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SAPHO: Treatment options including bisphosphonates

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ABSTRACT

Introduction: Both the diagnosis and treatment of the syndrome of synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) remain difficult. We describe a case series of 21 patients with SAPHO and their response to several pharmacological treatments.

Methods: Clinical and biochemical data, along with medical imaging, were collected from the medical records of 21 patients, diagnosed as SAPHO during follow-up between 2005 and 2013. Symptoms and inflammatory markers were recorded twice, once at first patient presentation, and once at the end of follow-up. Synovitis, acne, pustulosis, hyperostosis, and osteitis were labeled as defining features. All treatment options were categorized according to their respective responses (full remission, partial remission, and no disease control).

Results: There was a female predominance and a median age of 32 years (range: 12–54 years). Median follow-up duration was 45 months (range: 0–188 months). Total prevalence of defining features in this cohort increased for each defining feature during follow-up, except for acne. All patients reached full or partial remission at the end of follow-up. A total of 14 patients were treated with bisphosphonates. Of which 8 of them went into full or partial remission.

Discussion and conclusion: In our case series, none of the patients had the full presentation of SAPHO at the first consultation. Some presented with symptoms suggestive for psoriatic arthritis. This explains why diagnosis of SAPHO can be challenging. Full remission was induced in the majority of individuals. Bisphosphonates seem to be a noteworthy treatment option. We suggest a prospective placebo-controlled clinical trial with bisphosphonates to confirm this observation.

Introduction

SAPHO is a rare chronic condition with variable symptoms, including synovitis, acne, palmoplantar pustulosis, hyperostosis, and osteitis. It has a variable outcome and unpredictable response upon conventional therapy.

Synovitis has a variable presentation, with a prevalence between 20% and 30% [1,2], up to 92% in a follow-up registration of 120 cases by Hayem et al. [3]. In the latter study, distribution of inflammatory lesions was predominantly axial, though a significant group of patients in this study developed peripheral arthritis (36%), most frequently involving knees, hips, and ankles [3]. Joint destruction is a rare feature. Advanced cases, may however, show joint space narrowing with marginal or central erosions, exceptionally followed by ankylosis and enthesopathy [4].

Hyperostosis and osteitis typically occur in the anterior chest wall [5–7], but any skeletal segments, such as the mandibula, the spine (with spondylodiscitis), intracranial manifestations, and even the ossicles [8–15], may be involved.

Aside from acne and palmoplantar pustulosis, hidradenitis suppurativa (acne inversa) and some forms of psoriasis have also been mentioned [6,16]. Some patients with SAPHO syndrome express psoriasis lesions three times as often as the general population [5,17].

In 1961, the association of acne and arthritis has been described for the first time by Windom et al. [18]. During the past 5 decades, different names and acronyms have been used, such as acquired hyperostosis syndrome [19], sternoclavicular hyperostosis [20], and chronic recurrent multifocal osteomyelitis (CRMO) [21]. CRMO is thought to be a juvenile variant of SAPHO but this is still under debate [4,17]. Furthermore, symptoms similar to those of SAPHO are part of even more rare ailments such as the Majeed syndrome (neutrophilic dermatosis, osteitis, and abnormal erythropoiesis) [22,23], and Sneddon–Wilkinson disease [24,25]. As several of these skin and bone diseases shared similar characteristics, Chamot et al. [26] coined the term SAPHO in 1987, after a survey of 85 patients. Because both in literature and in practice, a failure to recognize the link between these particular skin problems and

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Table 1
Kahn and Khan proposed criteria for the SAPHO syndrome

Chronic recurrent multifocal osteomyelitis
Usually sterile
Spine may be involved
With or without skin condition
Acute, subacute, or chronic arthritis with any of the following
Palmoplantar pustulosis
Pustular psoriasis
Severe acne
Any sterile[a] osteitis[b] associated with any of the following:
Palmoplantar pustulosis
Pustular psoriasis
Psoriasis vulgaris
Severe acne

Note: any of the three presentations is sufficient for diagnosis.
[a] With presence of *P. acnes*.
[b] One localization is sufficient, including spondylodiscitis.

musculoskeletal manifestations has been observed repeatedly, members of the same group proposed a refinement of its diagnostic criteria in 1994 (Table 1) [5].

SAPHO was formerly considered a part of the spondylarthropathy family [4], but recently, this is no longer the case due to the lack of association with HLA-B27 positivity, absence of anterior uveitis, no familial predisposition, no gender predominance, and absence of syndemophytes and spinal ankylosis [17].

SAPHO syndrome is considered a rare condition, but no actual data exist and therefore its actual prevalence may be underestimated due to lack of a correct diagnosis. In the original case series of Chamot et al. [26], the gender distribution was equal, though larger series report a female predominance. Children and young to middle-aged adults are most affected. Nevertheless, SAPHO may present at any age [3,7,27].

The pathophysiology remains unclear. Histological analysis of both bone and skin biopsies show aseptic osteomyelitis and neutrophilic pseudo-abscesses, respectively [5,7,20,28]. The role of *Propionibacterium acnes* is also controversial [29,30], for several reasons. Firstly, it can be isolated in some, but not all patients with SAPHO. Secondly, treatment with antibiotics had mixed results [31–33]. Thirdly, though *P. acnes* has been isolated from bone tissue and, to a lesser extent, from synovial fluid [34], the fact that this organism is also commonly grown from skin cultures, it is possible that its isolation in the aforementioned tissues is merely due to sample contamination. Finally, some reports propose an autoimmune or autoinflammatory process, with or without stimulation from *P. acnes* antigens, rather than a direct role of *P. acnes* in the pathophysiology of SAPHO [7,35]. HLA-B27 status is subject to debate, though most reports conclude that SAPHO does not seem to have a strong correlation with a positive HLA-B27 status [2,3,17,36].

The overall course of the disease is chronic, with a fairly good prognosis [7]. However, SAPHO has a high impact on general health and quality of life [37]. Until now, no formal guideline outlining treatment, or treatment algorithms exist, as large clinical trials are lacking [6]. The effect of several therapies have been discussed in case reports, case series and retrospective studies. Non-steroidal anti-inflammatory drugs (NSAIDs) provide symptom relief, but disease control is often not achieved [7,31]. Synthetic disease-modifying antirheumatic drugs (sDMARDs) have also been used and methotrexate has shown promising results, mostly in patients with peripheral arthritis [6]. The use of antibiotics has not been effective in general [3,7,32,33]. Favorable results with anti-tumor necrosis factor drugs (anti-TNF) have been described in case reports and small series [38–45]. However, the most promising results have been observed in patients under treatment with bisphosphonates [2,46–52]. We describe a case series of 21 patients with SAPHO and their response to bisphosphonates and several other pharmacological treatments.

Materials and methods

Between 2005 and 2013, 21 individuals have had a clinical diagnosis of SAPHO in our outpatient clinic, using the Kahn and Khan criteria (Table 1). Clinical and biochemical data, along with medical imaging, were collected from their medical records.

Synovitis, acne, pustulosis, hyperostosis, and osteitis were labeled as defining features. Clinical signs such as sacroiliitis, enthesitis, and psoriatic lesions were also registered, labeled as non-defining features.

We used MRI examination to diagnose non-infectious osteitis. This condition appears as increased osteosclerosis, involving the trabecular infrastructure of cancellous bone in response to the underlying inflammation, frequently involving the adjacent joint [53,54]. Infectious osteomyelitis was ruled out when no sequesters, brodie abscesses or fistulae had been detected on MRI, or when the patient was healthy in between flares and did not seem to respond to antibiotics. This approach has been suggested before for CRMO [55]. Nevertheless, when the diagnosis of infectious osteomyelitis remained suspicious, biopsies were performed.

Sacroiliitis was diagnosed using the modified New York grading system for plain radiographs. Concurrently or alternatively, MRI imaging was evaluated according to the definition of sacroiliitis proposed by the ASAS/OMERACT MRI working group [56].

To examine disease course during follow-up, we recorded data twice. In the first record, features the patient presented with at the initial contact were registered. The second record was created to represent a full feature complex. It listed all clinical and radiological signs and symptoms that each patient had suffered from during the follow-up, along with HLA-B27 status, biopsy results, and cultures, even if a certain feature was no longer present by the end of follow-up.

Additionally, a third record was created to compare levels of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) at the end of follow-up, with those at the initial patient contact.

Estimated disease duration at first presentation (months), estimated age of the patient when the first symptoms or signs developed and previous alternative diagnoses, were registered likewise. Follow-up duration and disease duration at the end of follow-up were calculated (months).

The sum of defining features was calculated from the total number of the defining clinical symptoms or radiological signs a patient presented with at first consultation, and during the course of follow-up.

Therapeutic strategies were categorized from first to fifth line therapy, on a mere chronological basis. Full and partial remission was evaluated by expert opinion. Full remission was defined as full regression of articular or locomotors signs or symptoms. Partial remission implied partial regression of articular or locomotors signs or symptoms. The presence or absence of skin lesions was not included in our appraisal of remission.

Results

Demographics have been summarized in Table 2. Defining features at presentation and by the end of follow-up have been summarized in Table 3. Osteitis was the most frequent feature both at presentation ($n = 13$; 62%) and by the end of follow-up