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Editorial

Valuable lessons from SAPHO syndrome

Keywords: SAPHO syndrome; Reactive osteitis; *Propionibacterium acnes*; Bisphosphonates; Anti-TNF agents

The acronym SAPHO (Synovite, Acne, Pustulosis, Hyperostosis, and Osteitis) used to assemble several eclectic features into a single entity was long controversial, both because of the diversity of these features and because of the many medical specialties potentially involved, which range from rheumatology, through pediatrics and stomatology, to dermatology. However, SAPHO syndrome is now firmly established as an independent medical entity. A set of converging arguments indicates that SAPHO syndrome can be classified with the inflammatory spondyloarthropathies (SpA) [1].

1. SAPHO syndrome is relevant to many medical specialties

Depending on age at onset and bone lesion distribution, patients with SAPHO syndrome may be seen outside the provinces of rheumatology and dermatology. The clinical picture described by pediatricians more than three decades ago under the name ''chronic recurrent multifocal osteomyelitis'' (CRMO) is now recognized as a form of SAPHO syndrome [2]. Similarly, diffuse sclerosing osteomyelitis of the mandible (DSOM) was described as a purely stomatological disease until several groups reported that many patients also had palmoplantar pustulosis (PPP), various forms of psoriasis, and/or osteitis at other sites [3].

2. SAPHO syndrome is rare, but not extraordinarily so

The prevalence of SAPHO syndrome has undoubtedly been underestimated over the last two decades, both because the concept is new and because the clinical manifestations are diverse. Numerical data are still inadequate in some parts of the world, and wide variations have been found across continents, although the prevalence is probably no greater than 1/10,000. The largest published series were established in France, Germany, and the Scandinavian countries. However, SAPHO syndrome has also been reported in other parts of the world, such as Japan [4] and Australia [5].

3. Diagnostic criteria are needed

Unfortunately, there are no validated diagnostic criteria designed specifically for SAPHO syndrome. Affected patients may fail to meet classification criteria for SpA or psoriatic arthritis. The bone lesions exhibit highly distinctive clinical and radiological features, which constitute the cornerstone to the diagnosis of SAPHO syndrome. However, Benhamou et al. did not include bone involvement in their criteria for SAPHO syndrome, in particular because joint involvement without bone lesions may occur in association with severe acne [6] The well-recognized existence of borderline forms between SAPHO syndrome and psoriatic arthritis does not detract from the relevance of separating these two entities. Similarly, there is a well-established practice of separating other joint diseases, most notably among the connective tissue diseases, although these may occur concomitantly or consecutively in a given individual.

4. Etiological hypotheses

The etiopathogenesis of SAPHO syndrome remains largely enigmatic, although important insights have been acquired in recent years. The infectious or post-infectious theory was long criticized but is now generating renewed interest. The corynebacterium *Propionibacterium acnes*, which is known to be involved in acne and may play a role in PPP and pyoderma gangrenosum, has been recovered by several groups from osteoarticular lesions in the anterior chest wall, spine, or appendicular skeleton [7–11]. In many instances, however, tests for *P. acnes* are negative, and the response to antibiotic therapy has usually been unconvincing [1]. Improvements have been reported in some patients given long-term antibiotic therapy, most notably with tetracyclines or azithromycin [11–13]. A pathogenic effect of *P. acnes* may occur against a backdrop of sluggishness of the antiinfectious immune responses, which may be related in part to dysfunction of some of the Toll-like receptors [14].

The prevalence of chronic inflammatory bowel disease (CIBD) is increased in patients with SAPHO syndrome [1]. This fact supports a role for infectious agents in the

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etiopathogenesis of SAPHO syndrome. Such a role is consistent with recent data on the potential involvement of *Mycobacterium paratuberculosis* in Crohn's disease [15].

Proinflammatory cytokines such as tumor necrosis factor alpha (TNFα) may be involved in generating or perpetuating the rheumatic manifestations of SAPHO syndrome. A group working in Germany documented TNF overexpression in a focus of mandibular osteitis [16]. Further support for involvement of TNF comes from the promising results obtained with TNFα antagonists in patients with SAPHO syndrome [16–18].

The presence of genetic susceptibility factors is probably required for the development of SAPHO syndrome in most cases. Familial clustering has been reported, with cases in a pair of monozygotic twins and in three siblings [19,20]. Nevertheless, familial clustering seems less common than for ankylosing spondylitis. Compared to other SpAs, HLA B27 may play a smaller role in the pathogenesis of SAPHO syndrome [1]. Whether specific ethnic groups are at greater risk is difficult to determine, although the predominance of Japanese patients in early reports contrast with the paucity of cases from the US.

The role for genetic factors in SAPHO syndrome can be investigated using a fortuitously discovered mouse model derived from a BALB/c.DBA/2 strain. The mice spontaneously develop chronic multifocal aseptic osteomyelitis similar to the bone lesions seen in humans with SAPHO syndrome. The susceptibility gene, which is located on chromosome 18 (at a locus designated ''cmo'' for chronic multifocal osteomyelitis) transmits the disease according to a recessive pattern [21]. Analysis of the cmo locus showed a missense mutation on gene *pstpip2* (proline-serine-threonine phosphatase-interacting protein 2) [22]. The PSTPIP proteins are involved in regulating the immune response via several mechanisms mediated by T cells [23] and apoptosis [24]. Several groups are currently investigating the potential role for PSTPIP2 (the human equivalent of pstpip2 in mice) in a number of chronic inflammatory diseases, including psoriasis. Furthermore, a study conducted in Germany in a cohort of 27 patients with chronic recurrent multifocal osteomyelitis (a form of SAPHO syndrome) and their parents suggests a role for a dominantly inherited gene with variable penetrance, also located on chromosome 18q, near the D18S60 marker [25].

PAPA syndrome shares several features with SAPHO syndrome. ''PAPA'' stands for Pyogenic sterile Arthritis, Pyoderma gangrenosum, and Acne. Patients with this autosomal dominant disease experience recurrent episodes of arthritis that respond to corticosteroid therapy, as well as severe acne and pyoderma gangrenosum [26] The susceptibility locus has been mapped to the long arm of chromosome 15 [27]. A study of two affected families identified two missense mutations in the *CD2BP1*/*PSTPIP1* gene (CD2-binding protein/proline-serine-threonine phosphatase-interacting protein 1) [28].

Majeed syndrome is another autoinflammatory disease, whose features include chronic recurrent multifocal osteitis, anemia due to congenital erythropoiesis abnormalities, and in some cases neutrophilic dermatosis reminiscent of Sweet syndrome [29]. The disease-causing gene was identified recently as a homozygous mutation of the *LPIN2* gene, which encodes lipin 2 [30].

The high prevalence of chronic IBD in patients with SAPHO syndrome [1,31] opens up yet another avenue of research targeting the genes that are associated with Crohn's disease, such as *NOD2*/*CARD15* [32]. This gene encodes the intracellular receptor for a bacterial wall component, muramyl-dipeptide [33], which is involved in NF-κB activation and in the caspase pathway [34]. Hypotheses put forward to date involve impaired production of intestinal defensins [35], changes in bacterial motif recognition [36] and NF-κB overactivation leading to an exaggerated response to intestinal bacteria [37]. Some of these mechanisms may be involved in SAPHO syndrome. More specifically, altered recognition of *P. acnes* by NOD2/CARD15 may lead to a disproportionate inflammatory response with NF-κB overactivation.

When attempting to put these bacteriologic, immunologic, and genetic data together in a coherent way, an appealing hypothesis involves a pathogenic sequence in which an opportunistic organism (*P. acnes*) takes advantage of genetically determined deficiencies in antibacterial defense mechanisms and subsequently induces auto-amplification of the inflammatory response, possibly with an autoimmune component. This hypothesis suggests the concept of ''reactive osteitis''.

5. Moving toward new treatment options

Important progress has been made regarding the treatment of SAPHO syndrome, notably the control of its osteoarticular manifestations. Intravenous pamidronate, usually given as a course of infusions, has been introduced over the last few years by several groups. Marked efficacy on chronic active osteitis was noted, usually with rapid and prolonged pain relief [38], even in pediatric patients [39]. Improvements in PPP have also been reported with pamidronate therapy [40]. These results are consonant with experience acquired at the Bichat-Claude Bernard Teaching Hospital in Paris, where bisphosphonates are widely used with excellent results, including in the treatment of mandibular lesions. Levels of bone turnover markers may predict the efficacy of bisphosphonate therapy [41].

Several potentially disease-modifying agents have been tried in refractory cases of SAPHO syndrome. Benefits have been reported, chiefly with methotrexate [1]. The promising results obtained with TNFα antagonists (infliximab or etanercept) need to be confirmed, although they have already opened up new avenues for research into the pathogenesis of SAPHO syndrome [16–18,42]. However, in 4 patients managed in Italy, infliximab seemed less effective in improving the PPP than the osteoarticular manifestations [43].

6. Information must be supplied to physicians and patients

SAPHO syndrome may carry a better long-term outcome than other SpAs, both in pediatric patients [44] and in adults