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Clinical Features of the SAPHO Syndrome and their Role in Choosing the Therapeutic Approach: Report of Four Patients and Review of the Literature

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SUMMARY Although the SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome was defined as a distinct entity more than 20 years ago, its classification within the spectrum of inflammatory rheumatic diseases and the proper therapeutic approach are still a matter of debate. We present four patients diagnosed with the SAPHO syndrome treated and followed-up in our Department, demonstrating the diversity of their clinical courses and their responses to different therapeutic approaches. We also review the clinical, laboratory, and imaging features of the SAPHO syndrome described in the relevant literature. Despite the growing quantity of published data on the clinical features of the syndrome and the recognition of two disease patterns (inflammatory and bone remodeling disease), it is still not clear whether these possible disease subsets require different therapeutic strategies. Tumor necrosis factor-alpha (TNF-α) inhibitors have been suggested to be effective in patients with the inflammatory pattern, whereas bisphosphonates seem to be effective in patients with bone remodeling disease; however, this is still a hypothesis not yet confirmed by adequately designed clinical studies. Further research is needed to assess disease features predicting favorable response to the two therapeutic modalities beyond the first line of therapy – TNF-α inhibitors and bisphosphonates.

KEY WORDS: spondyloarthropathies, acquired hyperostosis syndrome, psoriasis, therapeutics

INTRODUCTION

The synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) syndrome is an umbrella term covering a number of previously described conditions (1,2). It was previously considered to be rare with a prevalence of 1/10000 (3), but a Japanese study suggests that SAPHO is present in about 4% of patients with seronegative spondyloarthropathies (SpA) (4).

Diagnostic criteria proposed in 1988 (5) have not been validated, especially regarding the distinction from similar conditions, including other SpA (Table 1). Neither is it clear whether SAPHO is a distinct category within SpA, a subtype of psoriatic arthritis, or a primitive autoinflammatory reactive osteitis (1,6-8).

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Table 1. Diagnostic criteria for the SAPHO syndrome*

Inclusion criteria (the presence of one is sufficient for diagnosis)
Osteoarticular manifestations of acne conglobata, acne fulminans, or hidradenitis suppurativa
Osteoarticular manifestations of palmoplantar pustulosis
Hyperostosis (of the anterior chest wall, limbs, or spine) with or without dermatosis
Chronic recurrent multifocal osteomyelitis involving the axial or peripheral skeleton, with or without dermatosis
Exclusion criteria
Septic osteomyelitis
Infectious chest wall arthritis
Infectious palmoplantar pustulosis
Palmoplantar keratodermia
Diffuse idiopathic skeletal hyperostosis
Osteoarticular manifestations of retinoid therapy

* According to Benhamou *et al.*, 1988 (5)

Despite new insights into pathogenesis, the diagnostic and therapeutic approach is still based on the analogy to SpA and published data of a low level of evidence. The variable clinical picture and responses to therapy raise the question of the right approach to patients with this syndrome and the existence of disease subsets requiring different strategies.

We present four patients with the SAPHO syndrome describing different disease courses and therapeutic approaches used (Table 2). We also review the heterogeneous clinical presentation of the syndrome and the use of each of the available diagnostic tests. Finally, we review and discuss the role of therapeutic modalities used in the treatment of patients with the SAPHO syndrome, focusing on the recognition of two disease subsets that possibly respond differently to agents beyond the first line of treatment: TNF-α inhibitors and bisphosphonates. All patients described in this study gave appropriate informed consent.

PATIENTS

Patient 1

A 16-year-old male patient was referred to us in August 2010 due to a two-month painful swelling of the right jaw angle and recurrent arthralgias of several large joints of the extremities. He had a two-year history of acne conglobata of the trunk refractory to

Table 2. Overview of demographic and disease-related features of four patients with SAPHO syndrome

No.	Sex[a]	Age at diagnosis (years)	Time from onset of symptoms to diagnosis (years)	Follow-up (years)	Symptomatic osteoarticular sites	Bone biopsy	Skin involvement	Elevated inflammatory markers at diagnosis	HLA B27	Treatment	Other features
1	M	16	2	3	Right mandibular angle, LJE[c]	No	Acne conglobata	Yes	No	ABx[f], NSAR[g], isotretinoin, SSZ[i], pamidronate	Trismus, oral ulcers, osteopenia, sideropenia, suspected malabsorption
2	F	36	17	11	Left hip, left sacroiliac joint, ACW[b], LJE[c], MTP[d]	Yes	PPP[e]	Yes	No	GCS[h], NSAR[g], SSZ[i], MTX[j], pamidronate, alendronate, total hip alloplasty	Hashimoto's thyroiditis, Raynaud syndrome, livedo reticularis
3	F	46	19	<1	ACW[b]	No	PPP[e]	Yes	No	Etretinate, NSAR[g], SSZ[i]	None
4	M	15	<1	3	ACW[b]	No	Acne conglobata	No	Yes	ABx[f], NSAR[g], pamidronate, etanercept[l], tonsillectomy	Recurrent tonsillopharyngitis, subcutaneous abscess following introduction of etanercept

[a]M – male, F – female; [b]anterior chest wall; [c]large joints of the extremities; [d]metatarsophalangeal joints; [e]palmoplantar pustulosis; [f]antibiotics; [g]nonsteroidal antirheumatics; [h]systemic glucocorticosteroids; [i]sulfasalazine; [j]methotrexate

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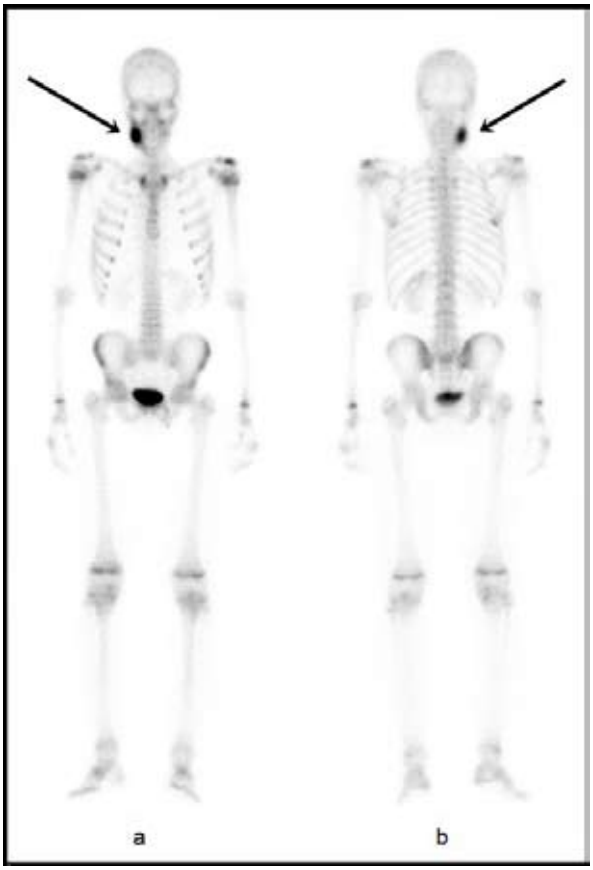

Figure 1. Whole-body technetium 99m bone scan of a 16-year-old male patient – (a) anterior and (b) posterior view. Increased tracer uptake was observed in the right mandibular angle (arrow).

doxycycline, azithromycin, and co-amoxiclav. One year prior to referral a course of isotretinoin was initiated but discontinued after two weeks due to large joint arthralgias. Recurrent arthralgias were partially controlled with nonsteroidal antirheumatics (NSAR). Several weeks before referral, extraction of the right mandibular third molar was performed, without signs of purulent inflammation. Co-amoxiclav, clindamycin, and metronidazole were administered without effect, and the patient developed trismus. The past medical history was unremarkable except for a tonsillectomy performed in 2002.

In addition to previous findings, physical examination revealed bilateral tender submandibular lymphadenopathy with prominent acne conglobata of the trunk. Laboratory evaluation revealed an elevated erythrocyte sedimentation rate (ESR) (53 mm/h, normal range (NR): 2-12 mm/h), C-reactive protein (CRP) (47 mg/L, NR: <5 mg/L), and a raised leukocyte count (13.3×10^9/L, NR: $4.4\text{-}11.6\times10^9$/L). Results of further laboratory workup were unremarkable, including coagulation tests, serum and urine biochemistry, urinalysis, serum protein electrophoresis, and immunoelectrophoresis (serum immunoglobulin classes G, M, and A), as well as immunologic tests. The patient was HLA B27 negative.

Mandibular X-ray revealed radiolucency of the right mandibular angle and hyperostosis of the coronoid process, with adjacent soft tissue swelling. A technetium 99m (Tc-99m) bone scan showed a marked tracer uptake in the right mandibular angle (Figure 1). T1- and T2-weighted magnetic resonance imaging revealed a heterogeneous intensity signal lesion involving the right mandibular ramus, with minimal gadolinium enhancement and periosteal reaction. The patient was diagnosed with SAPHO and treated with a regimen of intravenous pamidronate (90 mg at month 0, 45 mg at month 4) with daily peroral indomethacin and sulfasalazine.

Treatment led to reduction of mandibular swelling and acne and to normalization of inflammatory markers. Due to non-compliance to peroral therapy the patient experienced an aggravation of acne and bilateral hip and knee pain. Isotretinoin was added to the treatment, and indomethacin was switched to ibuprofen. Despite alleviation of acne, arthralgias persisted due to ongoing non-compliance to indomethacin and sulfasalazine. The patient also developed recurrent buccal aphthous ulcerations and right knee arthritis.

Lumbar densitometry revealed mild osteopenia and the patient developed sideropenia with a normal blood count. Stool was negative for occult blood and testing for serum antiendomysial antibodies was negative. The patient refused to undergo further evaluation of suspected malabsorption.

Patient 2

A 36-year-old female patient was referred to us in June 2002 due to recurring pain in the left gluteus and costosternal junctions, which began in 1985 and led to progressive impairment of the range of motion of the left hip. Since 1987 she had experienced recurrent palmoplantar pustulosis (PPP).

In 1998 the patient was evaluated in another department. Examination revealed limited internal rotation of the left hip and PPP (clinically and histologically). Laboratory findings were unremarkable, except for a polyclonal increase in IgA. Tc-99m bone scan revealed intensive uptake in the left sacroiliac joint and the left acetabular roof. Computed tomography (CT) revealed erosions and sclerosis of the left sacroiliac joint and adjacent bones. It also revealed narrowing of the left coxofemoral joint with multiple

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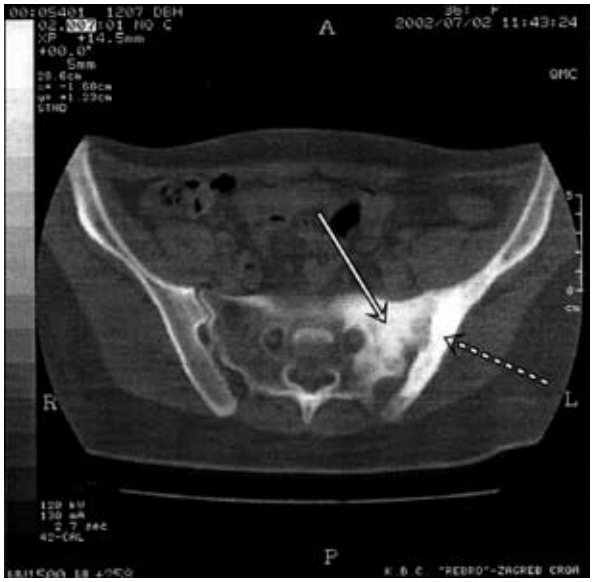

Figure 2. Pelvic computed tomography (CT) of a 36-year-old female patient revealing ankylosis of the left sacroiliac joint, as well as hyperostosis of the adjacent sacrum (full arrow) and the left iliac bone (dotted arrow) (A – anterior, P – posterior, R – right, L – left).

subchondral transparencies. No symptom relief was observed despite treatment with indomethacin. She was diagnosed with hyperthyreosis in the context of Hashimoto's thyroiditis and treated successfully with thiamazole.

In 2000 a left supraacetabular bone biopsy revealed marked cortical sclerosis and thickened periosteum. Symptoms were gradually worsening despite indomethacin and sulfasalazine, and the patient was referred to our Department in June 2002. Laboratory tests revealed a slightly elevated ESR (33 mm/h, NR: 2-12 mm/h), CRP (9.7 mg/L, NR: <5 mg/L), alkaline phosphatase (ALP) (160 IU/L, NR: 44-119 IU/L), and total serum calcium (2.62 mmol/L, NR: 2.14-2.53 mmol/L). Results of further laboratory workup were unremarkable, and the patient was HLA B27 negative.

Tc-99m bone scan revealed increased tracer uptake in the left sternoclavicular joint, sacroiliac joint, and hip. Plain X-ray revealed sclerosis with radiolucent zones in the medial portions of both clavicles. Pelvic CT findings were similar to those described in 1998 (Figure 2). The patient was diagnosed with SAPHO. Ineffectiveness of conventional treatment, including methylprednisolone, led to a decision to introduce intravenous pamidronate: the first application (60 mg) was in February 2003, followed by 7 monthly infusions. This resulted in a transitory relief of pain and normalization of inflammatory markers, with no effect on skin lesions. A flare of osteoarticular symptoms developed thereafter, associated with elevated inflammatory markers but normal levels of ALP and IgA. Tc-99m bone scan revealed less intensive uptake in the left sacroiliac joint and more pronounced accumulation in the left hip and both sternoclavicular joints. Bisphosphonate treatment was discontinued, and total left hip alloplasty was performed in September 2004. Analysis of the femoral head specimens revealed features of both acute and chronic SAPHO syndrome. Pamidronate was administered again in 7 monthly infusions from September 2004 to May 2005, leading to remission of osteoarticular symptoms. PPP was successfully treated with oral methylprednisolone.

In June 2005, the patient developed arthralgias of peripheral joints (radiocarpal, talocrural, and metatarsophalangeal) and symmetric Raynaud syndrome of the fingers, without laboratory evidence of inflammation. Methotrexate was introduced instead of sulfasalazine, helping to control both skin and osteoarticular symptoms. In 2006 she developed a flare of osteoarticular symptoms with elevated levels of urinary N-terminal telopeptide, responding well to alendronate. The further disease course was characterized by occasional flares of pain, PPP, episodes of Raynaud syndrome, and livedo reticularis of the thighs. At present the patient is receiving low-dose oral methylprednisolone and weekly methotrexate (7.5 mg).

Patient 3

A 46-year-old female patient was referred to us in November 2004 due to a 19-year history of recurrent palmoplantar pustules and ragades with sternoclavicular joint painful swelling. Palmoplantar lesions started occuring in 1985. At that time laboratory test results were completely normal. Skin biopsy revealed pustular psoriasis, and the lesions were treated with topical steroids and oral etretinate. No pustular lesions have been observed since 1989.

Meanwhile, the patient developed recurrent bilateral sternoclavicular painful swelling, prominent in the left sternoclavicular joint, without signs of neurovascular compression. Laboratory evaluation at our Department revealed a slightly elevated ESR (32 mm/h, NR: 2-12 mm/h). Despite normal levels of total serum ALP, the level of bone ALP isoenzyme was elevated (41 IU/L, normal values (premenopausal females): 11.6-29.6 IU/L). Results of other laboratory tests were normal and the patient was HLA B27 negative.

Thoracic X-ray revealed massive osteosclerosis of the anterior portions of first ribs with bilateral sternoclavicular joint ankylosis. Pelvic X-ray revealed an

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inhomogenous left sacroiliac joint, narrowing of both coxofemoral joints, and bilateral iliac crest entesopathy. A Tc-99m bone scan revealed elevated tracer uptake in both sternoclavicular joints, the sternal manubrium, both first ribs, the 5th costosternal junction on the right, and both sacroiliac joints.

The patient was diagnosed with SAPHO syndrome. Sulfasalazine and diclofenac were introduced but the patient was lost to our follow-up.

Patient 4

An 18-year-old male patient was referred to our transitional clinic in June 2013 after being followed-up at the Department of Pediatrics.

In early 2010 he developed acne of the trunk and face, refractory to a prolonged regimen of azithromycin. Six months later he developed anterior musculoskeletal chest pain with unremarkable laboratory findings. A Tc-99m bone scan revealed multiple areas of tracer uptake in the anterior chest wall, and an anterior chest X-ray revealed a mixed lytic-sclerotic affection of the sternoclavicular joints. He was diagnosed with SAPHO syndrome. Courses of antibiotics (macrolides, doxycyclin, and co-amoxiclav), ibuprofen, and intravenous pamidronate were administered with an unsatisfactory response. Tonsillectomy was performed in July 2011 due to recurrent tonsillopharyngitis. A control bone scan revealed intensive tracer uptake in the anterior chest wall and both humeral heads. Etanercept was introduced, resulting with complete relief of osteoarticular symptoms after the first application and an unremarkable bone scan finding following the third application. Unfortunately, etanercept was stopped due to development of a large subcutaneous abscess of the left upper arm, successfully treated with intravenous antibiotics: co-amoxiclav and clindamycin. In early 2013 the patient was started on methotrexate with an effect on both osteoarticular and cutaneous symptoms. Physical examination at our clinic revealed acne of the anterior trunk. Results of laboratory workup were unremarkable, including bacterial cultures of cutaneous lesions. A follow-up bone scan revealed normal findings in the early static scintigrams and symmetric late tracer uptake in both humeral heads.

DISCUSSION

Cutaneous and osteoarticular features of the SAPHO syndrome may occur synchronously but more often metachronously, causing a delay between disease onset and diagnosis (9), as demonstrated in our patients. Cutaneous affection is not mandatory for diagnosis, given that osteitis is the fundamental component of the syndrome (9,10). Skin lesions include acne fulminans and conglobata, PPP, hydradenitis suppurativa, pustular psoriasis, and, according to some authors, psoriasis vulgaris and a growing number of other neutrophilic dermatoses (8). Osteoarticular features comprise osteitis, hyperostosis, synovitis, and enthesitis. Related symptoms include inflammatory pain and swelling (8). Osteitis is defined as an osteosclerotic reaction with or without osteolysis adjacent to a joint, whereas extensive bone formation is termed hyperostosis (9). According to some authors, osteitis and hyperostosis are perceived as a continuum, with osteitis on one end and hyperostosis on the other (11). Periosteal thickening and involvement of the adjacent soft tissue are prominent in the initial phase (11).

In a study of 120 patients (9), the most commonly affected site was the anterior chest wall (63.0%), followed by bones adjacent to sacroiliac joints (40.0%) and the vertebrae (33.0%). Less frequently affected were the mandible (10.8%), the pubic symphisis (7.0%) and peripheral bones. Synovitis can develop independently or adjacent to osteitis. In the aforementioned study (9), axial arthritis was observed in 91.9% and peripheral in 36.0% of patients. Peripheral arthritis was observed in 2/4 of our patients. Spinal lesions include osteosclerosis, spondylitis with or without discitis, and syndesmophytes (9). Enthesitis was not found in patients with acne and hydradenitis suppurativa in a study of 15 SAPHO patients, possibly being a factor of distinction between the two disease subgroups (12). Mandibular osteitis commonly affects the ascending ramus and the posterior mandibular body, rarely the temporomandibular joint. It may present with bruxism and trismus (13), as described in Patient 1.

Chronic recurrent multifocal osteomyelitis is a pediatric condition now considered to be a part of the syndrome. In contrast to adults, long bones are commonly affected (14).

Several complications were described in the context of the SAPHO syndrome (9,14-20), none of which were observed in our patients. SAPHO was also described in association with inflammatory bowel disease (9,21) and multiple sclerosis (13).

Despite malignant bone disease being the clinically most important differential diagnostic feature, it was not included in the list of exclusion diagnostic criteria (5) (Table 1). The differential spectrum of the SAPHO syndrome also includes septic arthritis and osteomyelitis, osteoarthritis, diffuse idiopathic skeletal hyperostosis, Paget's disease, sarcoidosis, mastocytosis, tuberous sclerosis, and Langerhans cell histiocytosis (14,22).

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According to a study of the evolution of the disease, more than 50% of patients with the SAPHO syndrome had a chronic course (as described in patients from the present study), 35% experienced exacerbations and remissions, while 13% had a limited course (8).

Despite the proposed criteria, diagnosis is still based on clinical judgment. Laboratory workup is of limited value: it may reveal elevated inflammatory markers (10) and a polyclonal increase in IgA level (23).

Unlike "classical" SpA, HLA B27 was present in only 3/71 patients evaluated in a large study (8) and 1/4 patient in our study. The finding of antithyroid antibodies in 20/71 patients failed to be confirmed in another study of 90 patients, revealing antinuclear antibodies as the most common (24). Conversely, a study of 29 patients cast doubt on the role of autoimmunity in the pathogenesis of the syndrome, revealing no presence of antinuclear, RF, or CCP antibodies (23).

Imaging techniques are the cornerstone of the diagnostic process, given their ability to detect osteitis and hyperostosis. Conventional radiographs are of low sensitivity, and CT is the technique of choice (2). Nuclear scans are more sensitive, revealing sites of asymptomatic affection. They are a powerful diagnostic tool, also useful in patient follow-up, distinguishing active from quiescent disease (2,25). Whole body magnetic resonance imaging (MRI) and positron emission tomography combined with CT (PET/CT) can both detect subclinical/silent lesions, offering a greater spatial resolution (2). Affected bone sites are shown on T1- and T2-weighted imaging as hypointense and hyperintense respectively, displaying gadolinium enhancement (26), thus suggesting inflammation or a tumor. [18F]fluorodeoxyglucose (FDG) PET was shown to have a potential role in distinguishing inflammation from bony tumors: reported standard uptake values in inflammatory lesions were lower (27). Radiographic features may also aid in distinguishing bacterial from SAPHO oste(omyel)itis (11). Ultrasound is useful for establishing enthesitis (12).

Although skin biopsy is often performed, bone biopsy is reserved primarily for patients with an atypical presentation (10,26). Sterile pustules are typically found in the skin, whereas bone biopsy reveals two different stages. Hallmarks of the acute stage are polymorphonuclears, plasma cells, edema, and periostitis, whereas fibrosis and bone sclerosis are features of the chronic stage (10). Cultures of biopsy specimens are usually sterile or reveal atypical microbes, e.g. *Propionibacterium acnes* (22).

Despite the growing knowledge of the pathogenesis of the SAPHO syndrome, new findings still seem to fit in the classically proposed three mechanisms molecular mimicry, immune complex deposition, and immune barrier breakdown. All of them suggest the role of a potential infectious agent (10).

Treatment of SAPHO syndrome is based on the analogy with SpA and still relies on anecdotal reports from the literature. The first line of treatment includes NSARs and analgesics for osteoarticular symptoms and topical therapy for cutaneous lesions. Systemic glucocortcoids are an important treatment option, as indicated in the study conducted by Colina *et al.* (8), who administered glucocorticoids in 68% of 71 patients (daily dosage: 10-25 mg of a prednisone equivalent). The second line of treatment comprises disease modifying antirheumatic drugs – methotrexate, sulfasalazine, leflunomide, cyclosporine, and bisphosphonates – but also antibiotics and, less frequently, colchicine and calcitonin (28). The third line includes biological drugs, primarily tumor necrosis factor-alpha (TNF-α) inhibitors (28).

The rationale for the use of TNF-α inhibitors is based on high levels of TNF-α observed in bone biopsy specimens (29) and recent insights into the role of these agents in immune mechanisms in patients with SAPHO (23). Infliximab is most commonly used, and reported to induce a rapid clinical response in 16/17 patients, sustained in 13/17 patients (30). In addition to a positive clinical effect (30-32), etanercept has also demonstrated its role on the molecular level (23). Successful treatment with adalimumab was also described (33). Despite their beneficial effect, TNF-α inhibitors may cause aggravation of cutaneous features (34), as we have recently reported in our HLA B27 negative female patient with anterior chest wall osteitis and elevated inflammatory markers treated with infliximab (35). We also observed no effect of infliximab on the Tc-99m uptake pattern in this patient, despite regression of osteoarticular complaints (35). We also described the occurrence of *de novo* palmoplantar psoriasis, onychodystrophy and IgA nephropathy in a rheumatoid arthritis patient treated with adalimumab (36). In addition to the previously mentioned biological agents, it is noteworthy that anakinra showed benefit in the short term in 5/6 patients with the SAPHO syndrome, including two patients failing to respond to TNF-α inhibitors (37).

Bisphosphonates are another promising option for the treatment of refractory disease. Apart from their effect on bone remodeling, nitrogen-containing bisphosphonates also show anti-inflammatory activity (38,39). Intravenous pamidronate demonstrated a favorable effect on osteoarticular and other features in 9/10 patients, leading to complete remission in 6/9

(40). Despite concerns over its use in children, it led to alleviation of symptoms without significant adverse effects (41). Successful treatment with other bisphosphonates was also reported (42). The spectrum of adverse effects seems to differ between intravenous and oral bisphosphonates: the first may raise the risk of renal disfunction and osteonecrosis of the jaw, and the latter may lead to esophagitis (43).

The decision of whether to start treatment with TNF-α inhibitors or bisphosphonates may be influenced by the disease profile: an inflammatory disease pattern (morning pain and stiffness, elevated inflammatory markers, constitutional symptoms, increased early bone scan uptake) may respond favorably to TNF-α inhibitors, whereas bisphosphonates may be the therapy of choice in patients with marked bone remodeling (mandibular affection, elevated serum crosslaps, pronounced osteosclerosis, and increased late bone scan accumulation) (14,44). This hypothesis is yet to be confirmed by adequately designed clinical studies.

The idea of antibiotic use for the treatment of the syndrome stems from the findings of the Gram positive anaerobic bacillus *Propionibacterium acnes* and other bacteria in bone biopsy specimens of patients with SAPHO (22,45). Other than their antimicrobial effect, antibiotics have various other immunomodulatory effects (46), as described in the case of macrolides (47) and co-trimoxazole (48). The use of doxycycline and clindamycin was also reported, and long-term treatment recommended (49). However, the effect of antibiotic treatment is not convincing (22,45).

Surgery as a treatment option is of limited value in patients with the SAPHO syndrome, reserved for refractory disease or patients with severe structural or functional impairment (50).

CONCLUSION

The SAPHO syndrome is still a diagnostic and therapeutic challenge, especially in patients with a chronic and/or atypical disease course. There is still no clear evidence that identified disease patterns (inflammatory and bone remodeling disease) respond differently to TNF-α inhibitors and bisphosphonates. Further studies are needed to identify disease features predictive of a favorable response to each of the two medication groups.

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