

# SAPHO Syndrome: About Three Cases and Review of the Literature

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## Abstract

**Background:** SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, osteitis) is both a dermatological and a rheumatological entity, with the common denominator of an aseptic inflammatory process, the bone manifestations of which are the essential element of the diagnosis. Despite its chronic and recurrent nature, SAPHO syndrome is very rarely the cause of major disability, even after several decades of evolution. **Objective:** We want to illustrate through three clinical cases, the importance of the anamnesis, the clinic, the diagnostic criteria in the diagnosis of SAPHO syndrome. **Presentation of the cases:** We studied the clinical file of three patients consulted in the Rheumatology Department of the CHU Aristide LeDantec in Dakar, Senegal, between January 2012 and December 2020, suffering from SAPHO syndrome of diagnosis established in accordance with the diagnostic criteria of SAPHO syndrome proposed by Khan *et al.* of 1994. **Conclusion:** SAPHO syndrome is a rare pathological entity, over a period of 8 years we report 3 cases.

## Keywords

Anamnesis, Clinical, Diagnostic Criteria, Female, SAPHO Syndrome, Senegal

## 1. Introduction

SAPHO syndrome is referred to as “*Skibo-disease*” (short for skin-bone), which is a combination of bone and joint manifestations related to dermatologic signs [1], as defined by Kahn *et al.* in 1994 [2]. The epidemiological data available do not allow us to estimate its prevalence due to the lack of a precise census of proven cases. It is a painful and disabling disease that affects women more frequently than men, and especially young adults between 30 and 50 years of age [3]. The disease can occur in early childhood as osteitis [4]. The diagnostic criteria for SAPHO syndrome proposed by Kahn *et al.* in 1994 are 3: 1) aseptic mul-

tifocal osteomyelitis, with or without skin lesions; 2) acute or chronic joint involvement associated with palmoplantar pustulosis, palmoplantar pustular psoriasis, severe acne, hidrosadenitis (Verneuil's); 3) aseptic mono- or polyostotic osteitis associated with palmoplantar pustulosis, palmoplantar pustular psoriasis, severe acne [5]. According to Kahn, the presence of only one of these criteria is sufficient for the diagnosis of SAPHO syndrome. The pustular dermatological conditions associated with these criteria are: a) psoriasis (pustular psoriasis and palmoplantar pustulosis); b) acne (acne conglobata and fulminans or triad); c) neutrophilic dermatoses (rare). The clinical course is usually chronic, but the syndrome may sometimes regress spontaneously and never presents with malignant or septic lesions. [6] [7]-[15]. The objective of our study is to illustrate through three clinical cases, the importance of the anamnesis, the clinic, the diagnostic criteria in the diagnosis of SAPHO syndrome. The methodology was the study of the clinical file of three patients consulted in the rheumatology department of the CHU Aristide LeDantec in Dakar, Senegal, between January 2012 and December 2020, suffering from SAPHO syndrome of diagnosis established in accordance with the diagnostic criteria of SAPHO syndrome proposed by Khan *et al.* of 1994.

## 2. Observation of the Patient

### 2.1. Observation 1

A female patient born in 1969 (48 years old in 2017), black, Senegalese followed by the odontology department since September 2016, for a chronic diffuse sclerosing aseptic osteomyelitis of the left mandible, she is under antibiotic therapy despite a negative infectious workup (quantiferon, sputum-BAAR, HCV, HBV, HIV serologies and the culture of a bone biopsy of the site). She was referred to us in the rheumatology department in March 2017, for axial and peripheral joint pain, occurring in inflammatory flares, evolving for about 8 months. On history taking, we note that the patient was followed by the dermatology department for a palmoplantar rash in 2015, which evolved into palmoplantar pustulosis.

The rheumatological examination found a pelvic-spinal syndrome with lumbar spine stiffness and bilateral asymmetric chronic peripheral polysynovial polyarthritis (fusiform fingers of both feet, both ankles and left knee).

Biology revealed an inflammatory syndrome with a blood pressure of 48 mm at the first hour, a CRP of 97 mg/l and an alkaline phosphatase of 132 IU/l. On immunology, HLA B27 antigen was negative, as were rheumatoid factors, anti-citrullinated peptide antibodies and antinuclear antibodies. On imaging, the CT scan showed osteocondensation of the dorsal vertebral endplates (D10-D11-D12) and unilateral left sacroiliitis, Forestier stage III.

In view of the chronic diffuse sclerosing aseptic osteomyelitis of the left mandible followed by the dentistry department since 2016, her history of palmoplantar pustulosis treated by the dermatology department in 2017, synovitis, non-spe-

cific biological inflammatory syndrome, elevated alkaline phosphatase, condensation images on CT scan, and in view of the diagnostic criteria proposed by Khan *et al.* of 1994 (**Table 1**), we can evoke the diagnosis of SAPHO syndrome.

Our patient was placed on a biphosphonate infusion (pamidronic acid); after six months of treatment, no complications were observed.

## 2.2. Observation 2

A female patient born in 1976 (39 years old in 2015), black, Senegalese, consulted the rheumatology department in July 2015, for joint pain.

On history, mechanical and inflammatory low back pain evolving for more than 12 years was noted. On general examination, anorexia, asthenia and weight loss (BMI 14.86 kg/m<sup>2</sup>) were noted. The physical examination revealed a spinal syndrome with stiffness of the lumbar spine, fixed, without radiation and a deformation of the anterior chest wall with palmoplantar pustulosis. Biology showed a non-specific biological inflammatory syndrome with a sedimentation rate of 29 mm at the first hour and a CRP of 43 mg/l. Serum protein electrophoresis revealed an inflammatory profile, with hyperalpha1 (6.15 g/dl) and hyperalpha2 (12.37 g/dl). Alkaline phosphatase and blood calcium levels returned to normal. HLA B27 antigen is positive and antinuclear antibodies are negative. On imaging (CT scan), osteocondensing bone lesions of L2, L3 and L4 associated with stepped disc disease and bull's head hyperfixation coupled with MRI of the anterior chest wall were observed.

The diagnosis of SAPHO was retained in view of the epidemiological arguments, in particular the age (39 years), the clinical arguments (spinal syndrome with stiffness of the lumbar spine, deformation of the anterior chest wall and palmoplantar pustulosis), paraclinical arguments (non-specific biological inflammatory syndrome, osteocondensing bone lesions of L2, L3 and L4 and bull's head hyperfixation of the anterior chest wall) and above all the diagnostic criteria proposed by Khan *et al.* in 1994 (**Table 1**).

**Table 1.** Diagnostic criteria for the SAPHO syndrome proposed by Kahn *et al.* in 1994.

SAPHO: diagnostic criteria	
Principal criterion	Aseptic multifocal osteomyelitis or caused by <i>propionibacterium acnes</i>
Lesser criteria	1 - Osteoarticular Acute or chronic joint involvement Monostotic or polyostotic aseptic osteitis
	2 - Cutaneous Palmoplantar pustulosis
	Severe acne
	Hidradenitis suppurativa
SAPHO is diagnosed in the clinical radiological examination finds:	
One or other form of the principal criterion	
Or	
An association of 2 lesser criteria	
<b>Kahn MF, Khan MA. Baillieres. Clin Rheumatol 1994; 8(2):333-62.</b>	

After failure of treatment with non-steroidal anti-inflammatory drugs and then methotrexate, our patient was placed on a biphosphonate infusion (pamidronic acid). After 8 months of treatment, the visual analogue pain scale decreased significantly and weight gain was noted (BMI 18.28 kg/m<sup>2</sup>).

### 2.3. Observation 3

A female patient born in 1980 (33 years old in 2013), with no notable history, consulted the rheumatology department in February 2013, for low back and hand pain. On history, spinal pain evolving for about five years was noted. It is lumbar pain, radiating to the buttocks. Then, less than 4 months ago, we noted an increase in the lumbar pain, associated with pain in the fingertips of both hands, as well as onycholysis of the nails of both hands. The physical examination revealed a pelvic syndrome, synovitis of the 2nd, 3rd and 4th fingers of both hands and palmoplantar pustulosis.

The biology reveals a non-specific biological inflammatory syndrome with a CRP of 18 mg/l, the haemogram, the liver balance, the creatinine, the proteinuria, the haematuria and the leucocyturia are normal, the same is true for the calcemia, the phosphoremia, the serologies HCV, HBV, HIV and the serology of Chlamydia. The HLA B27 antigen test was negative. On imaging (CT scan), a bilateral sacroiliitis stage III of Forestier and discopathies with osteocondensation were observed, giving a raised aspect of the vertebral plates.

In view of the epidemiological arguments, in particular the age of our patient (33 years), the clinical arguments (pelvic syndrome, synovitis of the 2nd, 3rd and 4th fingers of both hands and palmoplantar pustulosis), the biological arguments (biological inflammatory syndrome), imaginary arguments (bilateral sacroiliitis stage III of Forestier and discopathies with osteocondensation giving a browed aspect of the vertebral plates) and especially in front of the diagnostic criteria proposed by Khan *et al.* of 1994 (**Table 1**), we can evoke the diagnosis of SAPHO.

After failure of treatment with non-steroidal anti-inflammatory drugs, our patient was placed on methotrexate 15 mg weekly per os associated with folic acid (Acfol 15 mg weekly), 48 hours after methotrexate. Blood counts, transaminases and creatinine every six months are the follow-up tests in our patient. After six months of treatment, no complications were observed.

## 3. Review of the Literature

### 3.1. From an Epidemiological Point of View

The prevalence of SAPHO syndrome worldwide is poorly known, with probable variations from continent to continent. In Japan, among SpA patients, the proportion of rheumatism related to palmoplantar pustuleux has been estimated to be 4.7%, with a national prevalence of about 1/10,000 [16]. During palmoplantar pustular disease, the frequency of osteoarticular manifestations ranges from 9.4% to 15% depending on the series [17] [18] [19].

In 1987, a large French multicenter survey was able to gather 85 observations of SAPHO syndrome, including 44 with palmoplantar pustuleux and 13 with acne [20]. More recently, a single-center, partially retrospective study collected 120 cases of SAPHO syndrome. Of these, 66 patients had palmoplantar pustuleux, and 30 had severe acne. Evidence of “overlapping” forms, palmoplantar pustuleux was associated with psoriasis vulgaris in 21 cases, whereas severe acne was combined with palmoplantar pustuleux or psoriasis vulgaris in 8 cases.

Females were slightly more frequently affected than males, whereas the opposite ratio was observed during acne [20]. Since the first pediatric observations, it is known that children are not spared [21]. However, the average age of onset of symptoms is between 30 and 40 years [20]. There is no ethnic predisposition, although the first reported cases were mainly from Japan, whereas the American continent seems to be relatively free of the disease.

As with psoriatic arthritis, the dermatological component of SAPHO syndrome may precede the first signs of rheumatic disease by many years or, on the contrary, may be extremely delayed [22]. It may even be absent throughout the course of the disease, but this does not prevent the diagnosis from being made on purely rheumatological grounds: in this case, it is the bone involvement that takes precedence, provided that it is characteristic. This was the case in 19 patients (16%) in the Bichat series. In the French multicenter series, 28 of 85 cases had no skin involvement at the time of diagnosis [20].

### 3.2. Diagnosis

1) The manifestations are primarily cutaneous and osteoarticular, although systemic involvement is possible.

a) The main cutaneous manifestations are palmoplantar pustuleux, severe acne in its three forms (acne conglobata, hidrosadenitis suppurativa and acne fulminans) and psoriasis. Sometimes these manifestations can be combined. Palmoplantar pustuleux is more frequent in subjects over 30 years of age, especially females, whereas acne is more frequent in men under 30 years of age [23]. Other skin lesions are increasingly described, such as pyoderma gangrenosum [24] and Sweet’s syndrome [25]. Skin involvement is missing in one third of cases. This should not rule out the diagnosis, especially as it may be seen years after the onset of osteoarticular symptoms or may be remote and go unnoticed. It may also be missed throughout the course of the disease. The skin manifestations evolve independently of the osteoarticular involvement. During the course of the disease, skin involvement may appear in patients who are completely asymptomatic from a rheumatological point of view.

b) Among the joints, the anterior chest wall is the most common location. It is seen in 65% - 90% of cases [26]. All its anatomical components may be affected, but in particular the medial fragment of the clavicle. The involvement is usually unilateral. It manifests itself as inflammatory pain in the anterosuperior part of the chest, which may radiate to the neck and shoulders. Clinical examination reveals swelling of the anterior chest wall structures in 93% of cases [27] with

local inflammatory signs in 83% of cases [28]. Spinal involvement is seen in 32% to 52% of cases. It is usually segmental and may involve all three spinal levels. The dorsal spine is the most affected. Spinal involvement is manifested by stiffness, inflammatory-type spinal pain or mixed back pain. Involvement of the sacroiliac joints results in inflammatory gluteal pain, sometimes with a pseudoradicular course. Bone involvement may involve the long bones, in particular the metaphyses of the lower limbs in one third of cases. The typical form is chronic recurrent multifocal osteomyelitis occurring in children, manifested by bone pain, tenderness or swelling of the affected areas without alteration of the general condition or signs of infection. The inclusion of this aseptic multifocal osteomyelitis, described more rarely in adults, in the SAPHO syndrome is controversial. Its association with cutaneous manifestations (palmoplantar pustule, acne) and inflammatory enteropathies brings it closer to the SAPHO syndrome. Nevertheless, its tropism for the long bones as well as the involvement of the anterior thoracic wall limited to a hyperostosis of the internal extremity of the clavicle and sparing the other anatomical components of this wall make it a separate entity for some authors. Mandibular involvement is seen in 10% of cases. Diffuse and sclerosing osteomyelitis of the mandible is considered a manifestation of the SAPHO syndrome. It is often unilateral and presents with hemimandibular pain sometimes associated with trismus or paresthesias. A secondary deformity may occur [29] [30]. This location seems to be the most painful. However, it may remain clinically silent and may be discovered on scintigraphy. Peripheral joint involvement may result from the extension of an aseptic inflammatory process from a focus of osteitis or it may begin in the joint. It may involve the elbows, hips, knees and ankles. It may involve small joints such as the metacarpophalangeal and proximal interphalangeal joints. Involvement of the distal interphalangeal joints is exceptional. It may be a mono or oligoarthritis, more rarely a polyarthritis. The joints are swollen. Sometimes arthralgia without arthritis can be found. Anterior chest wall locations are the most common in palmoplantar pustuleux. Sixty to 100% of patients with palmoplantar pustuleux have anterior chest wall involvement [31] [32]. Less common is the association with spinal involvement, sacroiliitis or peripheral arthritis. Spondylodiscitis is seen in SAPHO syndromes that include palmoplantar pustulosis or pustular psoriasis. It is exceptional in association with acne. Acne conglobata and hidrosadenitis suppurativa are frequently associated with peripheral joint manifestations with arthritis that can be destructive [33]. With acne fulminans, aseptic osteitis is more frequently observed. Peripheral arthritis is seen in only one third of cases and is usually non-destructive [34].

2) There are no biological markers for SAPHO syndrome. However, a biological inflammatory syndrome, hyperleukocytosis and elevated alkaline phosphatase may be observed. HLA B27 antigen is found in 8% - 14% of cases [35]. In a series of 85 cases, Chamot *et al.* [34] found a correlation between HLA B27 antigen positivity and anterior chest wall involvement. Imaging of SAPHO syn-

drome combines anterior chest wall, spinal, sacroiliac and peripheral osteoarticular images. Although radiographs can show lesions consistent with SAPHO syndrome, the sensitivity of these examinations remains low (13%), especially in the early stages of the disease. Fritz *et al.* [36] have shown that they detect only 16% of lesions detected early by MRI. The primum movens of hyperostosis is inflammation of the enthesis. This enthesitis goes through an erosive phase and then becomes mixed, erosive and ossifying. In the late stage, it has a purely ossifying aspect. In the case of clavicular involvement, costo-clavicular enthesopathy and a focus of hyperostosis of more than 5 mm in diameter on the sternum or the first ribs are signs suggestive of SAPHO syndrome [37]. Spinal involvement is characterised by a high degree of radiological polymorphism with aspects of localised or total condensing osteitis, vertebral hyperostosis, spondylodiscitis and sometimes vertebral compression. In one third of cases, several adjacent vertebrae are affected. This aspect, rarely seen in spondyloarthropathies, is quite characteristic of SAPHO syndrome [38]. Sacroiliac involvement is characterized by subchondral erosions and condensation predominantly on the iliac side. Lesions of the long bones mainly involve the lower end of the femur and the upper third of the tibia in their metaphyseal or metaphyseal portion. Initially, the damage is manifested by bone lysis with blurred edges and, in a secondary phase, by heterogeneous osteocondensation frequently associated with periosteal appositions that can lead to pseudo-tumoural enlargement of the bone. Peripheral joint involvement is manifested by swelling of the adjacent soft tissue or bone rarefaction. More rarely, erosions, chondrolysis or even joint destruction with periosteal apposition may be observed. Mandibular involvement results in areas of osteolysis and secondary bone condensation, usually unilateral, associated with a periosteal reaction [32]. Computed tomography (CT) is the reference examination for exploring the anterior chest wall and in particular the involvement of the sternocostoclavicular joints and the extension of the lesions to the soft tissues [35]. It also shows vascular lesions. It is known to help in the early detection of areas that are clinically silent and in standard radiographs of the sacroiliac joints and the spine. Nuclear resonance imaging (MRI) can be of great diagnostic value early in the course of the disease. Fritz *et al.* [36] showed that 67% of lesions detected on MRI were clinically asymptomatic. Because of its performance in the exploration of entheses, this examination makes it possible to establish a correlation between the stage of the disease and the clinical symptoms. MRI is more sensitive than CT in detecting adjacent joint and soft tissue involvement [37]. MRI can also demonstrate the effectiveness of treatment as remission is accompanied by the restoration of a normal fatty bone marrow signal [38]. Its use as a monitoring tool is preferable to bone scans as the latter are radiation exposed. MRI can also differentiate inflammatory spondylodiscitis from infectious pyogenic disease by showing the absence of microabscesses or epiduritis. The limited appearance of erosions is also in favour of a non-infectious cause [39]. Bone scans not only show hyperfixation of painful sites, but al-

so detect subclinical lesions not detected by other imaging methods. In the anterior chest wall, there is a scintigraphic sign highly suggestive of SAPHO syndrome, namely the bull head sign. Bone biopsy is only performed in atypical forms. It must be deep enough to reach the cancellous bone. Inflammatory lesions with neutrophil and mononuclear cell infiltrates are usually seen. Later, there is fibrosis of the bone and a rarefaction of the inflammatory infiltrate. Bone biopsy does not provide any specific information, but it is of major importance as it allows us to rule out an infectious or tumorous pathology in doubtful cases and especially in the case of a single lesion.

3) The positive diagnosis of SAPHO syndrome is most often based on the criteria proposed by Kahn in 1994 (**Table 1**) but some still use the Benhamou criteria published in 1988 [40]. The diagnosis is easy if the symptomatology combines typical osteoarticular signs and skin manifestations. It becomes difficult in the presence of atypical osteoarticular involvement or when skin manifestations are missing. The diagnosis of SAPHO syndrome is important as it avoids unnecessary investigations and inappropriate treatment.

### 3.3. Therapeutic Aspect

1) For inflammatory bone or joint manifestations, non-steroidal anti-inflammatory drugs (NSAIDs) are the mainstay of treatment, either on an ad hoc basis during intermittent inflammatory flare-ups or continuously in the case of linear progression of rheumatism. The efficacy of NSAIDs is considered satisfactory in about two-thirds of cases. Inadequate response may justify the use of corticosteroids, with equivalent results. Colchicine does not appear to be effective, except in exceptional cases [41]. For limited, mono- or oligoarticular forms of the disease, local cortisone infiltration or osmic acid synoviorthesis can be very beneficial. A case of refractory sternoclavicular osteoarthritis required surgical resection of the medial end of the clavicle.

2) Bone involvement led to the suggestion of intravenous administration of biphosphonates (pamidronate), which resulted in apparent good pain control, with a relatively prolonged suspensive effect [42].

3) In the rather exceptional situations where *Propionibacterium acnes* has been found in a bone or joint lesion, antibiotic treatment has logically been instituted, with generally satisfactory efficacy. Different therapeutic protocols were used; their administration took place over a period of several months. A wide variety of antibiotics have been chosen: tetracyclines (doxycycline), macrolides (roxithromycin, azithromycin), amoxicillin or rifampicin, as monotherapy or in combination [43] [44] [45] [46]. Based on these observations, various authors have proposed protocols for prolonged antibiotic therapy, even in the absence of initial isolation of any micro-organism. Doxycycline, in particular, has shown inconsistent results [47].

4) Refractory or particularly recurrent forms have led to the use of a “modifying” treatment. As with psoriatic arthritis, methotrexate has been proposed, es-

essentially to patients with a predominantly peripheral form of rheumatism, with a good efficacy profile. Ciclosporin has shown some good results [48]. On the other hand, sulfasalazine was rarely effective, with approximately one in three patients improved, at least partially, in the Bichat Hospital cohort. However, there are some more encouraging results in adults [49] and especially in paediatric forms [50]. Recently, two separate teams have proposed the use of anti-TNF treatment, by infliximab or etanercept, for four refractory forms of SAPHO syndromes [51] [52]: the promising results need to be confirmed in a larger number of patients.

### 3.4. Evolution

The evolution of the SAPHO syndrome, in its different components, is variable.

The hyperostotic pustulo-psoriatic spondyloarthritis described in 1985-1986 only affects adults, it is continuous and chronic and only appears after puberty. Cure occurs at the end of an active phase that can last for several decades. This cure does not exclude the persistence of partially disabling sequelae.

Chronic recurrent osteomyelitis, one of the frequent manifestations of OHPS, as its name indicates, is chronic and recurrent. However, subacute courses with rapid recovery after the first attack have been described [53].

Visceral complications occur in the soft tissues adjacent to the affected bones, in an inflammatory, oedematous and fibrosing environment [54].

These include [55] [56] [57] [58]:

- Vascular stenoses (subclavian in clavicle osteitis; pelvic veins related to retroperitoneal fibrosis in iliac osteitis);
- Vascular inflammation (aortitis related to spondylitis or sternal osteitis);
- Inflammation of nerves (plexitis in low cervical spondylitis, intercostal neuralgia);
- Pleurisy and pericarditis in case of upper thoracic osteitis.

Chronic recurrent multifocal osteomyelitis may be complicated by enteropathy (ulcerative colitis or Crohn's disease) [59].

Patients are followed up with MRI scans every 6 months or so and sometimes with follow-up bone scans for long-term follow-up.

Biological monitoring is of lesser importance, unless treatment-related complications arise.

## 4. Conclusion

SAPHO syndrome is mainly observed in children and young adults. Its exact pathogenesis remains unknown and although the inclusion of SAPHO syndrome within the seronegative spondyloarthropathies remains controversial, the diagnosis of ankylosing spondylitis is sometimes made at the beginning because, indeed, many similarities exist between these two entities.

## Consent

Informed consent was obtained from all three patients.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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