SAPHO syndrome: the value of classic drugs in the era of biologics

Francisco Gil[1], Paulina Mariano[2], Soraia Silva[2], José Gil[3], Maria Eufémia Calmeiro[2]

Affiliations: [1]Department of Dermatology, Hospital de Santarém EPE, Santarém, Portugal, [2]Department of Internal Medicine, Unidade Local de Saúde de Castelo Branco, Castelo Branco, Portugal, [3]Department of Dermatology, Unidade Local de Saúde de Castelo Branco, Castelo Branco, Portugal

Corresponding Author: Francisco Gil, Dermatology Department, Hospital de Santarém EPE, Avenida Bernardo Santareno, 2005-177 Santarém, Portugal, Tel: 35-1243300200, Email: franciscosgil@gmail.com

Abstract

SAPHO syndrome is a rare entity, composed of dermatologic and osteoarticular manifestations. There are no validated diagnostic criteria and treatment is empirical, with a recent focus on biologics. Herein, we present a 50-year-old woman who developed palmoplantar pustulosis and sternoclavicular osteitis, with typical findings on bone scintigraphy. Treatment with bisphosphonate, low-dose systemic corticosteroid, and cyclosporine allowed complete resolution of the articular and dermatologic manifestations with no side effects.

Keywords: SAPHO, palmoplantar pustulosis, cyclosporine

Introduction

SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis and osteitis) is a rare disease with a wide range of dermatologic and musculoskeletal manifestations [1]. As there are no randomized controlled trials, current treatment is multimodal, empirical, and mainly focused on relieving symptoms [2]. Outcomes are often disappointing, especially with the skin component of the disease [3].

Case Synopsis

A 50-year-old woman, with an unremarkable medical history presented with asymptomatic bilateral erythematous plaques on the soles, associated with pustules and desquamation (**Figure 1**), and scant scattered pustules on the palms. The dermatosis, consistent with palmoplantar pustulosis, had started one year prior and progressed with flares of variable severity. The patient had previously been prescribed topical corticosteroids and vitamin D analogs and systemic methotrexate and acitretin, with no improvement. The patient noted the recent onset of episodes of upper anterior chest and lumbar pain, associated with morning stiffness. These complaints had started one month earlier, caused functional disability in daily activities, and did not improve with nonsteroidal anti-inflammatory drugs.

The patient denied fever or weight loss. Upon physical examination, besides the skin lesions there was redness, swelling and tenderness at the right sternoclavicular joint (**Figure 2**). Blood analysis showed augmented erythrocyte sedimentation rate (97mm/h), (reference range <35mm/h and C-reactive protein (8.6mg/dL), reference range <0.50mg/dL. The results for all other laboratory tests

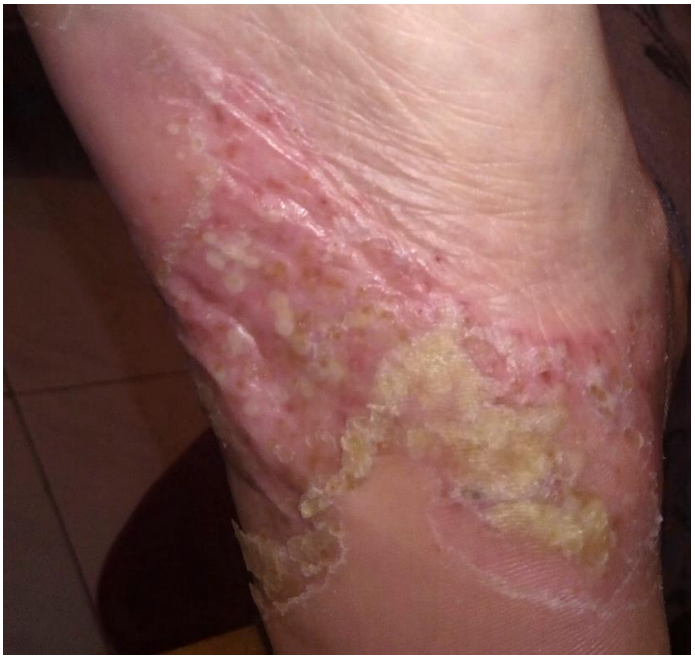

Figure 1. *Erythematous plaque with pustules and desquamation on the right sole.*

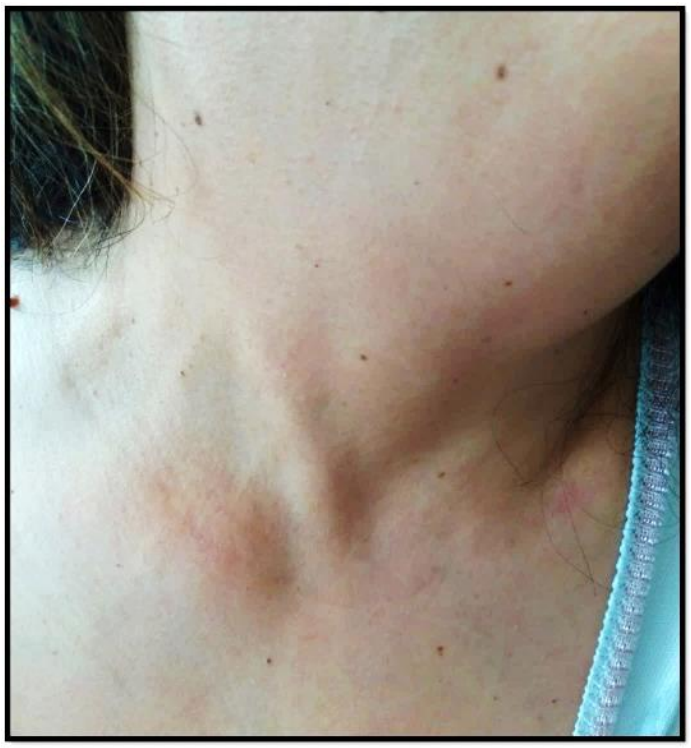

Figure 2. *Erythema and edema of the right sternoclavicular joint.*

that were carried out, including rheumatoid factor, human leukocyte antigen B27 tests, autoantibodies, and infectious serologies were negative or within normal range.

To evaluate the skeleton, a whole-body bone scan was performed, revealing intense uptake at the right sternoclavicular joint, the union of the manubrium with the body of sternum, and the left hip joint (**Figure 3**). At this point, the combination of the dermatologic and osteoarticular manifestations, elevated inflammatory markers, and the scintigraphic findings allowed the diagnosis of SAPHO syndrome. Because of the inefficacy of NSAIDs, low-dose prednisolone (5mg/day) and ibandronic acid (150mg/month) were started, resulting in a notable remission of the inflammatory articular signs and pain and normalization of the inflammatory parameters. However, there was no improvement of the skin lesions. Cyclosporine (200mg/day) was then added to the therapeutic regimen and there was an excellent and fast clinical response of the palmoplantar pustulosis, with an almost complete elimination of the lesions in three weeks and improvement of the joint symptoms.

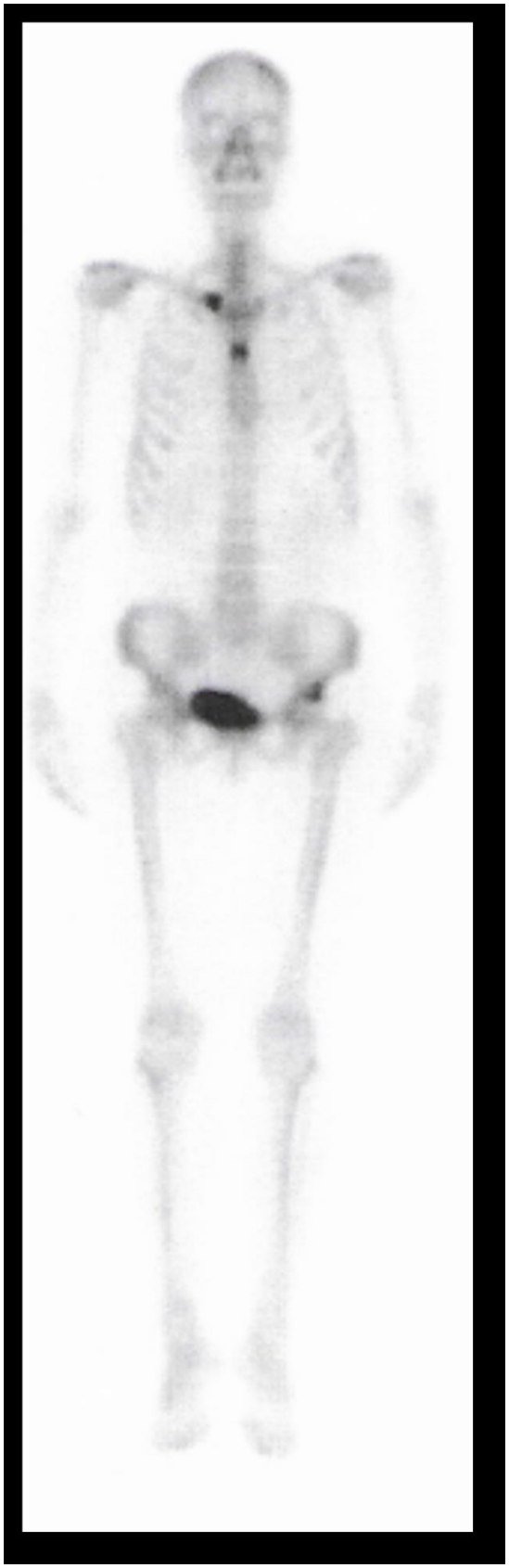

Figure 3. *^{99m}Tc-hydroxymethylene diphosphonate bone scintigraphy with intense uptake at the right sternoclavicular joint and sternum.*

Long-lasting disease control was achieved, without side effects, and oral prednisolone was reduced to an alternate-day regimen.

Case Discussion

The term SAPHO syndrome was proposed to encompass a group of conditions described under various denominations with similar inflammatory osteoarticular and cutaneous involvement [4]. It usually appears between childhood and middle age, follows a prolonged relapsing and remitting course [5], and is characterized by peculiar combinations of bone and skin lesions. These include palmoplantar pustulosis and inflammation of the axial and sternoclavicular joints most commonly [6].

Pathogenesis of SAPHO syndrome remains unclear, but evidence suggests it is an autoinflammatory disease triggered upon exposure to infectious agents such as *Propionibacterium acnes*, in genetically predisposed individuals [7-9]. Diagnosing SAPHO syndrome is difficult, particularly if the dermatologic manifestations are absent [6]. Additionally, skin lesions may occur years earlier or later than the osteoarticular manifestations [10].

There are several published diagnostic criteria but they are preliminary and need further validation [3]. The diagnosis of SAPHO syndrome is based on the combination of history, cutaneous and osteoarticular manifestations, and characteristic scintigraphic and radiological results [9, 10]. Bone scintigraphy is a sensitive imaging modality that is able to identify uptake in characteristic regions and the sternoclavicular junction is the most common site of involvement, followed by the spine and sacroiliac joints [2]. Authors suggested that it could be useful in disease activity evaluation of SAPHO patients, but recent evidence shows repeated bone scintigraphy is not recommended for disease assessment during follow-up [11]. In our case, characteristic bone and skin lesions coexisted and bone scan showed uptake at typical sites, contributing to the diagnosis. All data on treatment derive from case series and retrospective studies [1]. Nonsteroidal anti-inflammatory drugs are generally considered to be the first line treatment [1, 12]. Bisphosphonates display anti-inflammatory properties and act by inhibiting bone resorption [2] but have no effect on skin lesions [3]. Antimicrobial therapies are a reasonable choice since bacteria have been implicated in SAPHO pathogenesis [12]. Other treatment options include corticosteroids, colchicine, retinoids, and disease-modifying anti-rheumatic drugs agents such as methotrexate or sulfasalazine. Biologics have been used in several cases refractory to conventional treatment. TNF blockers appear to be the first choice but IL1 inhibitors and biologics targeting the IL17/IL23 axis can also be used [1].

Conclusion

Both diagnosis and treatment of SAPHO remain difficult. This syndrome, conceptualized as a constellation of musculoskeletal and dermatologic disorders, must be recognized as promptly as possible to allow an early effective treatment. In line with our case and in an era of growing use of biologics in the practice of dermatology, we wish to report the combination of bisphosphonate, low-dose systemic corticosteroid, and cyclosporine as an effective and safe treatment in a case of SAPHO syndrome. This combination induced a fast and complete control of the articular and dermatologic manifestations with no significant side effects.

Potential conflicts of interest

The authors declare no conflicts of interests.

References

1. Daoussis D, Konstantopoulou G, Kraniotis P, Sakkas L, Liossis S. Biologics in SAPHO syndrome: A systematic review. *Semin Arthritis Rheum*. 2019;48:618-25. [PMID: 29773231].
2. Song X, Sun W, Meng Z, et al. Diagnosis and treatment of SAPHO syndrome: A case report. *Exp Ther Med*. 2014;8:419–22. [PMID: 25009594].
3. Rukavina I. SAPHO syndrome: a review. *J Child Orthop*. 2015;9:19–27. [PMID: 25585872].
4. Chamot AM, Benhamou CL, Kahn MF, et al: Acne-pustulosis-hyperostosis-osteitis syndrome. Results of a

national survey. 85 cases. *Rev Rhum Mal Osteoartic*. 1987;54:187-96. [PMID: 2954204].

5. Hayem G, Bouchaud-Chabot A, Benali K, et al. SAPHO syndrome: a long-term follow-up study of 120 cases. *Semin Arthritis Rheum*. 1999;29:159–71. [PMID: 10622680].
6. Nguyen MT, Borchers A, Selmi C, et al. The SAPHO syndrome. *Semin Arthritis Rheum*. 2012;42:254-65. [PMID: 23153960].
7. Adamo S, Nilsson J, Krebs A, et al. Successful treatment of SAPHO syndrome with apremilast. *Br J Dermatol*. 2018;179:959-62. [PMID: 29034454].
8. Assmann G, Simon P. The SAPHO syndrome - are microbes involved? *Best Pract Res Clin Rheumatol*. 2011;25:423-34. [PMID: 22100290].
9. Firinu D, Garcia-Larsen V, Manconi PE, Del Giacco SR. SAPHO Syndrome: Current Developments and Approaches to Clinical Treatment. *Curr Rheumatol Rep*. 2016;18:35. [PMID: 27108452].
10. Hirosawa T, Kawamoto S, Shimizu T. *BMJ Case Rep*. 2019;12:e233221. [PMID: 31796447].
11. Li C, Wang L, Wu N, et al. A retrospective study of bone scintigraphy in the follow-up of patients with synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome: is it useful to repeat bone scintigraphy for disease assessment? *Clin Rheumatol*. 2019; 39:1305-1314. [PMID: 31858336].
12. Matzaroglou C, Velissaris D, Karageorgos A, et al. SAPHO Syndrome Diagnosis and Treatment: Report of Five Cases and Review of the Literature. *Open Orthop J*. 2009;3:100–6. [PMID: 19997538].