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ORIGINAL RESEARCH

The Diagnosis and Treatment of Adult Patients with SAPHO Syndrome: Controversies Revealed in a Multidisciplinary International Survey of Physicians

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ABSTRACT

Introduction: This study aimed to investigate the current practice in the diagnosis and treatment of SAPHO syndrome among the international rheumatology and dermatology communities.

Methods: We conducted an electronic survey among the members of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), the Japan Spondyloarthritis, and Israeli Societies of Rheumatology.

Results: A total of 78 physicians participated in the survey: rheumatologists (83%, *n* = 65), dermatologists (11.5%, *n* = 9), and orthopedics (3.8%, *n* = 3). SAPHO was considered a subtype of spondyloarthritis by 48.7% (*n* = 38), a subtype of psoriatic arthritis by 19.2% (*n* = 15), a separate entity by 25.6% (*n* = 20), and a subtype of reactive arthritis by 6.4% (*n* = 5). Palmoplantar pustulosis was the most prevalent cutaneous manifestation (*n* = 44, 56.4%) and anterior chest pain—the most prevalent osteoarticular manifestation (*n* = 66, 84.6%). The majority (84.6%, *n* = 66) voted for the update of the present diagnostic criteria by Khan 1994. Magnetic resonance imaging was considered the preferred imaging modality for the diagnosis of SAPHO by 41% (*n* = 32). Conduction of bone biopsy for diagnosis of non-infectious osteitis was supported only by 10.3% (*n* = 8). Patient-reported outcomes were considered the most appropriate measure for the assessment of disease activity by 47.4% (*n* = 37). The treatment approach was overall similar among the rheumatology and dermatology communities, including non-steroidal anti-inflammatory drugs, bisphosphonates,

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conventional disease-modifying anti-inflammatory drugs, and biologics.
Conclusions: Our study underlines the controversy on diagnosis and treatment of SAPHO syndrome among specialists in rheumatology and dermatology and emphasizes an unmet need for update and validation of diagnostic criteria and treatment approach.

Keywords: Diagnosis; Psoriatic arthritis; SAPHO; Spondyloarthritis; Survey SAPHO syndrome; Treatment

Key Summary Points
Controversy on diagnosis and treatment of synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome is reflected in an international survey.
There is an unmet need for update and validation of diagnostic criteria and treatment approach to SAPHO.
Multidisciplinary international collaboration is warranted to expand studies of SAPHO syndrome.

DIGITAL FEATURES

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INTRODUCTION

The SAPHO syndrome (acronym for synovitis, acne, pustulosis, hyperostosis, and osteitis), introduced by Chamot in 1987, represents a rare heterogeneous disease mainly targeting the skin and the skeleton [1]. The true incidence and prevalence of SAPHO are unknown, as the syndrome is commonly under-recognized or misdiagnosed. SAPHO mainly affects children and young adults, often diagnosed as chronic recurrent multifocal osteomyelitis (CRMO) in the young population. Clinical manifestations of SAPHO are variable and share common features with psoriatic arthritis (PsA) and spondyloarthritis (SpA)-related diseases. The main cutaneous manifestations include palmoplantar psoriasis, severe acne, and less commonly, hidradenitis suppurativa. Musculoskeletal manifestations typically include a non-infectious osteitis, hyperostosis, and synovitis of the anterior chest wall, with the sternoclavicular junction being commonly affected, followed by the spine, sacroiliac joints, and peripheral non-erosive arthritis. Skin lesions may precede, follow, or occur simultaneously with the onset of musculoskeletal manifestations [2, 3]. Several clinical patterns of SAPHO have been recognized, including a relapsing–remitting or chronic disease in the majority of cases and rarely a monophasic disease [4]. Non-infectious sterile osteitis with subsequent hyperostosis resulting in osteolytic and osteosclerotic bone lesions represent a distinct pathological and radiographic feature of SAPHO [5]. Etiopathogenesis of SAPHO is considered multifactorial. Low virulent pathogens, such as *Propionibacterium acnes*, may trigger an exaggerated inflammatory response of the bone marrow in genetically susceptible individuals, leading to a form of "reactive osteitis" [6].

Diagnostic criteria for SAPHO remain preliminary and lack validation. The first diagnostic criteria proposed by Chamot were based on the clinical grounds, including a wide spectrum of clinical features [1], further followed by criteria proposed by Kahn requiring pathological evidence of osteitis or osteomyelitis for establishing the diagnosis, with or without typical skin lesions [7]. The modified criteria proposed by Hayem, based on an observational cohort of 120 patients with SAPHO, suggested to base the diagnosis on the combination of typical osteoarticular and skin manifestations, following the exclusion of inflammatory bowel disease, bone infection, and tumors [8]. To date, no formal guidelines outlining a diagnostic approach to SAPHO exist. Bone scintigraphy is commonly used as first-line imaging in the systemic evaluation of osteoarticular lesions in

SAPHO syndrome [9]. In view of advances in imaging techniques, magnetic resonance imaging (MRI), computerized tomography (CT), and ultrasonography (US) application of an appropriate imaging modality for diagnosis and monitoring of disease activity is highly needed in patients with SAPHO, along with avoidance of unnecessary imaging tests. No specific core domain set of outcome measures were developed or applied in SAPHO. Furthermore, there are no evidence-based treatment algorithms in SAPHO due to a lack of clinical trials in this rare medical condition. Treatment choice is based on retrospective reports and case series. In fact, a wide spectrum of medications has been used to treat SAPHO, extrapolated from treatment approaches to psoriasis, severe acne, PsA, and SpA. To date, there are no data on long-term efficacy, adverse events, and outcomes of different treatments in SAPHO [10].

SAPHO is a rare disease involving skin and rheumatologic manifestations, with a potentially complicated and severe course. Clinical presentation may pertain to several specialties, including rheumatology, dermatology, orthopedics, physiotherapists, and pediatricians. Optimal management of these patients requires multidisciplinary collaborative care. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) is an international network platform of medical disciplines treating psoriasis and psoriatic arthritis and recent interest in this condition was reflected in a symposium on pustular psoriasis and SAPHO during the recent GRAPPA virtual annual meeting in July 2020 (www.grappanetwork.org). To further explore current concepts and practice on the approach and treatment strategies in SAPHO, a survey was conducted among the members of GRAPPA as well as the Japanese Sponsyloarthritis and Israeli Societies of Rheumatology, and the results are presented here.

METHODS

An electronic online survey was conducted among the members of GRAPPA, Japanese Spondyloarthritis, and Israeli Societies of Rheumatology. The questionnaire was distributed to 703 physicians, including 26 members of the Japanese Spondyloarthritis Society, 70 members of Israeli Society of Rheumatology, and 613 GRAPPA members (one Japanese responder and five Israeli responders belonged to GRAPPA as well). No selection criteria were applied. The survey took place in 2017, using a Google Forms platform. The language of the survey was English. The study, considered as less than 'minimal risk research', was certified as exempt by the Tel Aviv Sourasky Medical Center Institutional Review Board (Helsinki Committee) and participants' written informed consent was waived as the participation in the study was voluntarily and each participant had an option to fill out the survey anonymously. In the survey, responders were asked to state their medical subspecialty and the country of origin. SAPHO-related questions included the total number of SAPHO patients under a physician's care, the annual number of new SAPHO cases, the most commonly encountered osteoarticular and skin manifestations, and preferable imaging modality for the diagnosis of SAPHO in the clinical practice. The use of ultrasound in the assessment of sternoclavicular or other sternal joints and the performance of bone biopsy in cases of osteitis or hyperostosis for the diagnosis of SAPHO was posed. The responders were asked whether the 1994 diagnostic criteria for SAPHO reflected the characteristics of SAPHO patients in their practice and whether there was a need for the update or modification of the SAPHO diagnostic criteria. Responders' points of view on the classification of the SAPHO syndrome to one of the following diseases' subgroups: psoriatic arthritis, spondyloarthropathy, reactive arthritis, or a separate independent entity were evaluated. Further, measures for the assessment of disease activity were inquired. Survey participants were questioned about the treatment approach to SAPHO and whether there was a difference in the treatment approach in patients with psoriasis versus acne.

RESULTS

A total of 78 physicians completed the survey, reflecting a response rate of 11.1%. Among the

Table 1 SAPHO survey results presented by geographic regions of the responders

Geographic region of responders	No. of responders	Most prevalent skin manifestation	Most prevalent musculoskeletal manifestation	Preferable imaging modality for SAPHO diagnosis	US use for assessment of sternoclavicular/ sternal joints	Bone biopsy required for diagnosing SAPHO in cases of osteitis or hyperostosis	Khan 1994 criteria reflect SAPHO cases in your practice	Agreement to modify Khan 1994 diagnostic criteria	Most appropriate measure for disease activity in SAPHO	SAPHO nosology
North America and Canada	6	PPP 33.3% Acne 16.7% HS 16.7%	Anterior chest 33.3% Peripheral arthritis 16.7% CRMO 33.3% Sacroiliitis 16.7%	MRI 50% XR 16.7% depends on clinical presentation 33.3%	50%	Not required 50% Not sure 50%	Mainly yes 66% Partially yes 16.7% No 16.7%	66.7%		SpA 66.7% Separate entity 16.7% Reactive arthritis 16.7%
Europa	11	PPP 45.5% Acne 27.3% HS 27.3%	Anterior chest 100%	MRI 36.4% Bone scan 27.3% US 18.2% CT 9.1% Clinical 9.1%	81.8%	Not required 100%	Mainly yes 81.8% Partially yes 18.2%	72.7%	PRO 54.5% PhRO 18.2% ASDAS 18.2% Inflammatory markers 9.1%	SpA 36.4% PsA 36.4% Separate entity 27.2%
Middle East (Israel, Turkey)	24	PPP 45.8% Acne 37.5% Pustular psoriasis 16.7%	Anterior chest 95.8% Peripheral arthritis 4.2%	MRI 54.2% Bone scan 20.8% CT 20.8% US 4.2%	50%	Not required 66.7% Required 12.5% Not sure 20.8%	Mainly yes 45.8% Partially yes 50% No 4.2%	75%	PRO 50% PhRO 16.7% US 12.5% ASDAS 8.3% PRO + PhRO + CRP 12.5%	SpA 45.8% PsA 20.8% Separate entity 33.3%
South America	5	PPP 20% Acne 60% Pustular psoriasis 20%	Anterior chest 60% Peripheral arthritis 20% Sacroiliitis 20%	MRI 20% Bone scan 60% CT 20%	40%	Not required 40% Required 40% Not sure 20%	Mainly yes 40% Partially yes 60%	100%	PRO 40% PhRO 20% Inflammatory markers 20% Bone scan 20%	SpA 20% PsA 20% Separate entity 60%
Far East (Japan, Korea, Singapore)	28	PPP 82.1% Acne 17.9%	Anterior chest 89.3% Peripheral arthritis 3.6% Enthesitis 3.6% CRMO 3.6%	MRI 35.7% Bone scan 35.7% CT 21.4% XR 3.6% US 3.6%	32.1%	Not required 32.1% Required 10.7% Not sure 57.1%	Mainly yes 64.3% Partially yes 35.7%	96.4%	PRO 53.6% PhRO 10.7% ASDAS 14.3% Inflammatory markers 7.1% US 10.7% Bone scan 3.6%	SpA 64.3% PsA 14.3% Separate entity 14.3% Reactive arthritis 7.1%

Table 1 continued

Geographic region of responders	No. of responders	Most prevalent skin manifestation	Most prevalent musculoskeletal manifestation	Preferable imaging modality for SAPHO diagnosis	US use for assessment of sternoclavicular/sternal joints	Bone biopsy required for diagnosing SAPHO in cases of osteitis or hyperostosis	Khan 1994 criteria reflect SAPHO cases in your practice	Agreement to modify Khan 1994 diagnostic criteria	Most appropriate measure for disease activity in SAPHO	SAPHO nosology
India	1	PPP	Enthesitis	MRI	0	Not sure	Mainly yes	Yes	PhRO	Reactive arthritis

CT computerized tomography, *CRMO* chronic recurrent multifocal osteomyelitis, *MRI* magnetic resonance imaging, *HS* hidradenitis suppurativa, *PPP* palmoplantar psoriasis, *PRO* patients reported outcomes, *PhRO* physicians reported outcomes, *PsA* psoriatic arthritis, *SpA* spondyloarthropathy, *US* ultrasound, *XR* X-ray

responders, there were 63 (80.7%) adult rheumatologists, two (2.6%) pediatric rheumatologists, eight (10.3%) dermatologists, one (1.3%) double-board certified rheumatologist and dermatologist, three (3.8%) orthopedic surgeons, and one (1.3%) radiologist. There was a wide geographic representation among the responders: North America (n = 5) and Canada (n = 1), Europe (n = 11); Far East: Japan (n = 26), Korea (n = 1), Singapore (n = 1); Middle East: Israel (n = 23), Turkey (n = 1), South America (n = 5), and India (n = 1). Three responders did not identify their country. Table 1 summarizes the results of the survey based on the geographic region. The majority of the responders (n = 67, 86%) reported experience in the management of patients with SAPHO. Forty-four responders reported caring for 1–10 SAPHO patients, 14 responders reported caring for 11–20 SAPHO patients, and seven responders reported caring for up to 50 SAPHO patients in total. The annual incidence of 1–5 SAPHO cases/year was reported by the majority (n = 61, 78.2%). Eight responders (10.3%), mainly from Japan, reported an annual incidence of 6–10 cases/year in their practice. Palmoplantar pustulosis (PPP) was the most prevalent cutaneous.

Table 2 Preferences in the treatment choice of SAPHO

Treatment	Responders (%)
NSAIDs	76.6
Glucocorticoids	32.5
Conventional DMARDs	57.1
Bisphosphonates	48.1
Anti-TNF biologic therapy	75.3
Other biologic therapy	20.8
Antibiotic	14.3
Tonsillectomy	5.1
Isotretinoin	5.2
Topical therapy	10.4
Intra-articular steroid injection	7.8

NSAIDs non-steroidal anti-inflammatory drugs, *DMARDs* disease-modifying anti-rheumatic drugs

Manifestation among all regions (n = 44, 56.4%), with a particularly high prevalence in Japan (n = 23, 82.1%), followed by acne (n = 20, 25.6%), pustular psoriasis (n = 7, 9%), and rarely hidradenitis suppurativa (n = 5, 5.1%). Anterior chest pain and swelling (osteitis, hyperostosis, and joint inflammation of the anterior chest bones and joints) was the most prevalent osteoarticular manifestation (n = 66, 84.6%), followed by peripheral arthritis (n = 5, 6.4%), sacroiliitis (n = 2, 2.6%), and enthesitis (n = 2, 2.6%). Chronic recurrent multifocal osteomyelitis (CRMO) was reported by three responders (3.8%). MRI was considered the preferred imaging modality for SAPHO diagnosis by 41% (n = 32) of the responders, whereas 26.9% (n = 21) preferred bone scan, and 19.2% (n = 15) voted for computerized tomography (CT) scan. Four responders (5.1%) reported using US applied for sternum joints for SAPHO diagnosis. Regarding the indication for bone biopsy to confirm the diagnosis of SAPHO in cases of osteitis or hyperostosis, only 10.3% (n = 8) supported the conduction of biopsy, whereas 55% (n = 43) found no need for this test in the diagnostic work-up of SAPHO. A third of the responders (34.6%) were uncertain regarding this item. Whereas 59% (n = 46) stated that the Khan diagnostic criteria mainly reflected SAPHO cases in their practice, the vast majority (84.6%, n = 66) still voted for modification and update of these criteria. SAPHO was considered as a subtype of SpA by 48.7% (n = 38), a subtype of PsA by 19.2% (n = 15), a separate entity by 25.6% (n = 20), and reactive arthritis subtype by 6.4% (n = 5). Patient-reported outcomes, including patient global and pain assessment (VAS), were considered the most appropriate measures for assessment of disease activity by 47.4% (n = 37), followed by clinical physician disease assessment by 16.7% (n = 13), Ankylosing Spondylitis Disease Activity Score (ASDAS) by 10.3% (n = 8), and blood inflammatory markers by 9% (n = 7). Six (7.7%) responders suggested a follow-up of disease activity by US, 2.6% (n = 2) by bone scan, and one (1.3%) by MRI. Three responders (3.8%) suggested a combination of clinical, laboratory, and imaging measures for assessment of disease activity and follow-up. The list of preferable medications and treatments used for SAPHO is presented in Table 2. The question related to the treatment approach to SAPHO was formulated as a multiple-choice question, presenting a list of potential therapeutics. Overall, the treatment approach was similar among the rheumatology and dermatology responders. Non-steroidal anti-inflammatory drugs (NSAIDs) were the first choice universally listed by most responders (colchicine was not specifically mentioned), followed in decreasing order of frequency by anti-TNFa biologics, conventional DMARDs, bisphosphonates, other biologics (not specifically named), and finally antibiotics. Remarkably, only Japanese responders (n = 4) suggested tonsillectomy as an additional mode of treatment. Comparing treatment approaches among different regions, European and Middle East responders reported a significantly more common use of bisphosphonates (63.6%, n = 7 and 62.5%, n = 15, respectively) compared to Japanese responders (n = 11, 39.3%). Whereas 27.3% (n = 3) of European and 17.8% (n = 5) of Japanese responders reported the use of antibiotics, none of the Israeli responders used this treatment.

DISCUSSION

Our survey provides insight into the current approach and treatment practices of an international community of physicians, mainly rheumatologists and dermatologists, experienced in the care of patients with SAPHO. This syndrome is not only rare and heterogeneous but also presents in different subsets around the globe. SAPHO manifestations in Asian and Caucasian populations show different characteristics. Asian patients with SAPHO mainly present with PPP and only rarely with severe acne or hidradenitis suppurativa. In fact, pustulotic arthro-osteitis (PAO) is the most common form of SAPHO in the Japanese population. PAO was first reported by Sonozaki et al. in 1979 based on a case series of 22 cases with PPP and anterior chest involvement [11], further expanded to 53 cases [12]. Histologic examination of the anterior wall tissues revealed non-suppurative chronic

inflammation of the soft tissues around the sterno-costo-clavicular region or nonspecific chronic inflammation of bones. Spondylitis, sacroiliitis, and peripheral non-erosive arthritis were observed in up to 30% of this cohort. All patients were HLA-B27 negative. Whether PAO in Japan is a genetically and clinically distinct entity or not requires further investigation. Radiologically, spinal lesions are more common in Asians versus Caucasians [4, 13–15]. Limited reports point to a particularly severe form of SAPHO in the African-American population, characterized by acne fulminans and hidradenitis suppurativa [16]. There is a lack of data on SAPHO characteristics from other geographic regions. Our survey seems to be unique representing an insight into the features of SAPHO among a widespread community of rheumatologists and dermatologists. In terms of clinical features, PPP represented the most common cutaneous manifestation across the globe, followed by acne in the Middle East and European communities. Hidradenitis suppurativa was reported only in the North American, Canadian, and European communities. The involvement of the anterior chest wall was the most common osteoarticular manifestation, consistent with the observational data from Europe [15] and Japan [14]. The prevalence of peripheral arthritis, enthesitis, sacroiliitis, and CRMO was variable in different geographic regions. The nosology of SAPHO was mainly viewed as a subtype of SpA, followed by PsA subtype, except for the South American subgroup, which categorized SAPHO as a separate and independent entity. The survey demonstrated a wide range of opinions regarding the preferred imaging modality in SAPHO, ranging from MRI (most commonly applied in North America, Canada, and the Middle East), CT (equally applied in the Far East, South America, and the Middle East), USA (most commonly applied in Europe), and bone scan (most commonly applied in South America). Notably, the choice of the imaging modality should be dependent on the stage of the disease, as early and late radiographic findings significantly differ. For example, early lesions tend to be osteodestructive and best demonstrated by MRI or bone scintigraphy, whereas late lesions tend to be osteoproliferative, resulting in hyperostosis and sclerosis that are best assessed on CT scanning [9]. Further, a discussion regarding the need for bone biopsy in the diagnosis of SAPHO-related osteitis was demonstrated, with the majority of responders voting for no need for biopsy (for example, 100% of European responders) or being unsure regarding this item. Consensus for the update of the diagnostic criteria was reached across all regions. Other discussion points included the measures for disease assessment and the therapeutic approach.

Limitations of our study relate to the inherent limitations of the study design as a survey. Notably, there was a low response rate, which might be explained by the rarity of SAPHO syndrome around the globe. In fact, some of the responders reported no personal experience with SAPHO patients. Yet, we decided to include their views on the diagnosis and treatment of SAPHO, as they reflected the current concepts on SAPHO of the corresponding medical society. A discrepancy in recall accuracy of the responders was another inherent limitation of the survey design. Furthermore, the questionnaire used in this survey was in particular constructed for this study, without prior validation. All the mentioned limitations might potentially affect the validity of the study.

CONCLUSIONS

In summary, the results of our survey reflect the diversity in the current diagnostic and therapeutic approach to SAPHO syndrome in clinical practice. An unmet need for the update, modification, and validation of the SAPHO diagnostic criteria and setting disease activity measures was reflected by most of the participants. Future directions include establishing an international registry for SAPHO, which will lead to the development of classification and diagnostic criteria for SAPHO.

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Compliance with Ethics Guidelines. The study, considered as less than 'minimal risk research', was certified as exempt by the Tel Aviv Sourasky Medical Center Institutional Review Board (Helsinki Committee) and participants' written informed consent was waived as the participation in the study was on a voluntarily and each participant had an option to fill out the survey anonymously.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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