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Palmoplantar pustules and osteoarticular pain in a 42 year-old woman

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Keywords

SAPHO; CRMO; chronic recurrent multifocal osteomyelitis; neutrophilic dermatoses; autoinflammatory; palmoplantar pustulosis

CASE SUMMARY

History

A 42 year-old Caucasian woman was evaluated at the NIH Clinical Center for bilateral palmoplantar pustular plaques and joint pain. Her dermatologic history was notable for significant acne involving her face and back in her youth. At age 22, the patient developed a recurrent rash with pustules on the bilateral palms, which progressed to involve her bilateral soles and was associated with pruritus, skin pain and fissuring. Treatment with topical steroids, coal tar, PUVA and UVB therapy was of limited benefit.

At age 29, she developed pain, swelling and morning stiffness involving her right sternoclavicular joint, fingers, hips and knees which improved with physical activity. Whole

Correspondence: Haley B. Naik, MD, Dermatology Branch, Center for Cancer Research, National Cancer Institute, Bldg 10/Room 12N238, 10 Center Dr. MSC 1908, Bethesda, MD 20892-1908., haley.naik@nih.gov, Phone: 301-594-3208, Fax: 301-402-2943. Drs. Naik and Cowen are currently conducting a phase 2 study to evaluate the efficacy of the IL-1 antagonist anakinra for the management of autoinflammatory pustular skin diseases, including SAPHO syndrome. Clinicians can refer interested patients to NCISkin@mail.nih.gov or 301-594-3457.

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body scintigraphy revealed increased tracer uptake in the right sternoclavicular joint and left knee. Bone biopsy of the right sternoclavicular joint showed no evidence of tumor or infection. The patient was treated sequentially with NSAIDs, methotrexate, sulfasalazine and intralesional steroids with modest improvement in pain and stabilization of right sternoclavicular joint swelling.

The patient was a current non-smoker, but had a 50 pack-year smoking history. Her family history was remarkable for several first- and second-degree relatives with palmoplantar pustulosis or plaque psoriasis.

Physical Examination

On examination at the NIH, discrete pink plaques with scattered pustules and overlying thick coarse scale were noted on the medial aspects of bilateral soles (Fig 1). Coarse adherent white scale was present on the left elbow and fine scale was noted on the palmar surface of the right thumb. The right sternoclavicular joint was notably enlarged and tender to palpation. The left 2nd metacarpophalangeal (MCP) joint was notable for swelling and synovial thickening. There was tenderness without swelling of the sternomanubrial, left sternoclavicular, bilateral shoulder, left 3rd MCP, right 2nd–4th metatarsophalangeal and medial right knee joints.

Histopathology

Histopathologic examination of a punch biopsy obtained from the right sole revealed hyperparakeratosis, acanthosis, loss of the granular layer, intraepidermal and subcorneal neutrophils and neutrophilic pustules (Fig 2).

Significant Diagnostic Studies

Laboratory investigations were notable for elevated high-sensitivity C-reactive protein of 6.6 mg/L. Noncontrast whole-body magnetic resonance imaging (MRI) revealed STIR enhancement in the soft tissue adjacent to the left medial clavicle and small bilateral knee effusions.

Diagnosis

Synovitis-Acne-Pustulosis-Hyperostosis-Osteitis (SAPHO) syndrome with palmoplantar pustulosis, hyperostosis of the right sternoclavicular joint and inflammatory arthritis.

Discussion

Synovitis-Acne-Pustulosis-Hyperostosis-Osteitis (SAPHO) syndrome is a rare, chronic, autoinflammatory disorder that includes a spectrum of recurrent osteoarticular and neutrophilic cutaneous manifestations. The prevalence of SAPHO has been estimated at 0.04%¹, however it may be under-reported. A female predominance has been reported and disease may present at any age, however onset is most frequently in childhood or early adulthood². A subset of SAPHO syndrome, known as *chronic recurrent multifocal osteomyelitis (CRMO)*, predominates in children, although it has been reported in adults.

Greater than 60% of individuals with SAPHO and 30% with CRMO develop cutaneous manifestations^{2–5}. The cutaneous manifestations of SAPHO and CRMO consist of neutrophilic and pustular dermatoses and may present concurrently with, before or after the onset of musculoskeletal symptoms⁶. The most frequent dermatologic finding is palmoplantar pustulosis (PPP), representing 50–75% of SAPHO skin manifestations⁷. Other skin manifestations include severe acne (i.e., acne conglobata and acne fulminans), pustular psoriasis, psoriasis vulgaris, hidradenitis suppurativa, pyoderma gangrenosum, pyoderma vegetans, erythema nodosum, Sweet syndrome, and subcorneal pustular dermatosis^{2, 8–13}. Acne and hidradenitis suppurativa occur more commonly in males in the setting of SAPHO^{4, 14}.

The hallmark feature of SAPHO/CRMO is osteoarthropathy, characterized most prominently by hyperostosis and osteitis. Onset of osteoarticular manifestations is usually insidious¹⁵. The most frequently affected skeletal site in adults is the anterior chest wall (65–90%). Spinal involvement (33%), sacroiliitis (13–52%), long bone involvement (5–10%), mandibular lesions (1–10%) and synovitis in peripheral joints (30%) can also occur^{7, 16, 17}. In contrast, long bones represent the most frequent site of involvement in children^{3, 18–20}.

Other systemic features are uncommon, however fever and elevated inflammatory markers can be seen⁴. Inflammatory bowel disease, most often Crohn disease, has been reported in up to 10% of patients with SAPHO syndrome⁴.

The disease course of SAPHO is highly variable. Approximately one-half of cases have a chronic relapsing-remitting course. The remainder exhibit either monophasic disease or a relapsing-remitting course for several years followed by remission². Predictors of chronic disease course include female sex, anterior chest wall involvement, peripheral arthritis, dermatologic manifestations and markedly elevated acute phase reactants². Disabling complications and major sequelae are rare, however patients may experience chronic pain, pathologic fractures²¹ and permanent bone deformities³.

A diagnosis of SAPHO should be considered in patients presenting with episodic bone or joint pain and neutrophilic skin lesions. Although no validated diagnostic criteria exist for SAPHO, the criteria proposed by Benhamou *et al.* is widely used (Table I)²². Culture and skin biopsy may be helpful to exclude infectious etiology of cutaneous findings. Noncontrast MRI or whole body scintigraphy can be used to identify bone lesions. Osteoarticular malignancy and infection should be ruled out by bone biopsy.

First-line therapy for osteoarticular manifestations of SAPHO/CRMO is nonsteroidal anti-inflammatory drugs (NSAIDs), although 50% of patients do not respond to therapy^{2, 14}. Second-line agents include bisphosphonates²³, methotrexate²⁴ and TNF- α antagonists^{11, 25}. Antimicrobials²⁶ and oral or intra-articular corticosteroids have been used with mixed results²⁷. A recent case series demonstrated clinical response in 5 of 6 SAPHO patients within one month of IL-1 inhibition with anakinra, two of whom were refractory to TNF blockers²⁸. Furthermore, complete symptom resolution within a few weeks of anakinra therapy was reported in two patients with CRMO refractory to steroids, sulfasalazine,

pamidronate and NSAIDs^{29, 30}, suggesting that IL-1 mediated pathways may play an important role in the pathogenesis of SAPHO.

The etiology of SAPHO is poorly understood. A number of familial cases have been reported, suggesting a genetic component in disease pathogenesis^{31–34}. Interestingly, the corynebacterium *Propionibacterium acnes* has been isolated from SAPHO bone lesions³⁵. Recent studies have demonstrated that *P. acnes* may activate inflammasomes, leading to IL-1 β production³⁶. This opportunistic organism may potentiate the inflammatory response in genetically predisposed individuals with partially defective antibacterial defense mechanisms. Further research is needed to better understand the pathophysiology of the cutaneous and bony manifestations of SAPHO.

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Abbreviations/acronyms

CRMO	chronic recurrent multifocal osteomyelitis
MCP	metacarpophalangeal
MRI	magnetic resonance imaging
NSAIDs	nonsteroidal anti-inflammatory drugs
PPP	palmoplantar pustulosis
SAPHO	Synovitis-Acne-Pustulosis-Hyperostosis-Osteitis

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KEY TEACHING POINTS

- Synovitis-Acne-Pustulosis-Hyperostosis-Osteitis (SAPHO) syndrome is characterized by distinctive osteoarticular manifestations and a spectrum of neutrophilic dermatoses.
- The most common dermatologic manifestations include palmoplantar pustulosis, acne conglobata and acne fulminans.
- SAPHO should be considered in patients presenting osteoarticular pain, particularly involving the anterior chest wall and/or spine, and neutrophilic skin lesions.

Figure 1. Palmoplantar pustulosis (PPP). Pink plaques with scattered pustules and overlying thick coarse scale on the medial aspect of the right sole.

Figure 2. Histopathology of palmoplantar pustulosis (PPP). Hyperparakeratosis, acanthosis, loss of the granular layer, intraepidermal and subcorneal neutrophils and neutrophilic pustules.

Table I

Diagnostic criteria for SAPHO syndrome

Inclusion criteria ^a	Osteoarticular manifestations of acne conglobata, acne fulminans, or hidradenitis suppurativa (i.e., inflammatory synovitis, anterior chest wall hyperostosis or osteitis, hyperostosis or osteitis at another site, or spondylitis or spondylodiscitis)
	Osteoarticular manifestations of PPP (i.e., inflammatory synovitis, hyperostosis +/- osteitis, or spondylitis or spondylodiscitis)
	Hyperostosis (of the anterior chest wall, limbs or spine) with or without dermatosis
	CRMO involving the axial or peripheral skeleton with or without dermatosis
Exclusion criteria	Septic osteomyelitis
	Infectious chest wall arthritis
	Infectious PPP
	Palmoplantar keratoderma
	Diffuse idiopathic skeletal hyperostosis, except for fortuitous association
	Osteoarticular manifestations of retinoid therapy
Other reported features	Possible association with psoriasis vulgaris
	Possible association with an inflammatory enterocolitis
	Features of ankylosing spondylitis
	Presence of low-virulence bacterial infections

^aThe presence of 1 of the 4 inclusion criteria is sufficient for diagnosis of SAPHO syndrome. *Adapted from* Benhamou CL, Chamot AM, Kahn MF. Synovitis-acne-pustulosis-hyperostosis-osteomyelitis syndrome (SAPHO). A new syndrome among the spondyloarthropathies? Clin Exp Rheumatol 1988;6(2):109–12.