Editorial

SAPHO syndrome: Is a range of pathogen-associated rheumatic diseases extended?

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Abstract

SAPHO syndrome, representing a constellation of synovitis, acne, palmo-plantar pustulosis, hyperostosis, and osteitis, is now recognized as a distinct medical entity: a reactive infectious osteitis. Genetic, immunological, and bacterial mechanisms are implicated in the development of the disease. Diagnostic problems may arise due to non-complete manifestations of SAPHO: either acne and arthritis or acne and anterior wall osteitis with an unclear pustulosis history. The interventional study of Assmann *et al*. is a significant addition to a long range of publications showing an association of SAPHO with *Propionibacterium acnes*. Randomized control studies are needed to confirm the effects of antibiotic therapy.

In the previous issue of *Arthritis Research & Therapy*, an interventional study of patients with SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome, a skin-osteo-articular inflammatory disease, showed positive bacteriological cultures for *Propionibacterium acnes* in 14 of 21 (67%) patients who had undergone a needle biopsy of osteitis lesions [1]. This is a significant addition to a long range of publications showing an association of SAPHO with *P. acnes* in 42% of patients (Table 1). The activity of SAPHO, by assessment of skin disease, health assessment score, radiological activity score, and osteitis lesions by magnetic resonance imaging, decreased significantly after 16 weeks of antibiotic therapy. The indices demonstrating disease activity increased after discontinuation of the antibiotic treatment.

The relationship between infection and autoimmunity has been increasingly defined over the last 20 years. In genetically susceptible individuals, environmental factors (mainly infections) play a critical role in the pathogenesis of autoimmune diseases. It is believed that infections contribute to the maturation of the immune system from innate to adoptive phases and that bacterial and viral infections are arthritogenic stimulants leading to various rheumatic conditions. Infectious agents may be the initial trigger of the production of cross-reacting antibodies (molecular mimicry) and may also induce the inflammatory 'second hit' mediated by Toll-like receptors (TLRs) [2]. Molecular similarity of microbial and host antigens (molecular mimicry) has recently been proposed as a promoting factor for pathogen expansion when microbial agents are not recognized as alien and not completely eliminated [3].

Infectious agents isolated from SAPHO patients have merited special attention for many years. Their possible etiological role is supported by the pathogen isolation from different sites: anterior chest wall, spine, synovial fluid, bone tissue, and skin pustules. A range of pathogens have been found, including *Staphylococcus aureus*, *Hemophilus parainfluenzae*, actinomyces, and even *Treponema pallidum* [4]. *P. acne*s is a much more frequent pathogen and plays a particular role. Of note, speculation about contamination of bone biopsy samples from skin seems to be inconsistent after standard antiseptic procedures in the operation field. *P. acnes* is a Gram-positive, motionless, non-spore-forming bacillus with maximum growth in anaerobiosis. The microorganisms involved in human disease have five biotypes, of which biotypes I and III are the most frequently involved in the etiopathogenesis of acne. They form part of the normal flora of the oral cavity, large intestine, conjunctiva, external ear conduit, and the skin, particularly the sebaceous follicles. In 1987, Trimble and colleagues [5] observed that intra-articular injection of inactivated *P. acnes* in laboratory animals can cause joint lesions and bone erosions.

A genetic background of *P. acnes* seems to be especially relevant since its complete genome sequence has been

IL = interleukin; SAPHO = synovitis, acne, pustulosis, hyperostosis, osteitis; TLR = Toll-like receptor; TNF = tumor necrosis factor.

Table 1

Positive findings of *Propionibacterium acnes* in bone lesions in cases of SAPHO syndrome

Authors	Investigated	*Propionibacterium acnes*-positive
Sherusan *et al*. [16] 1982	1	1
Collert and Isacson [17] 1982	1	1
King *et al*. [18] 1987	7	1
Edlund *et al*. [19] 1988	15	7
Gerster *et al*. [20] 1990	1	1
Kotilainen *et al*. [21] 1996	1	1
Reith *et al*. [22] 1996	8	2
Hayem [10] 1999	15	1
Kirchhoff *et al*. [23] 2003	14	8
Colina *et al*. [14] 2007	6	1
Assmann *et al*. [1] 2009	21	14
Total	90	38 (42%)

SAPHO, synovitis, acne, pustulosis, hyperostosis, osteitis.

detected and it clearly reveals numerous gene products involved in the degradation of host molecules. This justifies the ability of the germ to colonize and survive in human skin, bone, and synovial fluid [6].

A genetic background in patients may be relevant given that familial clustering has been reported [7]. A murine model characterized by a spontaneous chronic recurrent multifocal osteomyelitis related to a missense mutation of the gene for proline-serine-threonine phosphatase interacting protein 2 (*PSTPIP2*) located on chromosome 18 also exists [8]. Some similarities with two inherited genetic diseases, Majeed syndrome and PAPA (pyogenic arthritis, pyoderma gangrenosum, and acne) syndrome, further support a genetic background [9]. There is growing evidence that an exaggerated response to intestinal bacteria mediated by the NOD2/CARD15 (nucleotide-binding oligomerization domain protein 2/caspase recruitment domain 15) system in the inflammasome (associated with Crohn disease) leading to a nuclear factor-kappa-B overactivation may be involved in SAPHO syndrome [10].

Multiple affected members who segregated a SAPHO syndrome-like phenotype had neutrophil dysfunction and reduced internal oxydant production [11]. That may explain the inability of the innate system to eliminate the pathogen from affected sites. This justifies long-term or permanent antibiotic therapy.

It has been demonstrated that *P. acnes* may trigger a non-specific activation of the complement system and cell-mediated immunity in order to eliminate the germ-inducing perpetuation of the inflammation. The ability of the germ to persist in bone lesions in a form incompatible with culturing is a possible explanation for its difficult isolation. The strong humoral and cellular pro-inflammatory response has recently been reported due to *P. acnes* with elevated interleukin (IL)-1, IL-8, and IL-18 plasma levels and increased IL-8 and tumor necrosis factor-alpha (TNF-α) production by purified polymorphonuclear cells [12]. *P. acnes* products have chemoattractant properties, and their immunomodulatory activity is mediated by TLR9 [13].

This justifies long-term or permanent anti-inflammatory therapy. SAPHO syndrome is commonly refractory to non-steroidal anti-inflammatory drugs, glucocorticoids, and disease-modifying anti-rheumatic drugs. Intravenous biphosphonate pamidronate with its strong anti-inflammatory and lymphopenic effect proved to be effective in achieving long-term remission of SAPHO syndrome [14].

At least six uncontrolled studies showed efficacy of antibiotic therapy (azithromycin, doxycycline, sulfamethoxazole/trimetoprim) in SAPHO syndrome. Long-term antibiotic therapy is recommended in most cases. Some patients may respond to repeated 6-week to 3-month courses with 1- to 2-month intervals in order to prevent resistance to antibiotics.

Anti-TNF-α therapy proved to be effective against osteoarticular manifestations of SAPHO syndrome, but deterioration of skin pustulosis was observed in some patients [15]. Combined therapy, including anti-TNF medication and an antibiotic, may be a reasonable solution.

SAPHO syndrome, representing a constellation of synovitis, acne, palmo-plantar pustulosis, hyperostosis, and osteitis, is now recognized as a distinct medical entity: a reactive infectious osteitis. Genetic, immunological, and bacterial mechanisms are implicated in the development of the disease. Diagnostic problems may arise due to incomplete manifestations of SAPHO: either acne and arthritis or acne and anterior wall osteitis with an unclear pustulosis history. The physician needs to make a careful inquiry about a past history of pustulosis. An early bone scanogram is strongly advised in patients with anterior chest pain and a suspicion of SAPHO syndrome. Due to the remitting course, decreased disease activity might be related to the natural course of the disease and not to the efficacy of the antibiotic therapy. Thus, randomized placebo control studies are needed to document the effects of antibiotic therapy. Further trials are needed to create a model of SAPHO disease using *P. acnes* transfer to healthy animals. Mechanisms of ineffective host responses for neutralizing and eliminating *P. acnes* should also be investigated.

Competing interests

The author declares that they have no competing interests.

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