Prevalence of Autoantibodies in SAPHO Syndrome: A Single-center Study of 90 Patients

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ABSTRACT. *Objective.* To determine the prevalence of the most often tested autoantibodies in synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome.

Methods. We identified 90 patients seen in our unit between June 2002 and June 2009, and diagnosed according to the proposed criteria for SAPHO syndrome. Demographic and clinical data were collected as well as immunological results, including antinuclear, antithyroid peroxidase (TPO), antithyroid globulin (Tg), antigastric parietal cell, antismooth muscle, antimitochondria, and anti-liver-kidney microsome (LKM) antibodies. Anticyclic citrullinated peptide (CCP) antibodies were analyzed in 69 patients, antibodies to soluble extractable nuclear antigens in 43, anti-double-stranded DNA (dsDNA) antibodies in 22 [depending on the type of fluorescence of antinuclear antibody (ANA)], and antiendomysium antibodies in 55.

Results. Autoantibodies were found in 20 patients (22.2%): 14 patients (15.5%) had positive ANA (titer $\geq 1/160$); among them, 10 (11%) patients never took a lupus-inducing drug. Antithyroid antibodies (anti-TPO and/or anti-Tg antibodies) were found in only 3 patients (3.3%). Three patients (3.3%) were positive for antigastric parietal cell antibodies and 4 (4.4%) were weakly positive for antismooth muscle antibodies. Antimitochondria and LKM antibodies were negative in all 90 patients. Anti-CCP and anti-dsDNA antibodies were negative in the 69 and 22 patients tested, respectively. One out of 43 patients (2.3%) had anti-SSA antibodies. Antiendomysium antibodies were negative in the 55 patients tested.

Conclusion. Our study indicates an increased prevalence of autoantibodies in SAPHO syndrome, with no specific profile. We failed to confirm the reports of an increased prevalence of antithyroid antibodies. These results tend to support a link between autoimmunity and SAPHO syndrome. (First Release Feb 1 2010; J Rheumatol 2010;37:639–43; doi:10.3899/jrheum.090863)

Key Indexing Terms:

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SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis) was first described by Chamot, *et al* in 1987¹. However, the etiopathogenesis of SAPHO syndrome remains to be identified, although there is some evidence that slow-growing bacteria, such as *Propionibacterium acnes*, either as dead or live antigens, could play a trigger-

ing role^{2,3}. The elicited immunological response could follow a self-perpetuating process, explaining the longterm persistence of inflammation. Other convergent arguments support the incorporation of SAPHO syndrome within the group of inflammatory spondyloarthropathies (SpA): frequent involvement of the axial skeleton, with sacroiliitis^{4,5}; unexceptional presence of enthesitis, in classic sites as well as in the spine or the anterior chest wall⁵; possible association with inflammatory bowel diseases (Crohn's disease, ulcerative colitis)^{4,6,7}; and initial positive response to nonsteroidal antiinflammatory drugs.

Recently, an Italian group reported an unexpectedly high prevalence of antithyroid peroxidase (TPO) or antithyroid globulin (Tg) antibodies in patients with psoriatic arthritis (PsA), leading to a new etiological approach to this disease⁸. In SAPHO syndrome, which is considered relatively close to PsA, another Italian cohort study of 71 patients revealed a prevalence of 28% of antithyroid antibodies (at the end of followup, anti-TPO antibodies 15/71 and anti-Tg antibodies 16/71)⁹. Additionally, a German study found a prevalence of

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39% of antinuclear antibodies (ANA) in chronic recurrent multifocal osteomyelitis (CRMO), an entity that is considered by most authors a particular form of SAPHO syndrome¹⁰. Such results were not confirmed by Hurtado-Nedelec and coworkers, who found only 1 patient with antithyroid antibodies, out of a smaller cohort of 29 subjects¹¹.

Our aim was to investigate the prevalence of the most frequently tested autoantibodies in SAPHO syndrome.

MATERIALS AND METHODS

Subjects, blood collection, and study design. All subjects were seen at the Rheumatology Department of Bichat Teaching Hospital, Paris, France. Inclusion criteria were those proposed by Benhamou, *et al*¹². These criteria included (1) the osteoarticular manifestations of palmoplantar pustulosis, severe acne (conglobata or fulminans), or hidradenitis suppurativa; (2) hyperostosis of anterior chest wall, spine, pelvis, or limb, with or without dermatosis; or (3) CRMO with or without dermatosis. Exclusion features were septic osteomyelitis, infectious osteoarthritis of the anterior chest wall, infectious palmoplantar pustulosis, palmoplantar keratoderma, diffuse idiopathic skeletal hyperostosis (excepting the fortuitous association with SAPHO syndrome), osteoarthritis, and osteoarticular manifestations (mainly hyperostosis) of retinoid therapy. Clinical data were collected during routine followup visits, prospectively between 2005 and 2009 and retrospectively between 2002 and 2005. The following clinical data were systematically registered: age, sex, disease duration, age at first symptom, and treatments previously received, including drugs potentially responsible for the induction of ANA or lupus syndromes [e.g., sulfasalazine (SSZ), cyclins, antitumor necrosis factor- α (anti-TNF) agents]. The most recent followup was conducted in February-May 2009.

Autoantibody assays. All sera were tested for autoantibodies in the Immunology Department of Bichat Teaching Hospital.

ANA were assayed by indirect immunofluorescence on Hep-2 cells (Kallestad, Bio-Rad Laboratories, Redmond, WA, USA), with a positive titer $\geq 1/160$. Anti-TPO antibodies and anti-Tg antibodies (normal values < 60 U/l) were assessed with a radioimmunoassay (Brahms, Saint-Ouen, France). Antigastric parietal cell antibodies, antismooth muscle (ASM) antibodies, antimitochondria antibodies, and anti-liver-kidney microsome (LKM) antibodies (positive titer $\geq 1/40$) were tested by immunofluorescence on rat liver, kidney, and stomach sections (Kallestad, Bio-Rad). Anticyclic citrullinated peptide (CCP) antibodies (normal value < 25 U/l) were tested with ELISA (Immunoscan RA, Eurodiagnostica, AB, Malmö, Sweden). Depending on the positivity and the resulting fluorescence of ANA, antibodies to double-stranded DNA (dsDNA) or to soluble extractable nuclear antigens (ENA) were tested in 22 patients and 43 patients, respectively. Immunoglobulin G (IgG) anti-dsDNA antibodies (normal value < 15 U/ml) were measured by an ELISA (Elia Symphony, Unicap, Phadia, Uppsala, Sweden). Anti-ENA antibodies were assayed with an ELISA (Elia Symphony, Phadia) with the following antigens: Sm, ribonucleoprotein, SSA, and SSB. IgG and IgA antiendomysium antibodies (positive titer $\geq 1/20$) were analyzed with an indirect immunofluorescence technique on cryostat sections of monkey esophagus (The Binding Site, Birmingham, UK). For technical reasons, anti-CCP antibodies were analyzed in only 69 patients, and antiendomysium antibodies in 55 patients.

RESULTS

Clinical characteristics. We identified 90 patients who fulfilled the Benhamou, *et al* criteria for the SAPHO syndrome (Table 1)¹². Since these criteria have not yet been validated, we chose to exclude from the study the patients who pre-

Table 1. Main features of the 90 patients with SAPHO syndrome.

Gender (sex ratio)	25 men/65 women (0.4)
Age at first symptom (yrs)	32* (9–57)
Age at autoantibody testing (yrs)	42* (15–74)
Disease duration (yrs)	7* (1–56)
Patients previously treated with ANA-inducing drugs	17 (18.9%)

* Mean (range). SAPHO: synovitis, acne, pustulosis, hyperostosis, osteitis.

sented without at least 1 site of typical osteitis. These patients were followed up in our unit from 2002 until 2009.

There were 25 men (28%) and 65 women (72%), yielding a gender ratio of 0.4. Median age was 42 years (range 15 to 74) and median age at first symptom (osteoarticular or cutaneous) was 32 years (range 9 to 57). The median disease duration was 7 years (range 1 to 56). Seventeen patients (18.9%) had been previously treated with cyclins, SSZ, and/or anti-TNF therapy.

Autoantibody serum levels. Fourteen patients (15.5%) had ANA at a titer that was considered significant ($\geq 1/160$), while 37 patients (36.7%) had ANA at a titer $\geq 1/80$ (considered much less specific; Tables 2 and 3). Ten patients (11.1%) had positive ANA with a significant titer ($\geq 1/160$) and never took any drug capable of inducing ANA (including cyclins, SSZ, anti-TNF agents, but also hydralazine, procainamide, diltiazem, penicillamine, isoniazid, methyl-dopa, chlorpromazine, β blockers, and others). All 22 patients tested for anti-dsDNA antibodies were negative.

One patient had anti-SSA antibodies. She fulfilled the European Study Group in Classification Criteria for

Table 2. Autoantibody serum levels in patients with SAPHO syndrome with at least 1 autoantibody. Numbers in parentheses are percentages.

ANA $\geq 1/80$	
All patients	37 (36.7)
Patients who never took ANA-inducing drugs	24 (26.6)
ANA $\geq 1/160$	
All patients	14 (15.5)
Patients who never took ANA-inducing drugs	10 (11.1)
Anti-dsDNA Ab ¹	0 (0)
Anti-Tg Ab	2 (2.2)
Anti-TPO Ab	2 (2.2)
Anti-ENA Ab (anti-SSA Ab)	1 (1.1)
Antismooth muscle Ab	4 (4.4)
Antimitochondria Ab	0 (0)
Antigastric parietal cell Ab	3 (3.3)
Anti-LKM Ab	0 (0)
Anti-CCP Ab ²	0 (0)
Antendomysium Ab ³	0 (0)

¹ 22 patients tested. ² 69 patients tested. ³ 55 patients tested. SAPHO: synovitis, acne, pustulosis, hyperostosis, osteitis; ANA: antinuclear antibody; dsDNA: double-stranded DNA; Ab: antibody; anti-Tg: antithyroid globulin; anti-TPO: antithyroid peroxidase; anti-ENA: antiextractable nuclear antigens; anti-LKM: anti-liver-kidney microsome; anti-CCP: anticyclic citrullinated peptide.

Table 3. Clinical features of 14 patients with SAPHO syndrome with positive ANA at high titers ($\geq 1/160$).

Gender	11 women/3 men
Age at diagnosis (yrs)	27.5* (range 11–57)
Disease duration (yrs)	8* (range 1–27)
Skin diseases (no. of patients)	10
PPP, isolated	2
PV, isolated	6
SA, isolated	1
PPP + PV, isolated	1
No skin disease (no.)	4
Osteitis (no.)	14
Peripheral arthritis (no.)	8
Patients previously treated with ANA-inducing drugs (no.)	4 ¹

PPP: palmoplantar pustulosis; PV: psoriasis vulgaris; SA: severe acne.

* Mean. ¹ SSZ then anti-TNF agents for 2 patients, anti-TNF agents for 2 other patients.

Sjögren's syndrome (SS)¹³. A labial salivary gland biopsy revealed a grade III in the Chisholm scoring system. She was naive for any anti-TNF biotherapy.

One patient had anti-TPO antibodies, a second had anti-Tg antibodies, and a third had both types of antithyroid antibodies. Two of these 3 patients had histories of autoimmune thyroiditis.

Three patients (3.3%) were positive for antigastric parietal cell antibodies, 2 of them at high titers (1/1280 and 1/320). Two of these 3 patients were examined by endoscopy of the upper digestive tract that revealed an atrophic gastritis, compatible with pernicious (Biermer's) anemia. However, none of these 3 patients had anemia or vitamin B12 deficiency.

Four patients (4.4%) were weakly positive for ASM antibodies (titer 1/80), without clinical or biological related symptoms.

All patients were negative for antimitochondria antibodies and anti-LKM antibodies.

All of the 55 patients tested for antiendomysium antibodies were also negative, as were the 69 patients who were screened for anti-CCP antibodies.

Among the cohort, only 1 patient was found to have several antibodies, i.e., anti-Tg antibodies, anti-TPO antibodies, and ANA. She had previously received anti-TNF therapy.

Among the 20 patients who were positive for at least 1 autoantibody, the median disease duration of SAPHO syndrome was 10 years, while it was 6 years among the remaining 70 patients.

DISCUSSION

Since this disease was first described by Chamot, *et al*¹, there have been no consistent data about the possible implication of autoimmunity in SAPHO syndrome. Yet various tests for autoantibodies are currently available in daily rheumatology practice, in order to guide the diagnosis in

early inflammatory rheumatic diseases. As the best example, ANA are widely used to distinguish several connective tissue diseases, mainly represented by systemic lupus erythematosus and SS. However, significant titers of ANA have also been detected in other rheumatic diseases, including inflammatory SpA, although this category of rheumatic diseases has usually been viewed as seronegative. For example, ANA were found in the sera of 5 of 88 patients with ankylosing spondylitis and in 7 of 52 cases of psoriatic arthritis (PsA)¹⁴. Antonelli, *et al* found that anti-TPO antibodies were significantly more frequent in women with PsA (28%) or rheumatoid arthritis (RA; 31%) than in female controls (12%)⁸.

We present the first results of the testing for several autoantibodies in a large cohort of 90 patients with SAPHO syndrome. We selected these autoantibodies based on their current use in clinical practice, particularly in rheumatic inflammatory diseases. Median age at first symptom onset (osteoarticular or cutaneous) was 32 years (range 15 to 74). This confirms that SAPHO syndrome is primarily a disease of young and middle-aged adults^{4,9}. There was a female predominance (25 men vs 65 women; gender ratio 0.4), a trend that was already observed in previous SAPHO cohorts^{1,4,9}.

Until now, SAPHO syndrome has been considered as a distinct form of the so-called seronegative SpA, close to PsA¹⁵. It has even been suggested that psoriasis was “the missing link between SAPHO and SpA”¹⁶. Although SAPHO syndrome and PsA probably have different immunogenetic backgrounds, they clearly share some clinical and radiological features¹⁷. Additionally, it has been found that autoantibodies probably appear more frequently in PsA and in SAPHO syndrome than in the general population. This is especially true for ANA, whose prevalence (titer $\geq 1/80$) reaches 14% in biologic-naïve patients with PsA¹⁸. Relevant data about acquired autoimmunity are still scarce in SAPHO syndrome, mainly because this is a rarer and frequently underdiagnosed disease^{2,19}. In a study of 19 cases of SAPHO syndrome, Maugars, *et al* found negative results for rheumatoid factor and ANA, while anticytoskeletal antibodies were weakly positive in 6 cases⁵. More recently, a German study reported positive ANA in 39% of a subset of 36 patients with CRMO, considered the pediatric form of SAPHO syndrome¹⁰. However, the threshold for ANA positivity in that study was lower than in our study ($\geq 1/120$ vs $\geq 1/160$). Also, the authors did not look for any previous administration of ANA-inducing drugs. On the other hand, in an Italian cohort of 71 adult patients with well defined SAPHO syndrome, the prevalence of ANA was only 2.8% (2 patients with concomitant autoimmune thyroiditis)⁹. Similarly, among a cohort of 29 adult patients with SAPHO syndrome, Hurtado-Nedelec, *et al* failed to detect ANA or anti-CCP antibodies, with only 1 patient having significant levels of antithyroid antibodies¹¹. In our series of 90 SAPHO patients who were screened for ANA, a positive

result with a significant titer ($\geq 1/160$) was registered in 14 patients (15.5%). Of those, 10 patients (11%) never took cyclins, SSZ, or anti-TNF agents, all drugs that have been implicated in the possible induction of ANA, or lupus syndromes. This proportion is higher than in the general population, since ANA titers $\geq 1/160$ were reported in only 5% of healthy controls²⁰.

Although several drugs are able to induce the development of ANA or even increase the titers of preexisting ANA, few are currently used in rheumatology practice: SSZ and anti-TNF agents are the major examples, followed by cyclins, occasionally prescribed in SAPHO syndrome^{4,21-23}. Gordon, *et al* reported a study of 72 patients treated with SSZ who were ANA-negative or weakly positive at outset, of whom 14 (19%) became strongly ANA-positive during a 5-year followup²⁴. In patients receiving TNF blockers for RA or inflammatory SpA, ANA appear or increase more frequently under infliximab than etanercept or adalimumab²⁵. In our cohort, among the 14 patients with SAPHO who were ANA-positive ($\geq 1/160$), 4 had previously received cyclins, SSZ, and/or anti-TNF treatments. Although these results remain higher than in a healthy population, they contrast with the 39% detected by Jansson, *et al* among patients with CRMO¹⁰. Such a discrepancy could be explained by the different cutoff threshold for ANA titers ($\geq 1/120$ vs $\geq 1/160$ in our study). Indeed, many more patients (41.1%) in our cohort had ANA titers $\geq 1/80$. Another explanation could be that the previous administration of potential autoantibody inducers was not considered by the authors.

In our cohort, 1 female patient had anti-SSA antibodies, with a labial salivary gland biopsy revealing a grade III in the Chisholm scoring system. She fulfilled the European Study Group Classification Criteria for primary SS¹³. The finding of these 2 diseases in the same person seems so rare that it does not allow us to draw any conclusion. There are few previous reports about the possible link between SpA and primary SS. In a French study that systematically looked for such an association, 7 of 70 patients with ankylosing spondylitis (10%) had concomitant SS²⁶.

Thyroid autoimmune diseases were also observed in 3 patients (3.3%) of this cohort. Recently, an Italian group reported an unexpectedly high prevalence of anti-TPO or anti-Tg antibodies in PsA⁸. Another Italian cohort study of 71 patients with SAPHO syndrome revealed a prevalence of 28% of antithyroid antibodies⁹. At the end of followup, anti-TPO antibodies and anti-Tg antibodies were found in 15 and 16 patients, respectively. However, such proportions were registered in 2 different countries and should have been compared with the local prevalence of spontaneous autoimmune thyroidopathies. For example, in a healthy Welsh population, 10% of subjects were found to be positive for anti-TPO or anti-Tg antibodies²⁷. For this reason, further studies with healthy paired control groups are highly warranted.

Three patients (3.3%) of our cohort had positive antigastric parietal cell antibodies. In 2 of these patients, an upper digestive tract endoscopy was done and revealed a diffuse atrophy of the gastric mucosa. However, these patients had neither anemia nor vitamin B12 deficiency that could suggest a pernicious (Biermer's) anemia. Four patients (4%) were weakly positive for ASM antibodies, without any evidence of related symptoms.

Overall, at least 1 type of autoantibody was found in 20 (22.2%) subjects in this unselected cohort of 90 patients. In this subset of patients, the median duration of SAPHO syndrome was 10 years, as compared with 6 years in the remaining 70 patients. These findings suggest that the occurrence of autoantibodies in SAPHO syndrome might depend on the duration of the underlying inflammatory process.

The relatively high frequency of autoantibodies found in our study is globally in agreement with previous reports, although the great variability, both in type and prevalence, must be underscored. Consequently, it seems very unlikely that any of these autoantibodies will become useful diagnostic tools for SAPHO syndrome. Whether SAPHO syndrome and autoantibody production share common pathophysiological pathways remains to be determined.

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