

A CASE OF SAPHO SYNDROME TREATED WITH ZOLENDRONIC ACID AND HYDROXYCHLOROQUINE

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Abstract. *SAPHO syndrome is characterized with a set of symptoms including skin lesions, osteoarticular manifestations like aseptic osteitis (of the anterior chest wall or other skeletal sites), peripheral synovitis. Due to the lack of randomized clinical trials and low prevalence of the condition, there are no established treatment guidelines for SAPHO syndrome. Here, we report a clinical case of SAPHO syndrome with osteitis of the sternum and palmoplantar pustulosis successfully treated with zoledronic acid and hydroxychloroquine.*

Key words: *SAPHO syndrome, zoledronic acid, hydroxychloroquine*

INTRODUCTION

SAPHO syndrome (acronym for Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis) has been described in the 1960s and includes a set of symptoms, i.e., skin manifestations such as palmoplantar pustulosis, pustular psoriasis, hidradenitis suppurativa, severe acne (fulminans or conglobata) and osteoarticular manifestations like peripheral synovitis or aseptic osteitis of the anterior chest wall or other skeletal sites. In adults, the most commonly affected skeletal area is the anterior chest wall (65% to 90%). However, other skeletal sites may be also involved, and spine is the second most common skeletal involvement (30%) in its thoracic region followed by the lumbar and then the cervical spine. Sacroiliitis could be observed in 13% to 52% of patients, while the appendicular skeleton and mandibula are rarely involved in up to 10% of cases [1]. The disease is mainly observed in young and middle-aged adults and predominates in females. Male gender is more commonly affected in the form with development of acne conglobata as skin involvement [2]. SAPHO syndrome is observed also in children and is suggested to be rare in subjects older than 60 years [3].

In a proportion of cases, the bone and joint complaints are the initial disease manifestation, while in others they manifest simultaneously with the skin involvement. There are observations that isolated bony lesions are more common in children. Chronic recurrent multifocal osteomyelitis has been observed in young patients. Of note, cutaneous manifestations may follow the osteoarticular pathology

by many years, sometimes more than 20 years. It has been suggested that peripheral synovitis is commonly of short duration and responds well to systemic and local anti-inflammatory drugs. However, bony lesions persist for many years and the patients have episodes of bone pain in the affected area. In the evolution, the hyperostosis remains stable on successive radiographic examinations and symptoms improve. There are reports also about monocyclic course of the disease as well as about persistence of disease activity for more than 20 years and subsequent involvement of new bone areas in the disease evolution. A moderate inflammatory reaction with elevation of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels could be found [4].

Factors associated with chronic disease course were female sex, elevated ESR and CRP, anterior chest wall involvement, peripheral synovitis, presence of skin involvement at disease onset [5].

Osteitis and hyperostosis are characteristic findings in SAPHO syndrome that represent chronic inflammatory reactions involving the cortical and trabecular bone, respectively, and manifest radiologically mainly with increased sclerosis. Hyperostosis is visualized as chronic endosteal and periosteal thickening, narrowing of the medullary canal that is commonly homogeneous, but heterogeneous structure with osteolytic lesions could be also observed. Histological findings in SAPHO syndrome include signs of acute that evolve into chronic inflammation, inflammatory granuloma with activated osteoclasts in the early stages, hyperostosis and fibrosis of

medullary tissue in the late stages. The awareness of SAPHO syndrome is of significant importance in clinical practice as the findings require differential diagnosis with other pathological conditions such as osteomyelitis, Ewing's sarcoma, metastasis, Paget's disease, etc. [5].

PATHOGENESIS

Etiopathogenesis of SAPHO syndrome remains unclear, but it is generally considered to be an autoinflammatory syndrome that might be associated with various factors including immune dysfunction, infection, genetic predisposition [6, 7]. An association with *Propionibacterium acnes* in the involved area has been described (either alive bacteria or presence of bacterial antigen) [5]. *P. acnes* is a common skin saprophyte and has been implicated in the pathogenesis of severe acne. However, in many cases bone and joint cultures have been negative [4]. Elevation of proinflammatory cytokines, i.e., tumor necrosis factor (TNF)- α , interleukin (IL)-1, IL-8, IL-17, IL-18, receptor activator nuclear factor kappa-B ligand (RANKL) has been found [7].

Criteria for the diagnosis SAPHO syndrome that are commonly used in clinical practice are those suggested by Kahn MF and Khan MA (1994) (Table 1) [4].

Table 1. Diagnostic criteria of Kahn MF and Khan MA (1994) for SAPHO syndrome [4].

<i>The presence of any three presentations is sufficient for the diagnosis</i>	
I. Chronic recurrent multifocal osteomyelitis	
– Usually sterile	
– Spine may be involved	
– With or without skin condition	
II. Acute, subacute or chronic arthritis associated with any of the following:	
– Palmoplantar pustulosis	
– Pustular psoriasis	
– Severe acne	
III. Any sterile osteitis (one localization is sufficient, including spondylodiscitis) associated with any of the following:	
– Palmoplantar pustulosis	
– Pustular psoriasis	
– Psoriasis vulgaris	
– Severe acne	

It has been suggested that SAPHO syndrome should be considered as a clinical entity from the group of seronegative spondyloarthropathies [8]. However, not all authors support this notion and there are diverse data about the association with HLA-B27 antigen [5, 9, 10]. In 71 patients with SAPHO syndrome, an association with the HLA-B27 antigen was not found. HLA-B27 antigen was

positive in 4% of the examined patient population [5] vs 8% of the white healthy population [11]. There are also data that show higher prevalence of HLA-B27 antigen varying from 15% to 1/3 of cases [4, 10].

Due to the lack of randomized clinical trials and low prevalence of the condition, treatment guidelines for SAPHO syndrome do not exist and the treatment is empirical according to the clinical manifestations.

CASE REPORT

Here, we report a case of 63-year-old woman who presented in our department with history of severe pain in anterior chest wall with more than 6 months duration. In the last 3 weeks prior consultation, the patient noted pustular rash of her palms (Fig. 1). No synovitis of peripheral joints was present. Her past medical history includes presence of postmenopausal osteoporosis without pathological fractures for 10 years, without anti-osteoporotic treatment in the last 3 years. The patient has also spine osteoarthritis, knee osteoarthritis 1st radiological stage, mild Raynaud's phenomenon.



Fig. 1. Palmar pustulosis

Laboratory tests revealed peripheral blood count – within normal values, no evidence for inflammation – ESR 10 mm/hour, CRP – 1.9 (< 6). Biochemistry tests, i.e., serum calcium, transaminases, creatinine, alkaline phosphatase, were within normal values. Focus of infection has not been found. X-ray of the sternum revealed osteosclerotic structure (manubrium and the body of sternum). Computed tomography of the chest has shown uneven bony contour in the lower part of sternal manubrium and in the upper part of the sternal body, heterogeneous bony structure of the affected area with predominant osteosclerosis (Fig. 2).

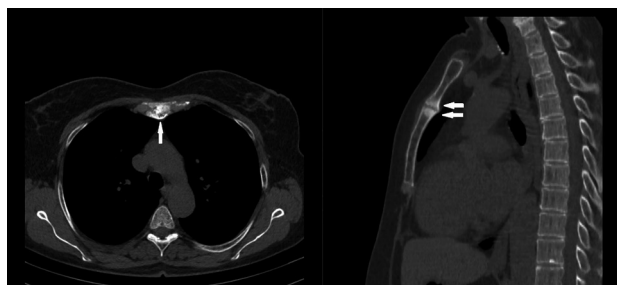


Fig. 2. Computed tomography images that demonstrate osteitis of sternal bone. Heterogeneous bone structure with predominant osteosclerosis and uneven bone contour in the lower part of sternal manubrium and in the upper part of the sternal body are demonstrated (arrows)

A single infusion of zoledronic acid induced complete resolution of pain syndrome in the anterior chest in 48 hours. Hydroxychloroquine was initiated for skin lesions at the dose of 200 mg daily. The follow-up of the patient continued 2-1/2 years since the initial diagnosis. No episodes of anterior chest pain were registered for a period of one year after the first infusion of zoledronic acid. 12 months after the infusion the patient presented with mild anterior chest pain when the second infusion of zoledronic acid was administered. After the second infusion the patient was asymptomatic for 1 year and 2 months when recurrent chest pain appeared again. The administration of nonsteroidal anti-inflammatory drugs (NSAIDs) was ineffective and the patient received a third infusion of zoledronic acid. The overall period of follow-up is 2-1/2 years. The palmar pustulosis had recurrent course in the first 6 months of treatment with hydroxychloroquine without skin lesions in the next 2 years.

DISCUSSION

There are no established treatment guidelines for SAPHO syndrome. The therapy is empirical based on disease manifestation and available experience from case reports, observations in case series and publications based on single-center experience. First-line therapy for pain relief includes NSAIDs and analgesics. Antibiotics are generally ineffective [1], although cases with a good clinical response have been reported [5, 8].

Bisphosphonates are synthetic analogues of pyrophosphate and are potent inhibitors of bone resorption. They are suggested to have also some anti-inflammatory activity [1, 12]. Bisphosphonates are supposed to inhibit the secretion of IL-1, 6, and TNF- α by macrophages [13]. There are observations for good therapeutic effect of bisphospho-

nates for osteoarticular manifestations in SAPHO syndrome [7, 9, 10, 12, 14, 15, 16, 17, 18, 19, 20]. Moreover, increased osteoclast activity has been described at histological examination in the areas of bony involvement [5]. Zwaenepoel et al. (2016) have reported the results from treatment with bisphosphonates in a retrospective study that included 21 patients with SAPHO syndrome. Bisphosphonates were administered in 14 cases, of whom 8 have responded and achieved full or partial remission [9]. Colina et al. (2009) have reported 14 cases with SAPHO syndrome (10 females and 4 males, mean age at onset 40 years) refractory to NSAIDs, glucocorticoids and conventional DMARDs (sulfasalazine, methotrexate), who were treated with intravenous pamidronate at the dose of 60 mg pamidronate for 3 consecutive days. Improvement of bone pain was defined as reduction in the values of the visual analogue scale for pain greater than 50%. In all cases anterior chest wall occurred early in the disease and in 2 patients there was a peripheral monoarthritis. In one case there was no cutaneous involvement. A good response was observed in 12 patients after 3 infusions and in 8 of them a sustained remission was achieved [15]. Amital et al. (2004) performed an open-label study of 10 patients with SAPHO syndrome (of whom 7 females, the age at the time of diagnosis ranged from 26 to 68 years) who did not respond to NSAIDs, oral corticosteroids, colchicine, methotrexate, sulphasalazine and the TNF- α blocker – infliximab. The patients were treated with intravenous infusion of 60 mg pamidronate. Additional infusion was given within a month in the absence of response and within 4 months in cases of a partial response. Nine cases responded to therapy with pamidronate, 6 with complete and 3 with partial remission. Six patients needed two infusions, 2 – four infusions, one patient responded to three and one to a single infusion [16]. Kopterides et al. (2004) reported a clinical case of SAPHO syndrome successfully treated with zoledronic acid. 18-year-old male patient with jaw pain and swelling and mandibular bone lesion on scintigraphy has been treated with 4 mg zoledronic acid that led to symptom resolution for 6 months when mild symptoms recur. A second dose was administered and the improvement after the second infusion has continued 1 year, when the third dose was given empirically [17]. Monotherapy with zoledronic acid has shown good therapeutic effect and resolution of symptoms in a clinical case of SAPHO syndrome with osteoarticular involvement of sterno-clavicular joints and clavicles [18]. Other bisphosphonates such as oral alendronate [19]. and

intravenous ibandronate [20]. have also demonstrated efficacy in clinical cases with SAPHO syndrome.

Systemic corticosteroids and conventional DMARDs have been used in SAPHO syndrome [1, 21]. Hayem et al. (1999) have reported the results of treatment in 120 patients with SAPHO syndrome. Promising results were observed under treatment with methotrexate that was administered in 10 patients, of whom 6 had peripheral arthritis. Efficacy was not observed among 18 patients treated with sulfasalazine [8]. Conventional DMARDs (sulphasalazine, methotrexate, hydroxychloroquine), isotretinoin and methylprednisolone have been used successfully in a case report of SAPHO syndrome with bony, joint and cutaneous manifestation [21]. Low-dose methotrexate therapy is gold standard for rheumatoid arthritis treatment. It is also used usually as first-line agent in psoriatic arthritis with high efficacy for both peripheral arthritis and skin lesions [22]. Considering this, methotrexate has been successfully used in patients with SAPHO syndrome and peripheral synovitis [23]. There are also reports about successful treatment of skin and articular involvement in SAPHO syndrome with leflunomide [24].

There are data about successful treatment of SAPHO syndrome with biologics and targeted synthetic DMARDs. In a systematic review, Daoussis et al. (2019) have found that in patients with SAPHO syndrome, who do not respond to conventional DMARDs, TNF- α blockers appear to be the first choice and have shown response rate in bone and joint manifestations of 93.3%. In patients, in whom TNF- α blockers are ineffective, biologics that target IL-17 and IL-23 pathway could be used. IL-17 blockade was associated with improvement in skin manifestations in 57.1% of cases (4/7) and in joint/bone involvement in 37.5% (3/8). Ustekinumab has shown efficacy in a part of the cases regarding skin (3/5) and bone/joint manifestations (2/4) [25]. In a clinical case, palmoplantar pustules and chest pain in the context of bilateral sternoclavicular joints and first anterior ribs involvement improved after treatment with methotrexate. However, synovitis was refractory to NSAIDs, methotrexate, hydroxychloroquine and the TNF- α inhibitor – etanercept. The JAK inhibitor – tofacitinib was started with good effect on the articular syndrome [26].

In the current clinical case, the cutaneous lesions were successfully treated with hydroxychloroquine. Hydroxychloroquine is an antimalarial drug used in different rheumatic diseases. Hydroxychloroquine has an immunomodulatory effect. It can delay or prevent organ damage and has antithrombotic

effects. Hydroxychloroquine is a weak base and accumulates in the lysosomes which maintain acidic pH. In rheumatology, it is indicated in mild rheumatoid arthritis, for articular and cutaneous involvement in systemic lupus erythematosus, etc. [27]. Antimalarials are commonly avoided in psoriatic arthritis as they have been reported to worsen psoriasis. However, this phenomenon has been questioned and very low prevalence of psoriasis activation has been reported by some authors in patients with psoriatic arthritis treated with hydroxychloroquine (2/114 for 3.5 years, Aydin et al., 2015).

CONCLUSION

The lack of accepted therapeutic protocol in SAPHO syndrome stimulates off-label empirical use of drugs according to experts' opinion adjusted to disease manifestations and the observed therapeutic response. The available literature data and the reported clinical case suggest that zoledronic acid may be a successful therapeutic option for osteitis. Hydroxychloroquine is a well-tolerated immune-modulatory drug that might be considered for the cutaneous involvement.

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