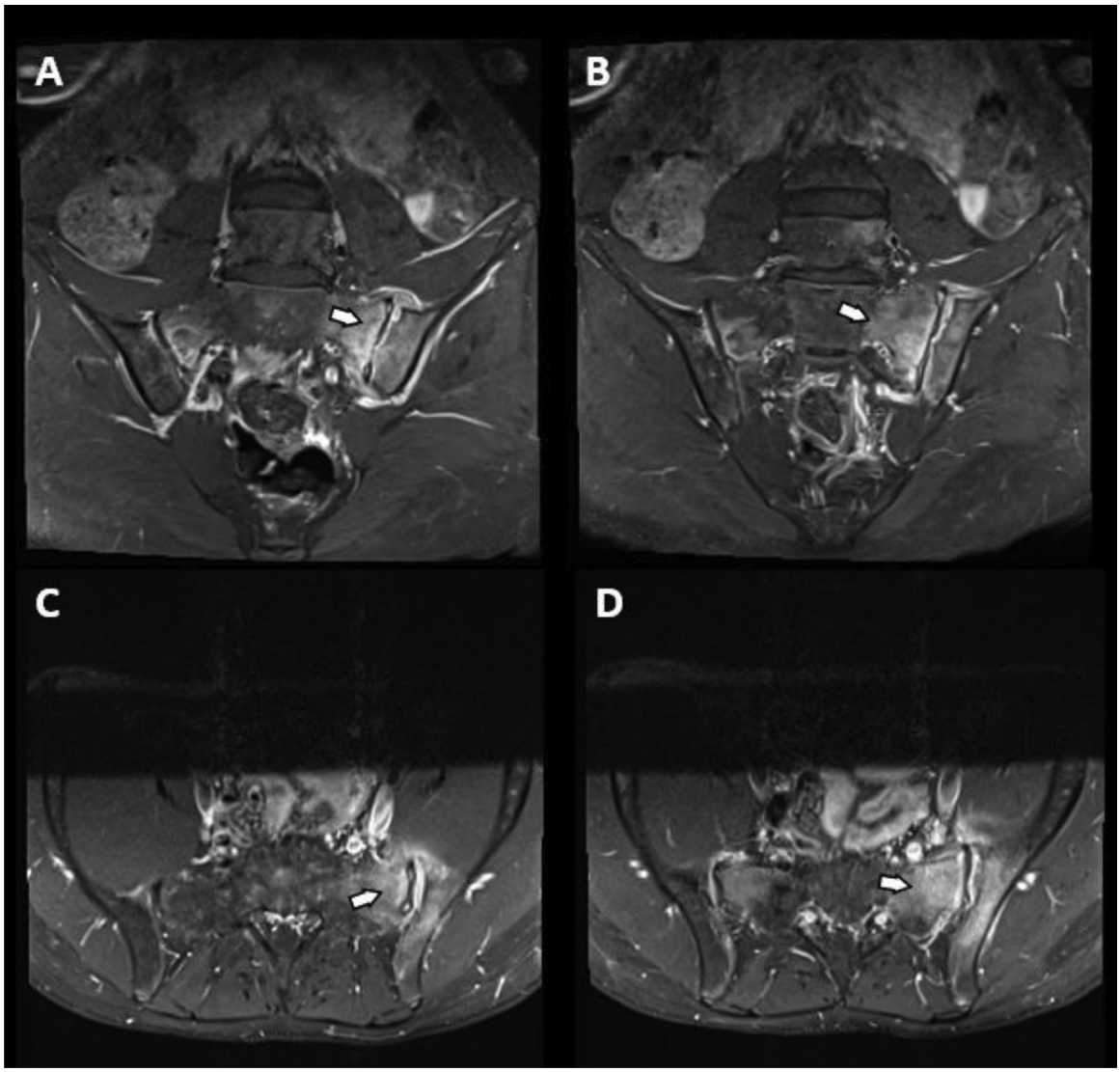

Fig. 8 – A, B - Coronal T1 sacroiliac joint magnetic resonance imaging (MRI) post gadolinium. C, D – Axial T1 sacroiliac joint MRI post gadolinium. Asymmetric bone marrow and para-articular enhancement, more extensive at left sacroiliac joint.

Table 1 – Three existing diagnostic criteria for SAPHO syndrome.

Benhamou et al. (1988) [12]	Kahn and Khan (1994)[13]	Kahn (2003)[14]
At least 1 of the 4 following conditions: 1 Osteoarticular manifestations of acne conglobate, acne fulminans, or hidradenitis suppurativa 2 Osteoarticular manifestation of PPP 3 Hyperostosis (of the ACW, limbs or spine) with or without dermatosis 4 CRMO involving the axial or peripheral skeleton with or without dermatosis	At least 1 of the following 3 conditions: 1 Chronic recurrent multifocal sterile and axial osteomyelitis, with or without dermatosis 2 Acute, subacute, or chronic arthritis associated with PPP, pustular psoriasis, or severe acne 3 Any sterile osteitis associated with PPP, pustular psoriasis, or severe acne	At least 1 of the following 5 conditions: 1 Bone–joint involvement associated with PPP and psoriasis vulgaris 2 Bone–joint involvement associated with severe acne 3 Isolated sterile hyperostosis/osteitis 4 CRMO (children) 5 Bone–joint involvement associated with chronic bowel diseases Exclusion: Infectious osteitis, tumoral conditions of bone, non-inflammatory condensing lesions of bone.

ACW, anterior chest wall; CRMO, chronic recurrent multifocal osteomyelitis; PPP, palmoplantar pustulosis; SAPHO, synovitis, acne, pustulosis, hyperostosis and osteitis.

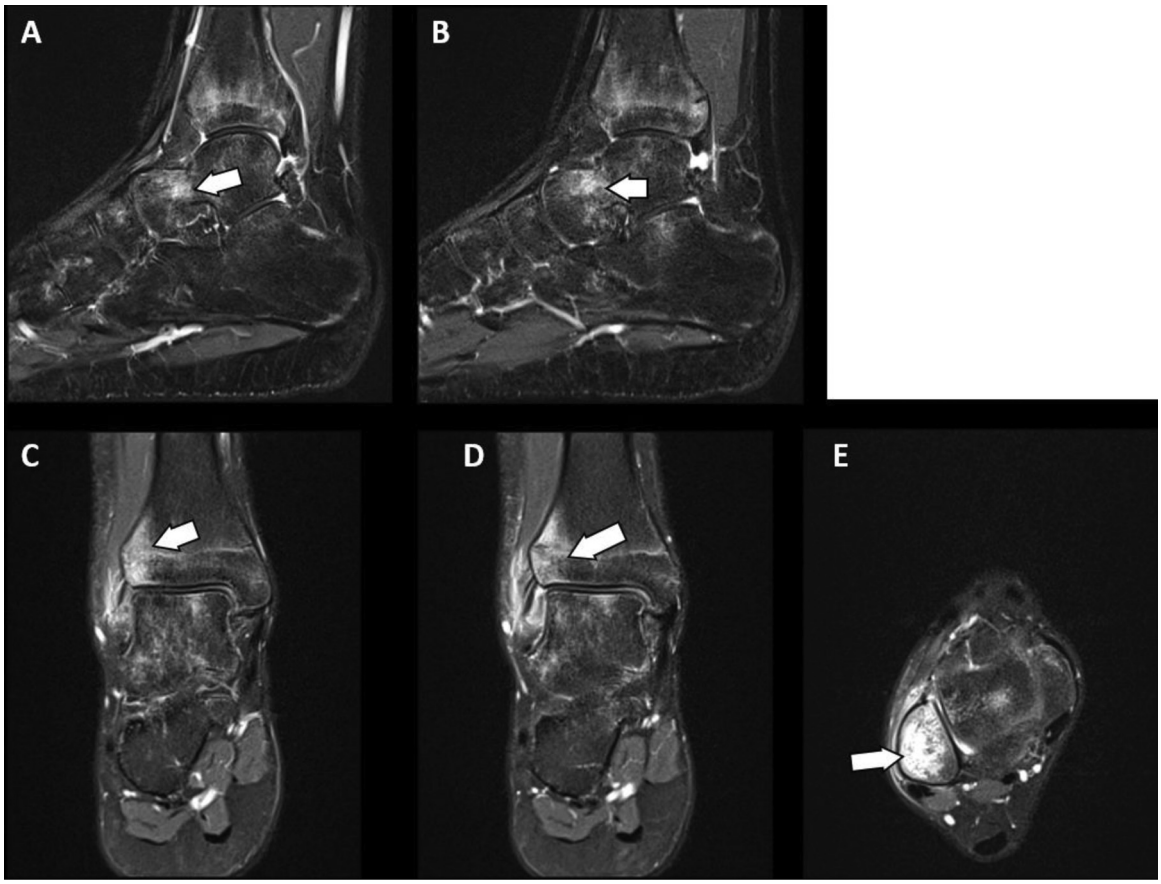

Fig. 9 – A, B: Sagittal STIR ankle (right) MRI. C, D – Coronal proton density (PD) fat saturation ankle (right) MRI. E – Axial PD fat saturation ankle (right) MRI. Osteitis with bone marrow oedema in the distal tibia, talus and fibula with adjacent soft tissue inflammation. MRI, magnetic resonance imaging; STIR, short time inversion recovery.

Thus, radiological examination is necessary in the diagnostic investigation of SAPHO syndrome. Plain radiography can detect hyperostotic changes, sclerosis and osteolysis [17], but these scans may remain unremarkable for months after disease onset [18]. Therefore, while plain radiography may be used in initial evaluation, further imaging is warranted if the diagnosis remains unclear.

Whole body bone scintigraphy is very useful in SAPHO, especially in localizing clinically occult inflammatory foci to guide localized radiological examination. Radiotracer uptake is increased in regions of active inflammation. In SAPHO syndrome, the characteristic and highly specific "bull head sign" can be appreciated on bone scintigraphy, denoting inflammatory involvement of the sternoclavicular joint [17].

CT imaging is very useful in detecting osteoarticular lesions in SAPHO syndrome, especially axial lesions. In SAPHO syndrome, the spine is the second most commonly involved site and can often be asymptomatic [1]. It has high utility in detecting lesions of the thoracolumbar spine, which are often underappreciated on bone scintigraphy owing to the spine's position deep within the chest [2].

The most sensitive modality for detecting lesions, however, is MRI. MRI has been shown to have a sensitivity of 98% in detecting osseus lesions in SAPHO syndrome, and a large cohort study reported that MRI revealed sacroiliitis in 89.7% percent of patients with SAPHO syndrome [3]. Also, its use is preferred in children and adolescents to minimize radiation exposure. MRI is useful in detecting bone marrow oedema, which appears hypointense on T1 and hyperintense on STIR (short time inversion recovery). This signifies active inflammation. It can also evaluate disease progression, being able to display bony erosions and ankylosis or be used to evaluate surrounding tissue for evidence of soft tissue inflammation [2].

While there are many case reports and series studying management strategies for SAPHO syndrome the rarity of the condition precludes evidence based on randomized clinical trials. In general, the condition is managed with the combination of NSAIDs and a short course of low dose oral glucocorticoids to treat acute flares. Options available to treat chronic disease, disease relapse or reduce steroid burden include methotrexate and tumor necrosis factor inhibitors. The patient is treated until they achieve a stable state of remission or low disease activity and then pharmacological therapy is weaned [1].

SAPHO, is ultimately, a chronic condition and follows a relapsing-remitting course. There is a wide variability in the severity of acute inflammatory flares, but, the long term prognosis is generally quite good [1].

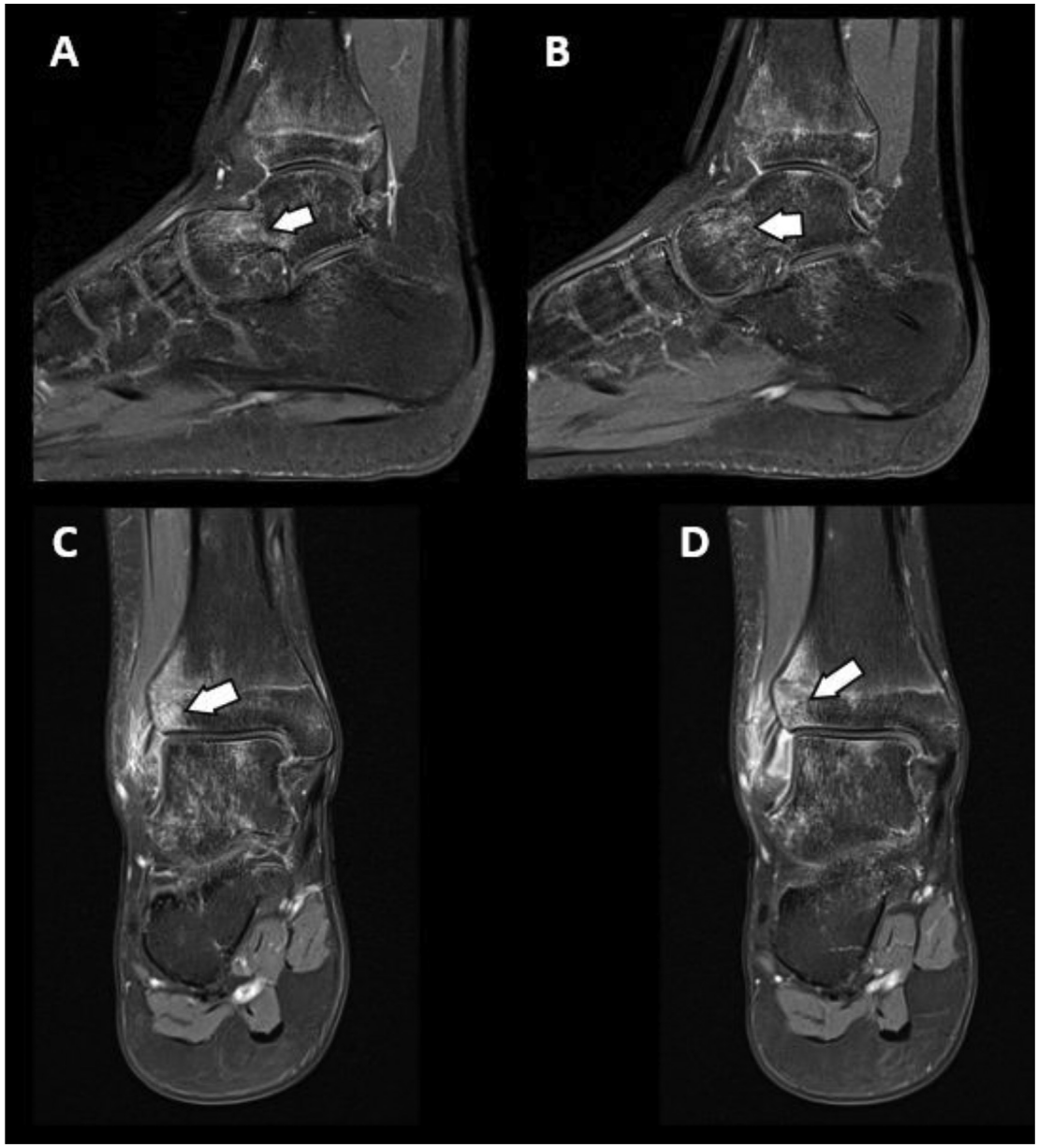

Fig. 10 – A, B – Sagittal T1 fat saturated ankle (right) magnetic resonance imaging (MRI) post gadolinium. C, D – Coronal T1 fat saturated ankle (right) MRI post gadolinium. Bone marrow enhancement in the distal tibia, talus and fibula with adjacent soft tissue inflammation.

This case report demonstrates the role of radiological examination, especially the sensitivity of MRI examination and its value in conjunction with bone scintigraphy in establishing a rapid and accurate diagnosis of SAPHO syndrome.

Patient consent

Written consent was obtained from the patient and his guardian for the publication of this case report.

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