

Clinical and Radiologic Evolution of Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis Syndrome: A Single Center Study of a Cohort of 71 Subjects

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Objective. To assess the basic features and outcomes of synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome.

Methods. We identified all patients seen in our unit between 1990 and 2008 diagnosed according to the proposed inclusion criteria with SAPHO syndrome, who had a followup of at least 2 years.

Results. Seventy-one patients (48 women, 23 men) with SAPHO syndrome were identified. The median disease duration at the end of followup was 10 years (interquartile range [IQR] 7–15 years), and the median followup duration was 11 years (IQR 6–11.5 years). Six patients were diagnosed with Crohn's disease. Fourteen patients had never had cutaneous involvement, but 8 patients presented >1 skin manifestation. Nine patients (13%) presented a limited (<6 months) monophasic disease course, 25 cases (35%) had a relapsing–remitting course, and 37 patients (52%) had an acute painful phase with a prolonged course lasting >6 months. A total of 4% of the patients were HLA-B27 positive. Female sex (odds ratio [OR] 7.2, 95% confidence interval [95% CI] 2.2–22.9) and the presence at onset of anterior chest wall (ACW) involvement (OR 5.7, 95% CI 1.8–18.1), peripheral synovitis ($P = 0.0036$), skin involvement (OR 10.3, 95% CI 3.4–31.1), and high values of acute-phase reactants (OR 7.7, 95% CI 2.7–22) were correlated with a chronic disease course and involvement of new osteoarticular sites.

Conclusion. A chronic course is the more common evolution of SAPHO syndrome. Female sex, elevated erythrocyte sedimentation rate and C-reactive protein values, ACW involvement, peripheral synovitis, and skin involvement at the onset seem to be associated with a chronic course.

INTRODUCTION

The acronym SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) represents a syndrome characterized by the variable association of peculiar osteoarticular manifestations and various chronic dermatologic conditions, in particular palmoplantar pustulosis and severe acne (1). Less commonly described are Sweet's syndrome, pyoderma gangrenosum, and other neutrophilic dermatoses (2–4). Inclusion of psoriasis vulgaris as the only skin le-

sion is still being discussed (5). Osteitis and hyperostosis are striking features that can be observed in any involved skeletal segment. The main affected area is the anterior chest wall (ACW), but the spine, pelvic girdle, peripheral bones, and mandibula may also be affected. A variety of articular manifestations may coexist, both arising from the extension of an adjacent osteitis or in the form of a peripheral mono- or oligoarthritis (6,7). To date, SAPHO is considered a rare disease, but the real prevalence could be underestimated because of the confusing symptoms and the possible lack of skin manifestations (8,9).

The nosologic framing of SAPHO syndrome is still a matter of debate (5,7,9,10). Although it has repeatedly been related to the spondylarthritis (SpA) family, especially psoriatic arthritis (PsA) (5,11), the emerging evidence suggests that SAPHO syndrome could be a primitive inflammatory osteitis (12,13). Different stimuli have been implicated as inciting factors, in particular the low-virulence pathogen *Propionibacterium acnes* either alive or as dead antigens (14–16), but an autoimmune or an autoinflammatory mechanism has not been ruled out (5,13,17).

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The natural history and long-term evolution of the disease have not been extensively investigated and are still not fully understood. Apart from anecdotal cases, only a few reports with a significant number of patients are available (1,7,18–21). These studies suggest that the disease tends to have a protracted course with flares and improvements that vary greatly from patient to patient. Most patients seem to have a fairly good prognosis, but sometimes SAPHO syndrome may become a severe disease leading to persistent pain and a significant deleterious effect on general well-being. Because of the rarity of the disease and the unknown etiopathogenetic mechanisms, targeted therapy is still unavailable. Apart from symptomatic and antimicrobial treatments, aminobisphosphonates and other disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, sulfasalazine, and anti-tumor necrosis factor α (anti-TNF α) agents have only recently been used (22–27).

The aim of this study was to describe the clinical, laboratory, and radiologic features of a cohort of patients with SAPHO syndrome observed in a tertiary referral center in North Italy from January 1990 to August 2008, including the long-term evolution of the disease for those patients with ≥ 2 years of followup.

PATIENTS AND METHODS

All adult patients admitted to our tertiary referral center between January 1990 and August 2008 who satisfied the proposed criteria for SAPHO syndrome were included in the study (Table 1). For the patients with psoriasis vulgaris as the sole skin manifestation, only those with typical osteitic/hyperostotic radiologic features were included ($n = 3$). Beginning with the first visit, the patients' data were collected by retrospective chart review from 1990 to 1996 (39 patients) and thereafter prospectively.

For each patient, data were recorded for the clinical picture and blood test results at presentation and, when possible, at the onset of the disease. Laboratory evaluation included acute-phase reactants (erythrocyte sedimentation rate [ESR], normal value <20 mm/hour, and C-reactive protein [CRP] level via the nephelometric method, normal value <5 mg/liter), alkaline phosphatase (Roche Diagnostics, Mannheim, Germany), normal value <270 units/liter for men and <240 for women, and serum immunoglobulins (Tina-Quant^a, Roche Diagnostics). Rheumatoid factor (RF; normal value <20 IU/ml) was quantified by electroluminescence (Roche Diagnostics). Antinuclear antibodies (ANA) were detected by immunofluorescence on HEp-2 cells (Alphadia, Italy). Antibodies to soluble extractable nuclear antigens (ENAs) were tested by enzyme-linked immunosorbent assay (Diastat; Eurodiagnostica, Malmoe, Sweden) with the following antigens: Sm, RNP, SSA, SSB, and Jo-1. Antibodies to double-stranded DNA were determined by the *Crithidia luciliae* method (Alphadia). Anti-thyroid peroxidase (anti-TPO) antibodies, normal value <35 IU/ml, and anti-thyroid globulin (anti-Tg) antibodies, normal value <115 IU/ml, were tested with electroluminescence (Roche Diagnostics). HLA-A, B, C, and DR antigens were analyzed by classical serologic methods.

Table 1. Inclusion and exclusion features of SAPHO syndrome (10)*

Inclusion features†	Osteoarticular manifestations of severe acne or <i>Hidrosadenitis suppurativa</i> Osteoarticular manifestations of palmoplantar pustulosis Hyperostosis: sternocostoclavicular hyperostosis, or other ACW hyperostosis, or limb hyperostosis, or spine hyperostosis, with or without dermatoses Chronic recurrent multifocal osteomyelitis, with or without dermatoses
Sometimes reported	Possible association with psoriasis vulgaris Possible association with inflammatory enterocolopathy Features of ankylosing spondylitis Presence of low-virulence germ infection (<i>Propionibacterium acnes</i>) in osteoarticular lesions Association acne vulgaris-ACW hyperostosis
Exclusion features	Septic osteomyelitis, with the exception of <i>P acnes</i> Infectious ACW arthritis Infectious palmoplantar pustulosis Palmoplantar keratoderma (Vidal-Jacquet syndrome) DISH, except fortuitous association of this frequent condition Osteoarticular manifestations (mainly hyperostosis) of retinoid therapy
* SAPHO = synovitis, acne, pustulosis, hyperostosis, and osteitis; ACW = anterior chest wall; DISH = diffuse idiopathic skeletal hyperostosis. † One of these 4 items is sufficient for a patient to be included in the syndrome. The patients may have several inclusion criteria.	

Routine laboratory analyses were repeated at each followup examination. Bacteriologic studies of appropriate specimens were carried out as necessary. When it was helpful for the diagnosis (6 patients), a bone biopsy was performed for culture and histologic examination.

Therapy and the course of osteoarticular and cutaneous manifestations (if any) were also recorded. The number and sites of osteoarticular involvement were tabulated. As in other studies, multifocal involvement of the ACW was regarded as a single site (7,19). The diagnosis of previous or current skin lesions was retained if it was clinically confirmed by a dermatologist.

Imaging data of current or past symptomatic sites were collected by conventional radiograph, ^{99m}Tc bone scintigraphy, sonography, high-resolution computed tomography (CT), and magnetic resonance imaging (MRI) scans, according to medical judgment. Osteitis and hyperostosis were considered present when formation of local or diffuse sclerosis with periosteal thickening was evident. Involvement of the surrounding soft tissue was also noted.

Table 2. Demographic characteristics of the 71 patients with synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome*

Characteristic	Value
Sex, no. women/men	48/23
Patients with/without skin disease, no.	57/14
Age at first osteoarticular symptom related to SAPHO syndrome, years	38.5 (33.7–50.2)
Age at SAPHO syndrome diagnosis, years	45.5 (35.7–54.0)
Followup duration, years	11 (6–11.5)

* Values are the median (interquartile range) unless otherwise indicated.

Additional imaging information was obtained during the followup, focusing on the evolution of the existing lesions and on any new ones. Radiologic pictures were read with the assistance of an expert skeletal radiologist (CO).

The most recent followup was conducted in May–August of 2008. All patients gave informed written consent after the nature of the procedures had been fully explained. A cutoff period of 6 months was used to define the course of the disease. Chronic disease course was identified as the presence of symptoms requiring a continuous full dose of nonsteroidal antiinflammatory drugs (NSAIDs) associated or not associated with steroids and other DMARDs (methotrexate, sulfasalazine, leflunomide, or anti-TNF α agents) for >6 months, and limited disease course was identified as the discontinuation of any treatment before 6 months. Exacerbations after remission were also tabulated, as well as any eventual involvement of new osteoarticular sites.

Results were expressed as median values with interquartile ranges (IQRs). To evaluate the correlation between the course of the disease and other independent variables such as sex, osteoarticular involvement, skin lesions, and laboratory indices at onset, a statistical analysis using multinomial logistic regression was performed using SyStat software, version 5 (SyStat, Evanston, IL). The strength of the associations were evaluated by odds ratio (OR), and the statistical significance of the associations were assessed with Fisher's exact test. *P* values less than 0.05 were considered statistically significant.

RESULTS

Seventy-one European adults (48 women and 23 men) who satisfied the SAPHO syndrome criteria and had an available followup of ≥ 2 years were identified. The median patient age at the onset of osteoarticular symptoms was 38.5 years (IQR 33.7–50.2 years), and the median time elapsed between the onset of osteoarticular symptoms and the diagnosis of SAPHO syndrome was 4.6 years (IQR 0.3–5.1 years). The median duration of the prospective followup period was 11 years (IQR 6.5–11.5 years) (Table 2). An additional 6 patients were not included in the study because they were lost from followup or had a disease duration of <2 years.

The patients' histories did not reveal any relationship

with recent trauma or overt infections, nor with familial spondylarthropathies or other systemic autoimmune diseases. Among the patients' first-degree relatives, a history of psoriasis without PsA was noticed in 8 cases. In 5 other first-degree relatives (not included in the present study) of 4 patients, an ACW osteitis consistent with the diagnosis of SAPHO syndrome was identified. Clinical presentation of osteoarticular symptoms was variable, usually insidious, and revealed by slight to severe inflammatory pain. Local tenderness with or without swelling was also usually present. ACW involvement was the most frequent and clinically relevant localization, followed by the spine (Table 3). Nineteen patients (32% of those with ACW involvement) had a history of several admissions to the emergency room for a suspected acute cardiac event. Nineteen patients reported persistent low-grade fever, which justified repeated investigations in order to exclude a systemic disease. In 8 patients (11%), the heralding manifestation was a subacute peripheral monarthritis, usually involving the knee or the wrist. Peripheral arthritis was more frequent in patients who were age <25 years at onset than in patients who were older. The synovial fluid analysis, performed 16 times, showed a mild inflammatory pattern, with a predominance of mononuclear cells (white cell count 1,200–3,800/mm³).

Different forms of dermatologic manifestations were seen in 57 patients (80%). In 40 patients, skin lesions appeared before or simultaneously with rheumatic symptoms. Eight patients presented, contemporarily or consecutively, with ≥ 2 cutaneous manifestations. In all of these patients a chronic course of the disease represented the most relevant clinical challenge and, at the end of the followup period, a progressive involvement of new bones and/or joints was observed. Moreover, in all patients, skin diseases ran independently of osteoarticular involvement, with eruptions also occurring when osteoarticular symptoms were absent. The patients without skin lesions were followed for a median period of 9.5 years (IQR 7–13.5 years); their pattern of musculoskeletal involvement was not dissimilar to that of the other patients.

Neither ocular inflammatory involvement nor dactylitis occurrence were observed during the followup period or noticed in patients' histories. In 6 patients, all with skin involvement, concomitant Crohn's disease was diagnosed (before the onset of SAPHO syndrome in 2 patients, and after the onset in the other 4). Three patients reported persistent intestinal disorders, but a histology evaluation showed only nonspecific inflammation (28).

In laboratory investigations, high inflammatory indices at onset (i.e., ESR and CRP level) were linked to a chronic course of the disease (OR 7.7, 95% confidence interval [95% CI] 2.7–22). The mean values for ESR and CRP level at disease onset and at presentation were compared without any statistically significant difference (data not shown). ANA results were positive in 2 patients, both with a concomitant autoimmune thyroiditis, whereas all patients were ENA and RF negative. At the end of the study period, indices of thyroid autoimmunity, namely anti-Tg and/or anti-TPO, were detectable in 20 patients, 14 with subclinical autoimmune thyroiditis (thyroid-stimulating hormone >3.5 μ U/ml, free tiroxine 4 [FT4] and FT3 within

	At onset	At end of followup	Chronic course (>6 months)	
			Patients, no.	OR (95% CI)
Osteoarticular manifestations†				
ACW involvement	50/71 (70)	59/71 (83)	32	5.7 (1.8–18.1)
Inflammatory back pain	17/71 (24)	9/71 (13)		
Spinal involvement	24/71 (34)	47/71 (66)		
Mandible, long bones involvement	3/71 (4)	8/71 (11)		
Peripheral synovitis (arthritis)	8/71 (11)	20/71 (28)	8	<i>P</i> = 0.0036‡
Perilesional florid soft tissue involvement	1/71 (1)	3/71 (4)		
Patients without skin involvement	31/71 (44)	14/71 (20)		
Patients with skin involvement	40/71 (56)	57/71 (80)	30	10.3 (3.4–31.1)
PPP only	20/40 (50)	34/57 (60)		
SA only	9/40 (23)	11/57 (19)		
PV only	3/40 (8)	3/57 (5)		
HS only	0/40	1/57 (2)		
PPP and SA	5/40 (12)	8/57 (14)		
PPP and PV	0/40	0/57		
PPP and HS	1/40 (2)	0/57		
SA and PV	0/40	0/57		
SA and HS	2/40 (5)	0/57		
PV and HS	0/40	0/57		
Other				
Inflammatory bowel disease	2/71 (3)	6/71 (8)		
Autoimmune thyroiditis	7/71 (10)	20/71 (28)		
Aspecific bowel disorder	0/71	3/71 (4)		
Laboratory indices				
ESR ≥20 mm/hour	15/71 (21)	25/71 (35)	26	7.7 (2.7–22)
CRP level ≥5 mg/liter	12/71 (17)	21/71 (30)	26	7.7 (2.7–22)
RF positive	0/54	0/71		
ANA positive	0/39	2/71 (3)		
ENA positive	–	0/71		
Anti-TPO ≥35 IU/ml	5/14 (36)	15/71 (21)		
Anti-Tg ≥115 IU/ml	4/14 (29)	16/71 (23)		
HLA–B27 present	–	3/71 (4)		

* Values are the number of patients/total number of patients (percentage) unless otherwise indicated. Only positive associations are expressed. SAPHO = synovitis, acne, pustulosis, hyperostosis, and osteitis; OR = odds ratio; 95% CI = 95% confidence interval; ACW = anterior chest wall; PPP = palmoplantar pustulosis; SA = severe acne; PV = psoriasis vulgaris; HS = hidrosadenitis suppurativa; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; RF = rheumatoid factor; ANA = antinuclear antibody; ENA = extractable nuclear antigens; anti-TPO = anti-thyroid peroxidase; anti-Tg = anti-thyroid globulin.

† Each single patient may have >1 osteoarticular manifestation.

‡ Calculated with Fisher's exact test.

normal range) and 6 with overt hypothyroidism. Other laboratory tests were within the reference range in all patients. The HLA–B27 antigen was present in only 3 (4%) of 71 patients. The results of histologic bone assessment performed in 6 patients showed various degrees of inflammation, from mild osteitis through an active inflammatory pattern to a healing process with osteosclerosis. Only one specimen resulted positive for *P acnes*, and this case is fully described elsewhere (16).

The main target area of clinical symptoms was the ACW, especially the proximal clavicle, sternum, first ribs, and adjacent joints. By multislice CT scan, the extent of the involvement of the ACW was accurately demonstrated, sometimes with striking evidence (Figure 1A and D). A florid expansion of the inflammation to adjacent soft tissue was observed in 3 patients, and in one case was the most relevant clinical challenge for the diagnosis (Figure 1B). Sometimes a grotesque periostitic evolution of lesions occurred (Figure 1C).

At the axial skeleton, lesions are usually segmental, with features including spondylodiscitis-like lesions with erosive discopathies and sclerotic reactive changes, and hyperostotic nonmarginal enthesophytes that are diffuse idiopathic skeletal hyperostosis–like with massive bridging. In the followup study, hyperostosis disappeared after ankylosis was achieved (Figure 2). Osteolytic areas were observed in 3 patients. Sacroiliitis was observed in 9 patients, and in 8 of these it was unilateral with sclerosis predominantly on the iliac side of the joint. Seventeen patients reported inflammatory back pain (29) at the onset of the disease, and by the end of the followup, this number reduced to 9. Peripheral bone and mandibula involvement were infrequent (observed in 7 patients and 1 patient, respectively). In the patients with peripheral arthritis, the knees, ankles, and wrists were the most frequently involved joints with erosions and space narrowing (Figure 3).

Bone scintigraphy was useful in the diagnostic evalua-

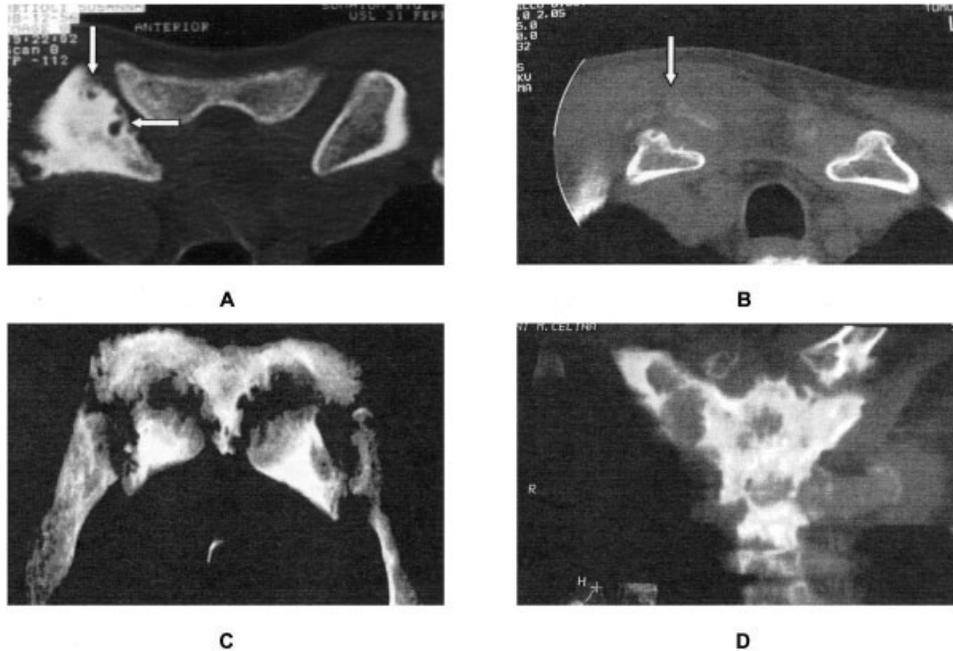


Figure 1. Computed tomography scans of **A**, the anterior chest wall showing sternocostoclavicular hyperostosis with subchondral erosions (**arrows**), **B**, soft tissue thickening and calcifications around the medial head of the clavicle (**arrow**) in a 62-year-old man with a disease duration of 6.9 years, **C**, hyperostosis and grotesque periostitic lesions, and **D**, massive osteitis with diffuse and osteolytic areas.

tion because it may demonstrate involvement of unusual and/or asymptomatic regions. On MRI, inflammatory bone changes appeared as hyperintense areas on fat-saturated T2-fast spin-echo sequences and showed pathologic enhancement after gadolinium administration.

NSAIDs were the most prescribed initial treatment, but the majority of patients (68%) needed corticosteroid therapy (10–25 mg/day of a prednisone equivalent). Antimicrobial agents (100 mg of doxycycline twice daily) were given to 9 patients, but improvement was noted only in 2. DMARDs (sulfasalazine 2–3 gm/day, methotrexate 10–20

mg/week, or leflunomide 20 mg/day) were given to 21 patients in order to minimize the use of steroids or to treat peripheral synovitis. Intravenous pamidronate was performed in 14 patients with persistent ACW pain and/or axial involvement and in 2 patients with additional peripheral arthritis with satisfying results (23). After a repeated failure to respond to nonbiologic DMARDs or pamidronate, 9 patients were treated with different anti-TNF α agents (all had ACW and/or axial involvement and 1 had additional peripheral arthritis) with good results, as has previously been partially described (27).

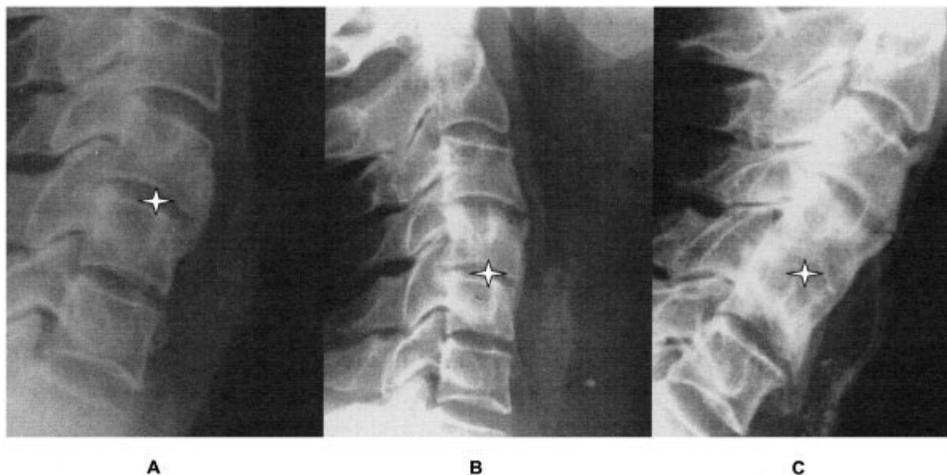


Figure 2. Lateral radiographs of the cervical spine showing the evolution of spine lesions in a case of synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome at **A**, baseline, **B**, 2-year followup, and **C**, 6-year followup. These show hyperostotic, nonmarginal enthesophytes that are diffuse idiopathic skeletal hyperostosis-like with bony bridging, and their evolution toward ankylosis.



Figure 3. Synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome with peripheral arthritis. Osteosclerosis, erosions, and loss of joint spaces are clear in the left carpal bones of a 29-year-old woman with a disease duration of 3 years.

The course of the disease was variable. Nine patients (13%) presented with a limited course lasting <6 but >3 months, with a single episode that afterward faded away. These patients had no disease flares during the followup (median 8 years) and needed no second-line therapy. In 25 patients (35%), after a first, limited course of <6 months, the patients experienced multiple remissions and exacerbations (1 to 4), and a prolonged time (up to 3 years) from 2 patients with relapses was observed. The duration of the flares was 2–8 months, and they did not demonstrate any apparent periodicity or recurrence. We could not identify the exogenous trigger factors associated with recurrences. The remaining 37 patients (52%) had a chronic course characterized by fluctuating intermittent periods of exacerbation and short improvement (median duration of followup 9 years), requiring almost continuous treatment. In the statistical analysis, female sex (OR 7.2, 95% CI 2.2–22.9), peripheral arthritis ($P = 0.0036$), ACW involvement (OR 5.7, 95% CI 1.8–18.1), skin manifestations (OR 10.3, 95% CI 3.4–31.1), or high values of acute-phase reactants (OR 7.7, 95% CI 2.7–22) at onset were associated with a chronic course of the syndrome.

The long-term prognosis seems to be rather good. At the end of a median followup of 10 years, only 2 of the 71 patients had severe disabling complications due to the osteoarticular symptoms, 1 patient with a thoracic soft tissue swelling (Figure 1B) and 1 with a crippling arthritis of the left wrist (Figure 3).

DISCUSSION

Since 1960 there have been several reports of patients with combinations of cutaneous lesions related to neutrophilic dermatitis (i.e., acne, palmoplantar pustulosis, and pyoderma gangrenosum), and osteoarticular manifestations mainly characterized by osteitic/hyperostotic involvement of the ACW. In the mid 1980s a team of French investigators grouped such heterogeneous conditions under the

SAPHO syndrome umbrella. Inclusion criteria were proposed in 1987, but have not been validated in comparison with closely related conditions such as SpA and particularly PsA. To date, the basic question is whether SAPHO syndrome represents an autonomous clinical entity or should be included with SpA (5,11,12). The majority of published papers are single case reports or limited case series, except for a few retrospective, multicenter studies (1,7,18–21). Therefore, the evolution of SAPHO syndrome remains not fully understood.

To date, SAPHO syndrome is considered a rare disease, but its prevalence is probably underestimated (9). Our case series is not meaningful for epidemiologic studies; however, our demographic data confirm that SAPHO is a disease of young to middle-aged adults with a female predominance (4,7,30).

Etiopathogenesis is also unclear. Although many hypotheses have been proposed, so far no specific etiologic agent has been identified. An infectious theory of a low virulence pathogen (i.e., *P. acnes*) acting as a trigger and then maintaining the progression of the disease through subsequent autoimmune response has often been proposed (15,16). Despite being usually regarded as a harmless commensal, *P. acnes* produces a number of microbial determinants that activate innate immune response through Toll-like receptor 2 (31,32). In our experience, this connection was confirmed in only 1 patient of 6 in whom a bone biopsy was performed. As in other reports, in this case doxycycline was effective in controlling the disease (33).

As far as genetic background is concerned, present results confirm the lack of association with the HLA-B27 antigen. This antigen, which is present in ~8% of the white Western European population (34), was found only in 4% of our patients. This result is in agreement with other large European case series (21,35,36). The extended HLA investigation also revealed no significant association with other alleles, namely those often associated with psori-

riasis or PsA (37). Moreover, in our cohort we noted an increased frequency of psoriasis in first-degree relatives, similar to the results of others (18). We found a prevalence of 11%, which is less than expected for PsA but high compared with the general population (1–3%) (38).

The finding of ACW osteitis in 5 first-degree relatives of 4 patients deserves attention and further consideration. To date, very few familial cases of SAPHO syndrome have been systematically investigated (12,39,40). More recently, a family history in patients with ACW osteitis has been reported (41), and a susceptibility gene located on chromosome 18t has been identified in a murine model of chronic recurrent multifocal osteomyelitis (CRMO), the pediatric subset of SAPHO syndrome (42–44).

Another intriguing feature related to the supposed link of SAPHO syndrome with SpA is the reported association with inflammatory bowel diseases (IBDs). In people with SAPHO syndrome, IBDs exceed the expected incidence of 0.5–1% in western Europe (an incidence of 8% was found in our series and in that of Hayem et al [7]). Like IBD, SAPHO has recently been included among the polygenic autoinflammatory disorders, considering aseptic osteitis to be due to a dysfunction of polymorphonuclear leukocytes (39,45). All of these data have to be better investigated in order to shed some light on the debate about the proper classification of the disease.

ESR and CRP levels are less reliable disease activity parameters in SAPHO syndrome than they are in other rheumatic conditions. Despite the clinical relevance of the inflammatory condition, high values were observed in only a third of the patients in this study. Apart from the recently reported increased incidence of ANA in 30% of patients with CRMO (41), few data on autoimmunity in SAPHO syndrome and related diseases are available. In our experience, the only relevant association is with clinical or subclinical autoimmune thyroiditis, which we found in 28% of the patients studied. Recently, a similar frequency of thyroid autoimmune diseases was also observed in PsA (46). Although it is not possible to establish the exact significance of this finding, it may suggest broader autoimmunity pathways.

Bone involvement is highly distinctive for the disease and osteitic/hyperostotic lesions are the mainstay of the diagnosis (4,11), suggesting that this disease is basically an inflammatory process arising from bone (47). The ACW is the typical target of the disease, but its involvement is not pathognomonic. A similar involvement may be seen in many other conditions, including SpA and PsA (34). The features of spine involvement have induced many authors to consider SAPHO syndrome to be related to SpA. In SAPHO syndrome, spondylodiscitis resembles that observed in SpA and is characterized by erosions of vertebral plates and surrounding sclerosis, in some cases involving the entire vertebral body. Discitis is combined with development of paravertebral ossification with massive bridging resembling that of diffuse idiopathic skeletal hyperostosis. In many papers these aspects have been described as syndesmophytes, but close observation of the published pictures may enable them to be more properly defined as enthesophytes. Moreover, spine lesions are segmental, in-

volving several adjacent vertebrae, evolving with the years toward vertebral fusion (4,18).

In our series, true syndesmophytes were never observed and hyperostosis disappeared when ankylosis was achieved. Some radiologic features (paraosteal ossification) may be confused with that of PsA. Nevertheless, some aspects of the clinical picture are different. In SAPHO syndrome the most typical symptom is a precocious ACW involvement, with inflammatory low back pain representing the most relevant clinical symptom only in a minority of cases (18,48). Otherwise, we did not observe patients with the inflammatory eye involvement or dactylitis that frequently occur in SpA and PsA. In our case series an asymmetrical oligoarthritis was not a common feature (incidence was 28% versus 43% found in patients with PsA), distal interphalangeal joint involvement was not observed (versus 46% found in patients with PsA), and radiographic sacroiliitis was present in 6% of our study population versus 14–25% in patients with PsA (49).

SAPHO syndrome was initially considered a condition with a fairly good prognosis, but recently several authors have suggested that this may not be true. From our case series the disease may be considered relevant due to the large number of patients with a chronic course and the occurrence of peripheral arthritis. We have found that female sex and the presence of ACW involvement, peripheral arthritis, skin lesions, and high inflammatory indices at the onset of the disease are associated with a chronic course. However, these findings should be regarded with caution as this is an observational descriptive study and did not include control cases.

To date, treatments have had to be tailored to each single patient, and NSAIDs and steroids have shown only partial efficacy. According to other studies, intravenous aminobisphosphonates (pamidronate and zoledronic acid) were effective in inducing remission. In recent years, anti-TNF α agents have been tried in open-label studies and case reports. Biologic treatment has usually led to sustained improvement of osteoarticular involvement, but skin manifestations may follow a less predictable course and relapses of palmoplantar pustulosis have been observed (50).

In conclusion, SAPHO syndrome continues to be a nosologic enigma. The chronic course of the disease and the need for using second-line drugs reflect the fact that it is a relevant entity, with a good prognosis *quoad vitam* but quite severe *quoad valetudinem*. Moreover, the course of the disease is heterogeneous. Female sex, the occurrence of high inflammatory indices, and the presence of cutaneous manifestation, ACW involvement, and peripheral arthritis at onset seem to be poor predictors of outcome, being associated with a chronic course of the disease.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Colina had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Colina, Govoni, Orzincolo, Trotta.
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