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J Rheumatol 2015;42;2514
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To the Editor:
I have read with great interest the article by Aljuhani, et al, regarding a large monocentric case series of patients with synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome. I fully agree with Aljuhani, et al on the frequent involvement of soft tissues around inflamed bone, with the consequent diagnostic difficulties. SAPHO syndrome, in fact, could be a real diagnostic challenge, and Aljuhani, et al described a significant diagnostic delay; this is important because the diagnostic delay leads to inappropriate investigations and prescriptions. With regard to diagnostic delay, it is worth recalling that skin lesions may not be accounted for when they are episodic or appear after bone lesions. In 1987, Chamot, et al suggested the acronym SAPHO to unify various conditions characterized mainly by osteitis/hyperostotic lesions of the anterior chest wall (ACW). Therefore, SAPHO syndrome could be considered a “useful concept” that unifies several disorders sharing some clinical, radiological, and pathologic characteristics, especially osteitic/hyperostotic lesions of the ACW. This means that the understanding of SAPHO syndrome is also very important in musculoskeletal radiology, because such awareness could facilitate the differentiation from other diseases that produce similar radiographic findings but have different prognoses and treatments, such as osteomyelitis, Ewing sarcoma, metastasis, and Paget disease of bone.

In a case series described in *Arthritis and Rheumatism*, my colleagues and I found that osteitis has sometimes been associated with soft tissue involvement. I also agree with the authors that when inflammation of the surrounding soft tissue of osteitic bone is detected, a biopsy should be mandatory to exclude malignancy or infections. It is also worth recalling that SAPHO syndrome is probably a primitive reactive osteitis in genetically predisposed subjects and that *Propionibacterium acnes*, *Staphylococcus aureus*, and other germs have been isolated from osteoarticular lesions in the ACW, spine, pustules, and synovial fluid tissue. In 2007, Trotta and I described a case of a patient with SAPHO in which we were able to isolate *P. acnes* from a bone biopsy, and in that case we successfully treated the osteoarticular complaints of the patient with doxycycline. As *P. acnes* is often implicated in the pathogenesis of comedones and acne, its presence in osteitic lesions could indicate a subset of SAPHO patients, characterized by a notable response to antibiotic therapy. In these cases, antibiotics could be very useful in the treatment of SAPHO syndrome; nevertheless, it has also been demonstrated that the efficacy of antibiotic therapy for SAPHO syndrome is lost after its discontinuation.

I agree with the observation of Aljuhani, et al that paravertebral ossification seen in SAPHO syndrome is completely different from syndesmophytes; in fact, close observation of the published pictures may enable them to be more properly defined as enthesophytes. Moreover, spine lesions are segmental.

As far as the elusive nosological framing of SAPHO syndrome, my colleagues and I first described a dysregulation of extracellular ATP-dependent P2X7-IL-1β axis in a case of SAPHO syndrome effectively treated with the interleukin 1 receptor antagonist anakinra, suggesting that SAPHO syndrome could be considered a polygenic autoimmune inflammatory disease.

In another study, we described 5 first-degree relatives of patients with SAPHO syndrome, and then we looked for single-nucleotide polymorphisms (SNP) in 3 genes (*PSTPIP2*, *LPIN2*, and *NOD2*), previously analyzed in a French cohort, as well as in 2 genes (*PSTPIP1* and *PTPN22*), which we looked at for the first time. In the French cohort, no SNP were found in association with SAPHO syndrome in our cohort of 53 Italian patients.

According to Aljuhani, et al, diagnosis of SAPHO syndrome could be challenging and the diagnostic delays are relevant. Moreover, it is very important to be cautious in those cases with involvement of soft tissues because in such cases it is necessary to exclude malignancy. Besides, in those cases the biopsy may also be useful for directing the treatment in case of isolation of pathogens.

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