SKIN

BRIEF ARTICLE

Chronic Nonbacterial Osteomyelitis, Hidradenitis Suppurativa, and SAPHO Syndrome

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ABSTRACT

Introduction: Synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome may represent one side of a spectrum of disease that also includes chronic nonbacterial osteomyelitis.
Case Report: A 23-year-old male with bone pain in the anterior chest, shoulder, clavicles, left elbow, and left ankle presented to rheumatology clinic after multiple evaluations for infectious osteomyelitis. Imaging and deep bone biopsies of affected areas were consistent with chronic osteomyelitis, with labs notable for elevated erythrocyte sedimentation rate, C-reactive protein, and positivity for HLA-B27. A full skin exam was consistent with hidradenitis suppurativa, and he was started on infliximab and methotrexate with improvement in both his osteoarticular and skin symptoms.
Conclusions: Patients presenting with features of follicular occlusion or neutrophilic dermatoses in conjunction with bone pain should be evaluated for SAPHO/CNO. In patients with SAPHO/CNO with vertebral involvement, bisphosphonates in addition to anti-inflammatory medications (such as methotrexate and TNF-inhibitors) can be effective.

INTRODUCTION

Synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome is a constellation of skin and osteoarticular findings attributed to genetic, autoimmune, and infectious causes. [1] Many studies suggest that SAPHO may not be an isolated disorder but rather represents one side of a spectrum of disease that also includes chronic nonbacterial osteomyelitis (CNO).[1] CNO is an aseptic autoinflammatory disorder with an insidious onset of painful bone lesions, with peak age of onset at 7-9 years old.[1] We present a case of a young adult with features of both SAPHO and CNO and review the literature on the overlap of the two conditions.

CASE REPORT

A 23-year-old male presented to rheumatology clinic for evaluation of chronic bone pain after workup was negative for infectious osteomyelitis. At age 21, he developed a tender lump on his chest, which was diagnosed as an epidermal inclusion

cyst that was drained (cultures negative) and later excised. Bony tenderness of his anterior chest persisted, and he also developed pain and swelling of his shoulders, clavicles, left elbow, and left ankle **(Figure 1)**. X-rays were normal; MRI of affected areas showed osteomyelitis. He had no fevers, weight loss, or lymphadenopathy. He was treated with multiple courses of oral and IV antibiotics without improvement. Deep bone biopsies of the right clavicle and left ulna were consistent with chronic osteomyelitis (**Figure 2**), with bacterial cultures growing *Cutibacterium acnes*. Laboratory studies were notable for elevated erythrocyte sedimentation rate and C-reactive protein. Whole body MRI showed increased signal of several bones, including the bilateral clavicles, sternal manubrium, iliac and sacral bones, vertebral bodies, and left fibula (**Figure 3**). He tested positive for HLA-B27. He was referred to dermatology clinic, where a full skin exam was notable for draining papulonodules, scarring, and extensive sinus tracts in his axillae and buttocks, consistent with hidradenitis suppurativa (**Figure 4**). He was also found to have a pilonidal cyst. He was treated with adalimumab (40 mg biweekly), methotrexate (7.5 mg weekly for anti-drug antibody prevention), and zoledronic acid (1.25 mg once) with significant improvement of his musculoskeletal symptoms. However, due to insufficient improvement in his hidradenitis, adalimumab was increased to 40 mg weekly and then switched to infliximab 7.5 mg/kg every 4 weeks. Methotrexate was also increased to 15 mg weekly. His osteoarticular and skin symptoms were well-controlled on this regimen over the next several months.

DISCUSSION

While both CNO and SAPHO are classified as autoinflammatory disorders, the relationship between these two conditions is not clear. They have been considered to be the same entity, overlapping but distinct entities, or similar entities that exist across an age spectrum, with CNO more common in children and SAPHO more common in adults.[1] Particularly in adults, those presenting with osteoarticular manifestations prior to the development of skin lesions are at risk of delayed diagnosis and prolonged suffering from debilitating disease while undergoing treatment for presumed infectious osteomyelitis.

The pathogenesis of SAPHO/CNO is thought to be multifactorial, including autoinflammatory and genetic factors, as well as a controversial link to infectious organisms. Though *Cutibacterium acnes* has been isolated from bone biopsies of patients with SAPHO/CNO, antibiotics with activity against *C. acnes* have not been found to be curative; therefore, *C. acnes* has been considered more recently to be a trigger for disease development or a contaminant, rather than a persistent pathogen.[1,2] Some researchers regard SAPHO/CNO as a part of the spondyloarthritis family of diseases that includes ankylosing spondylitis and inflammatory bowel disease, although the strength of association with HLA-B27 positivity remains unknown.[2]

SAPHO/CNO can present with a variety of osteoarticular and skin manifestations. CNO most commonly affects the long bones of the lower extremities; the clavicles, vertebrae, mandible, and pelvis are also considered classic sites.[3] In contrast, the anterior chest wall (including the clavicles, sternum, and sternoclavicular joints) and vertebrae are most commonly involved in SAPHO.[3] Though our patient's adult onset of disease and anterior chest wall involvement are typical of SAPHO, his involvement of the long bones are more typical of CNO. Skin manifestations are more characteristic of SAPHO when

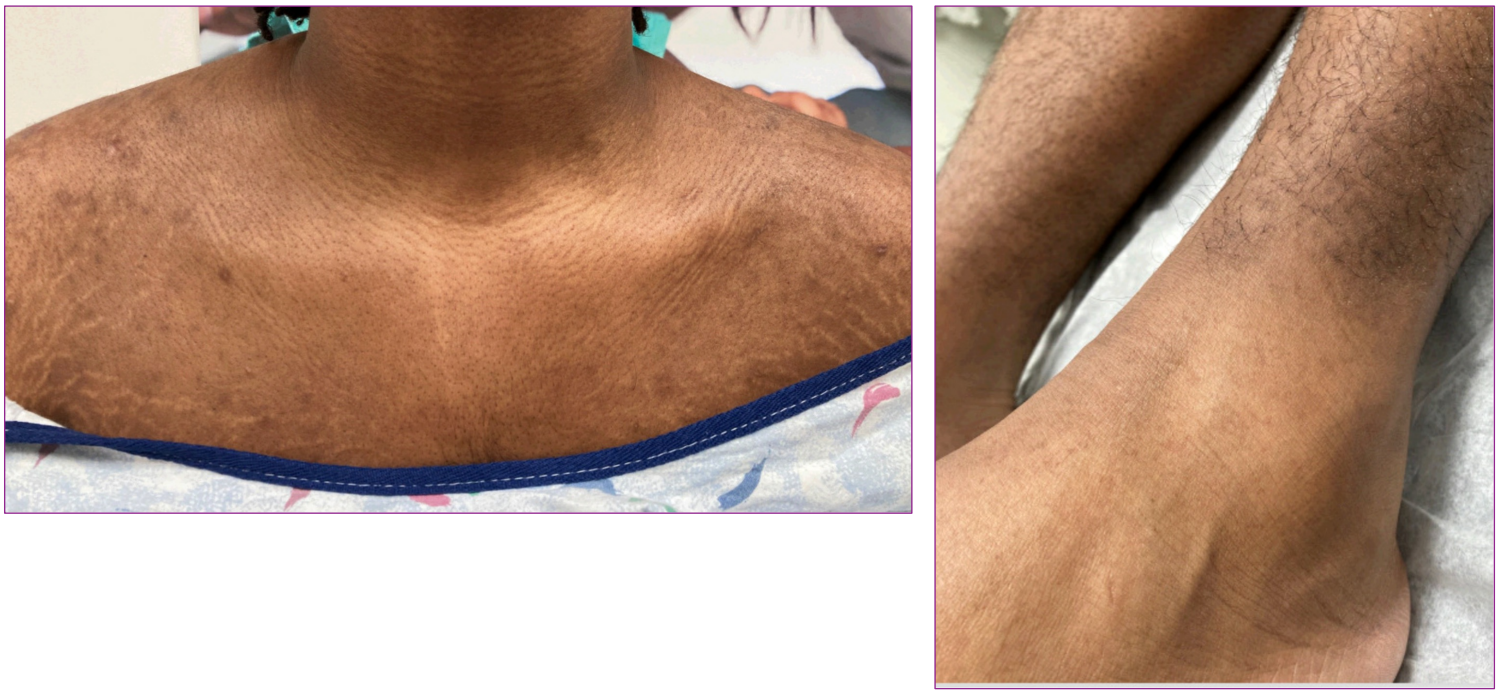

Figure 1. Representative physical exam findings showing A) swelling of the clavicles (L>R) and left shoulder, and B) left ankle.

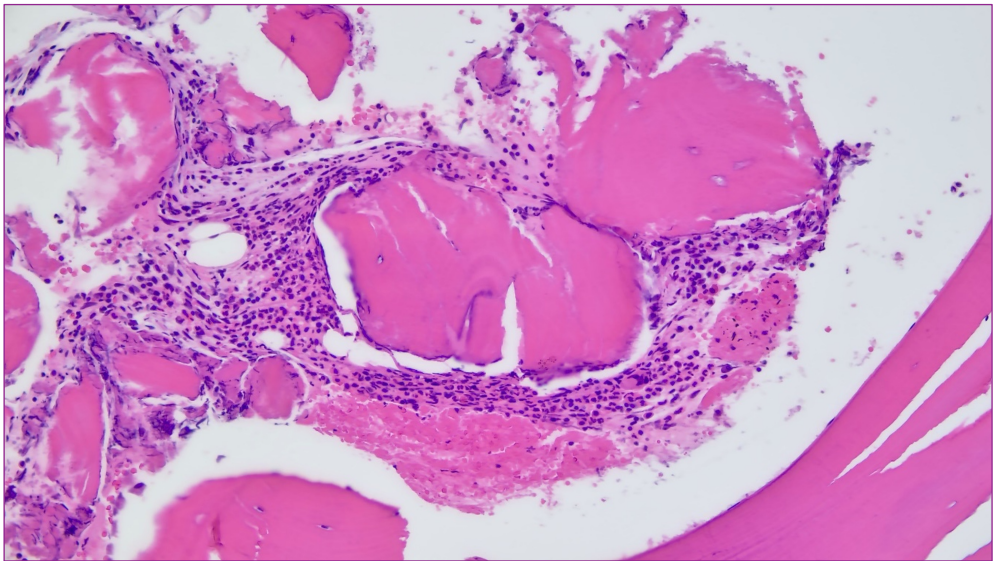

Figure 2. Biopsy of the right clavicle showing fragments of lamellar bone with partial osteocyte dropout and bone marrow space with lymphoplasmacytic inflammation and reactive changes, consistent with chronic osteomyelitis.

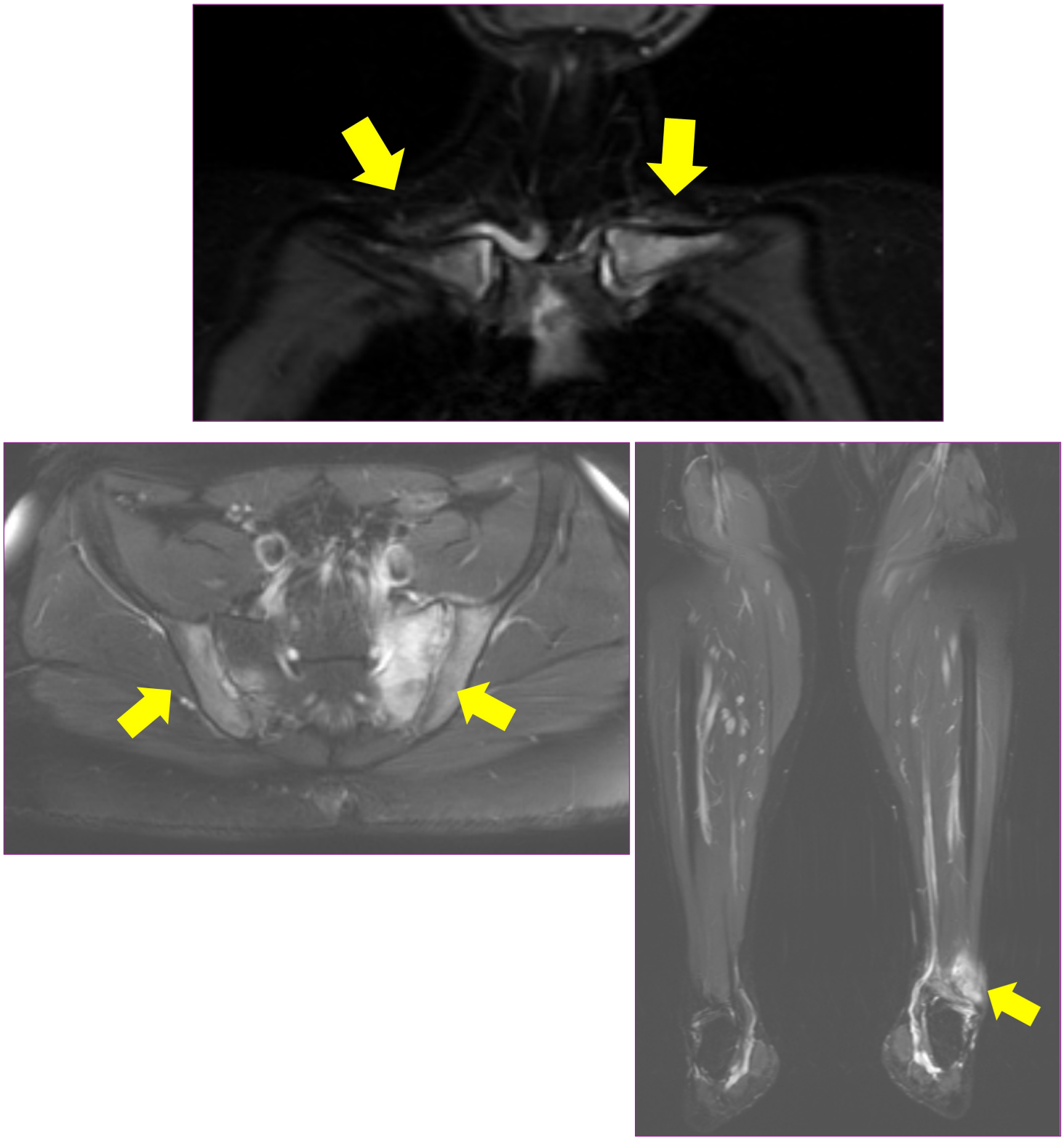

Figure 3. MRI showing an abnormal increase of bone marrow signal in A) medial clavicles, B) bilateral iliac and sacral bones, and C) left ankle.

compared to CNO; they include disorders of the follicular occlusion spectrum (such as acne conglobata, acne fulminans, and hidradenitis suppurativa), as well as neutrophilic dermatoses (such as palmoplantar pustulosis, pyoderma gangrenosum, and Sweet's syndrome).[3] Hidradenitis suppurativa (HS) in particular increasingly has been reported to be associated with SAPHO. [4-6] However, clinical presentations can be variable; some patients with SAPHO have presented with isolated vertebral lesions with no skin findings.[7]

Treatment for CNO, SAPHO, and isolated HS overlaps. Studies of HS and SAPHO have largely reported use of tumor necrosis factor (TNF)-inhibitors such as adalimumab and infliximab, although they may resolve osteoarticular symptoms more effectively than skin findings[8-10]. One case of SAPHO with HS reported improvement in both osteoarticular and cutaneous disease after 12 weeks of treatment with infliximab and methotrexate. [11] Biologics such as interleukin (IL)-17 inhibitors, IL-12/23 inhibitors, and phosphodiesterase (PDE)-4 inhibitors are under investigation to treat SAPHO.[12] Other possible treatments for SAPHO include non-steroidal anti-inflammatory drugs, dapsone, isotretinoin, intralesional and oral corticosteroids[6], and metformin[5]. Finally, bisphosphonates have been used as an alternative or adjunct therapy to immunosuppressants in patients with osteomyelitis, particularly with vertebral involvement.[3]

CONCLUSION

In patients presenting with features of follicular occlusion or neutrophilic dermatoses, the presence of bone pain should be investigated to evaluate for SAPHO/CNO. Our patient exhibited a wide spectrum of cutaneous manifestations (EIC, HS, pilonidal cyst) with osteomyelitis for two years before receiving therapy for SAPHO/CNO. Providers would benefit from increased awareness of the spectrum of SAPHO/CNO and the need to consider noninfectious causes of osteomyelitis in a patient whose bone inflammation has not responded to antibiotics. In patients with SAPHO/CNO with vertebral involvement, bisphosphonates can be added to anti-inflammatory medications such as methotrexate and TNF-inhibitors.

Acknowledgements: The authors would like to acknowledge Dr. Joe Coppock, at Penn Pathology, who assisted in preparation of the pathology slides, as well as Dr. Victor Ho Fung and Dr. Hamza Alizai, CHOP Radiology, who assisted with preparation of the MRI images.

Consent: Consent for the publication of all patient photographs and medical information was provided by the authors at the time of article submission to the journal stating that all patients gave consent for their photographs and medical information to be published in print and online and with the understanding that this information may be publicly available

Conflict of Interest Disclosures: MR has no relevant COI to disclose; he does have a research Grant from Processa and is a consultant at Processa, Novartis, Merck, AbbVie, j&j, Xentria, and CSL Behring. SDB, RB, AJC, LLW, SW, and KAW have no conflicts of interest to disclose.

Funding: None

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