Chapter 7

SAPHO Syndrome

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Additional information is available at the end of the chapter

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Abstract

SAPHO syndrome is an entity that associates musculoskeletal disorders with dermatological alterations. The most characteristic clinical manifestation of the SAPHO syndrome is pain in the anterior chest wall, due to the involvement of the sternoclavicular and costochondral joints. The etiology of SAPHO syndrome is unclear. The treatment is not protocolized. Nonsteroidal anti-inflammatory drugs (NSAIDs), sulfasalazine, systemic corticosteroids, colchicine, methotrexate, and antibiotics such as tetracyclines have been used with varying results. The use of bisphosphonates has been described as effective. Biological therapy also seems to be effective. More trials with these drugs are needed to evaluate their effectiveness against this disease and to establish the number of doses, the amount, and the interval between them. In this chapter we describe the case of a patient with SAPHO syndrome who had a good response to oral alendronate.

Keywords: SAPHO syndrome, palmoplantar pustulosis, hyperostosis, acne

1. Introduction

SAPHO syndrome is an entity that associates musculoskeletal disorders with dermatological alterations, which may appear simultaneously or successively throughout a patient's life. The term is an acronym for the most common manifestations such as synovitis, acne, palmoplantar pustulosis, hyperostosis, and osteitis (**Table 1**). Bone lesions may present without relation to the appearance of cutaneous lesions.

– Synovitis
– Acne
– Palmoplantar pustulosis
– Hyperostosis
– Osteitis

Table 1. Types of SAPHO syndrome.

2. Etiology

The etiology of SAPHO syndrome is unclear. It is thought that it may have a multifactorial origin where genetic, environmental, immunological [1], and infectious causes intervene. Some bacteria, such as the *Bacillus Propionibacterium acnes*, could act as a triggering factor [2]. However, the possible pathogenic role of this or other germs in a genetically predisposed patient has not been proven.

3. Epidemiology

Its prevalence is unknown, and it can be described in different ways (**Table 2**). A few cases have been reported in Spain to date. It usually occurs in childhood and adolescence and usually affects to the female gender.

A patient with SAPHO syndrome who had a good response to oral alendronate has been described, although this is not the first choice recommended for treatment (there are a few reports in the medical literature).

– Pseudoseptic acute arthritis and palmoplantar pustulosis
– Arthro-osteitis with palmoplantar pustulosis
– Manubrium-sternal arthritis and pustular psoriasis
– Symmetric multifocal chronic osteomyelitis
– Bilateral clavicular osteomyelitis with palmar and plantar pustulosis
– Chronic sclerosing osteitis
– Chronic multifocal osteomyelitis of unknown etiology
– Skeletal muscle syndromes associated with acne
– Pustular palmoplantar arthritis
– Hyperostosis of the sternal manubrium
– Recurrent hyperostosis of the mandible
– Bone lesions in palmoplantar pustulosis
– Sternocostoclavicular hyperostosis
– Sternocostoclavicular arthro-osteitis

Table 2. Synonyms of the SAPHO syndrome.

4. Literature review

The SAPHO syndrome is a rare entity that was first described in the 1980s [3]; since then many cases have been diagnosed in different regions, and it seems to maintain a certain geographic distribution, in which an increase in prevalence in Central European countries [4]. The syndrome can appear at any age, but it usually occurs in childhood and adolescence and usually affects the female gender [5]. Many authors have questioned the SAPHO syndrome as an independent entity since its discovery [6], although nowadays it seems that it is widely accepted, given its clinical and radiological characteristics that differentiate it from other diseases. Its physiopathology remains to be clarified. In the literature there are few cases described which hinder the development of controlled clinical trials to find an adequate treatment. Current treatments and their benefits are based on personal experiences [7]. In most cases NSAIDs manage to control the pain and inflammation of the affected joints, but cases in which this medication is not effective pose a difficulty for medical staff. Intravenous bisphosphonates, such as pamidronate and zoledronate, seem to be the most effective drugs due to the experiences described to date [8]. However, a suitable dosage has not yet been found. It is also being tested with another type of medication such as TNF-α antagonists [9, 10], which may be effective, but more studies and a larger number of patients are needed in order to obtain significant results.

5. Clinical case

The case of a 45-year-old woman who came for consultation due to costal pain and in the right renal fossa is presented. The pain was continuous, did not give in to rest, and did not increase with exercise; it was not related to any trigger, and she had it for 3–4 months. Any micturition syndrome or fever was not reported. She had not had any weight loss. The patient was a smoker [11] and had a history of hypercholesterolemia, renal lithiasis, osteoporosis in treatment with calcium/vitamin D, and palmoplantar psoriasis on treatment with acitretin.

On the physical examination, pustule-erythematous, confluent lesions were found in the palms of both hands and on both soles of the feet. In addition, although she described it as costal, she presented localized pain in the sternoclavicular and chondrosternal region that increased to acupressure. She also had pain in the right renal fossa with a positive percussion fist.

Before these findings, various tests such as hemogram, biochemistry, coagulation, systematic urine, and chest X-ray were requested, with normal results. SVS, autoimmunity, and HLA-B27 were negative. Chest and abdomen CT were requested with the following report: probable areas of atelectasis/fibrous tracts in both lung bases; small bilateral renal cortical cysts; nonobstructive right renal lithiasis; arteriosclerosis of the aortoiliac axis; apparent increase of density of the subcutaneous at the level of the interlabial cleft, to be assessed in the clinical context of the patient; and degenerative alterations in the axial skeleton.

A bone densitometry was performed, showing a T-score of −2.6 in the lumbar spine (L1–L4), compatible with osteoporosis. There was also a study in her neck, trochanter and total femur compatible with osteopenia.

Before the clinical suspicion, a bone scan [12] was requested. It showed a pathological focus on the right sternoclavicular joint, compatible with SAPHO syndrome, with hyperostosis of the joint (**Figure 1**).

Treatment was established with colchicine 0.5 mg 1/24 h. Methotrexate 15 mg IM/week (the Mantoux-Booster test was previously requested and serologies for HBV, HCV, and HIV that were negative): folic acid one tablet 1 day after the administration of methotrexate and alendronate one tablet/week. Treatment with oral bisphosphonates was decided [13] despite the scarce records in the literature (agreed with the patient who did not want intravenous treatment and opted for oral treatment). This dose and frequency of administration were decided since it is the one used in the treatment of postmenopausal osteoporosis.

At 6 weeks, the patient was reevaluated and presented an almost total decrease in sternoclavicular pain and a marked improvement in the palmoplantar lesions.

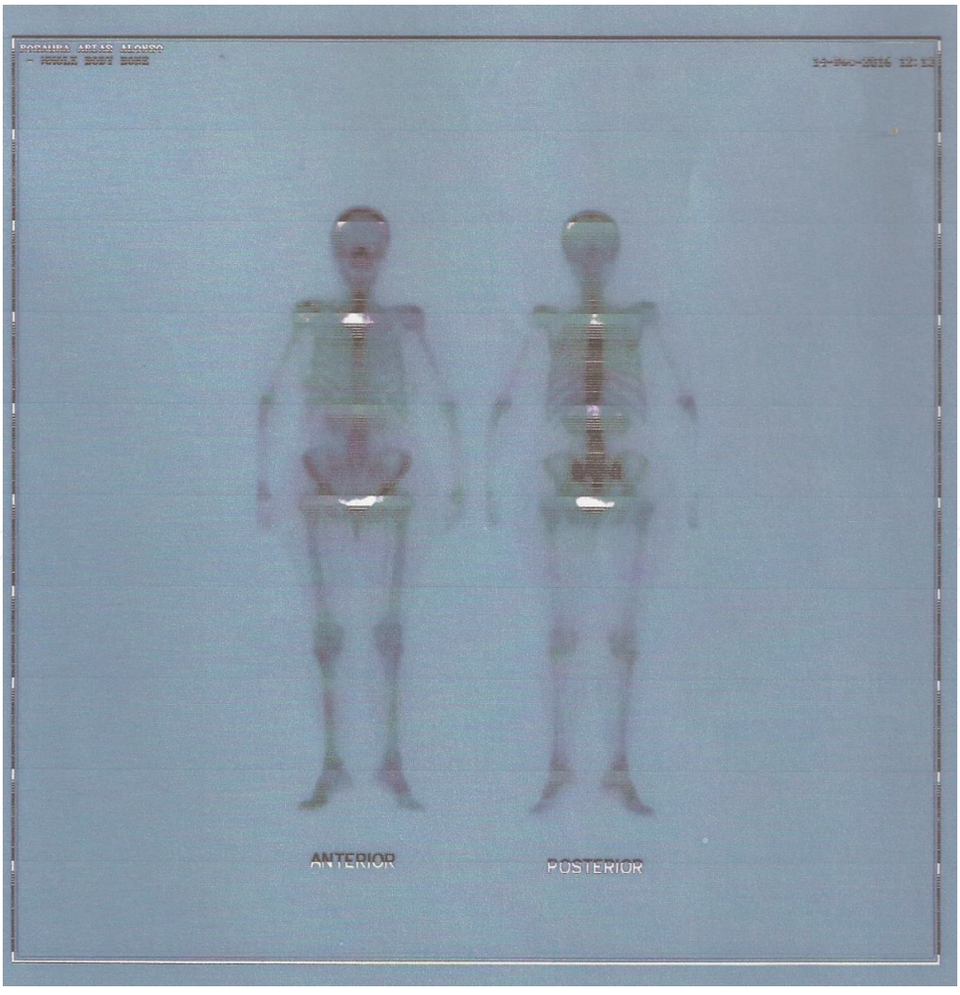

Figure 1. Hyperostosis on the right sternoclavicular joint, compatible with SAPHO syndrome, can be seen.

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6. Clinic

SAPHO syndrome is an entity that associates musculoskeletal disorders with dermatological alterations (**Table 3**).

The most characteristic clinical manifestation of the SAPHO syndrome is pain in the anterior chest wall, due to the involvement of the sternoclavicular and costochondral joints. Less commonly, the sacroiliac, intervertebral, or peripheral joints are affected. It could also affect the jaw. It is usually presented symmetrically, bilaterally, and in outbreaks. In adults, disease predominates in the sternocostoclavicular region (65–90% of patients). All the components of the anterior chest wall might be affected. The second affected region is the spine (33% of cases), mostly at the dorsal level. Nonspecific spondylitis, osteosclerosis of one or more vertebral bodies, and paravertebral ossifications could be observed. Ninety-two percent of patients have arthritis with involvement their knees, hips, ankles, feet, and hands.

1. Chronic multifocal relapsing osteomyelitis
Generally sterile
With/without coccyx affection
With/without skin affection
2. Acute/subacute/chronic arthritis in addition to:
Palmoplantar pustulosis
Pustular psoriasis
Severe acne
3. Sterile osteitis in any localization in addition to
Palmoplantar pustulosis
Pustular psoriasis
Vulgar psoriasis
Severe acne

Table 3. Diagnostic criteria: one of the three presentations is enough for diagnosis.

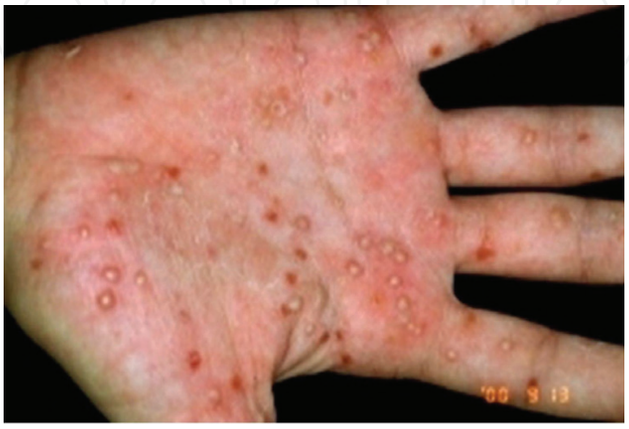

Figure 2. Inflammatory pustules with erythema that affect palms of hands.

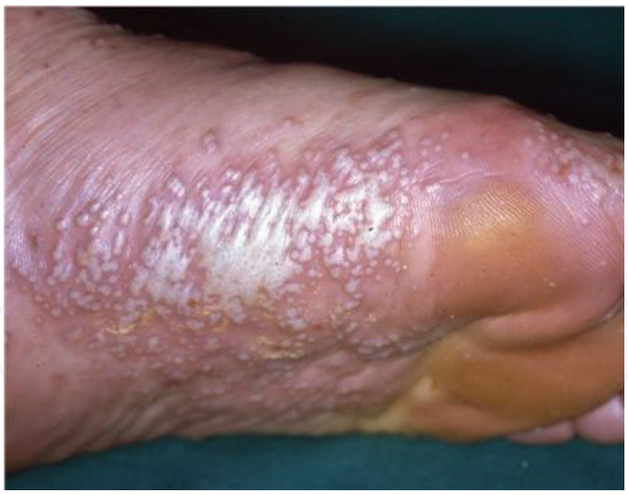

Figure 3. Pustular lesions, symmetric, with desquamation that affects the soles of the feet.

– Acne-associated syndrome
– PAPA syndrome
– PASH syndrome
– Arthritis associated with hidradenitis suppurativa
– Follicular occlusion triad
– Behçet disease
– Minocycline-induced autoimmune syndromes
– Isotretinoin side effect
– Pustular psoriasis
– Sneddon-Wilkinson disease
– Pustulotic arthro-osteitis
– Acquired hyperostosis syndrome
– Chronic recurrent multifocal osteomyelitis
– Diffuse sclerosing osteomyelitis of the mandible
– Majeed syndrome
– Nonbacterial osteitis
– Tuberculous spondylitis
– Secondary syphilis
– Primary bone tumors
– Metastatic tumors

Table 4. Differential diagnosis of SAPHO syndrome.

In children it usually affects to the long bones such as the tibia and femur, clavicle, and lumbar spine.

Skin involvement is more variable and includes palmoplantar pustulosis, acne conglobata or fulminating, suppurative hidradenitis, dissecting cellulitis, or pustular psoriasis. The most predominant is palmoplantar pustulosis, which is characterized by inflammatory pustules,

symmetric, and sterile, with erythema and desquamation, which affect palms of the hands (**Figure 2**) and soles of the feet (**Figure 3**). The pathogenesis of the disease remains unknown, and there is still a debate about whether palmoplantar pustulosis is a variant of psoriasis or a distinct condition.

The SAPHO syndrome could present several clinical manifestations and therefore originate different differential diagnoses (**Table 4**). This is very important in neoplastic disease context, since it is necessary to avoid errors in the diagnosis that lead to aggressive treatment in a disease that it usually develops benign.

7. Diagnosis

The diagnosis is basically clinical and is complemented by imaging tests. Due to its low prevalence, it is necessary to have a high index of suspicion. The analytical data are usually nonspecific but have value in excluding other pathologies. Mild leukocytosis, anemia, or an increase in inflammatory markers might occur. A simple radiography, bone scan with technetium 99 m, and CT are useful. Simple X-ray is of little use since it is usually normal. Bone scintigraphy provides much information, and the pattern of symmetrical sternoclavicular hypercaptation in "bull's head" (where the sternal manubrium represents the skull and the sternoclavicular joints and the clavicles correspond to the horns) is very typical. CT provides us with a lot of information as it is the technique that best visualizes the joints of the anterior thoracic wall, showing a hyperostosis of this zone.

Biopsy and cultures of the affected joints are reserved for doubtful cases and to rule out other diagnostic possibilities. Imaging allows differential diagnosis with other processes (osteomyelitis, Paget's disease, bone metastases, Tietze syndrome, other spondyloarthropathies).

In some patients, cutaneous manifestations might appear after years of nonspecific joint symptoms, making diagnosis even more difficult.

8. Evolution

SAPHO syndrome is a chronic disease that develops in form of outbreaks and remissions but in which radiological progression is slow [14]. Prognosis is usually good, but there are cases in which the pain that is produced is very intense and difficult to control it. Sometimes the onset of the disease could be acute and crippling. It has been observed that those factors such as female gender, anterior chest wall involvement, peripheral arthritis, skin lesions and elevation of acute phase reactants at onset of disease are related to the chronicity of the disease.

In a minority of patients, disease heals spontaneously or follows a chronically indolent course.

Complications are rare. Peripheral arthritis could become erosive in a minority of cases. Venous thrombosis could be observed due to an important disseminated inflammation from bones or joints to the adjacent tissue (especially as a result of clavicular hypertrophy), inflammatory masses in the anterior mediastinum, thoracic gorge syndrome that the swelling is

confused with a tumor (signs mainly observed at clavicular level), etc. Recurrent chronic multifocal osteomyelitis could cause permanent bone deformities, irregularities in limb length, and growth problems.

9. Treatment

With a little-known entity with few studies, this treatment is not protocolized [15] (**Table 5**). Nonsteroidal anti-inflammatory drugs (NSAIDs), sulfasalazine, systemic corticosteroids, colchicine, methotrexate, and antibiotics such as tetracyclines have been used with varying results.

NSAIDs and analgesics are used as a symptomatic treatment of disease. There is no NSAID that has shown to be more effective than other. Almost all patients receive NSAIDs, obtaining a good result, but due to recurrence, loss of efficacy, or progression of disease, it is necessary to establish other treatments.

As we have said before, it is believed that this disease might have an infectious origin, mainly *Propionibacterium acnes*, so several antibiotics have been used, although they have not been proved to be really effective. Tetracyclines have been shown to be effective in controlling severe forms of acne [16].

Immunosuppressants, such as sulfasalazine or methotrexate, have been used in cases resistant to NSAIDs [17] and antibiotics, and although they have shown improvement in some patients, results have not been conclusive, and there are studies in this regard.

The use of bisphosphonates has been described as effective, although the majority of cases in which it has been used have been endovenous. Bisphosphonates are synthetic analogs of pyrophosphate; their function is to inhibit bone resorption by altering the function and metabolism of osteoclasts. Due to these properties, they have been used in treatment of primary and secondary osteoporosis, Paget's disease, bone metastasis, and disorders of bone metabolism [18].

Pamidronate and zoledronic acid have been used. Pamidronate has been used at a dose of 60 mg/day IV in a single dose, during a very short cycle of days in a row or repeating the dose several months later [19]. In most cases an improvement in pain and in the evolution of

Symptomatic	Modifier of disease
– Analgesics	– Antibiotics
– NSAIDs	– Sulfasalazine
– Glucocorticoids	– Methotrexate
– Calcitonin	– Leflunomide
	– Bisphosphonates
	– TNF antagonists

Table 5. SAPHO syndrome treatment.

the disease was found. This is due to an action on bone remodeling that interferes with the production of proinflammatory cytokines.

Zoledronic acid is the most potent bisphosphonate and is usually used in hypercalcemias of tumoral origin. It has been used at a dose of 4 mg IV in a single dose with repetition at 6 months if there was no improvement [20], obtaining good results (decrease in pain and regression of disease).

In the treatment with biological therapy, anti-tumor necrosis factor (TNF) drugs have been used with promising results.

Although NSAIDs usually control pain and inflammation, it is often necessary to use disease-modifying drugs to improve symptoms. In this regard, it seems that IV bisphosphonates have been the most effective, but the dose and interval have not been unified.

Biological therapy also seems to show effectiveness [21]. More trials with these drugs would be needed to test their effectiveness against this disease and protocol the number of doses, the amount, and the interval between them.

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