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Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis, Palmoplantar Pustulosis, and Neutrophilic Dermatoses: A GRAPPA 2023 Annual Meeting Update

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ABSTRACT. Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome and chronic nonbacterial osteomyelitis (CNO) are rare autoinflammatory/autoimmune conditions seen in adults and children. Although osteoarticular manifestations are the primary distinguishing features of SAPHO, over half of patients also have palmoplantar pustulosis (PPP). These and other associated disorders such as acne, inflammatory bowel disease, and hidradenitis suppurativa are characterized, at least in the early stages, by neutrophilic infiltration. The bone and skin manifestations exhibit both innate and adaptive immune responses and therefore share similar pathogenic molecules and overlapping treatment targets. At the Group for Research and Assessment for Psoriasis and Psoriatic Arthritis (GRAPPA) 2023 annual meeting, a 3-part presentation provided an overview of current efforts at establishing consensus on diagnosis/classification, treatment, and core outcome sets for SAPHO/CNO; an overview of PPP in SAPHO and as a standalone condition; and finally, an overview of the role of the neutrophil in these disorders.

Key Indexing Terms: synovitis-acne-pustulosis-hyperostosis-osteomyelitis syndrome (SAPHO), autoimmune diseases, consensus, GRAPPA, neutrophil palmoplantar pustulosis, psoriasis, psoriatic arthritis

Introduction

Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome and chronic nonbacterial osteomyelitis (CNO) are rare autoinflammatory/autoimmune conditions seen in adults and children.[1] Osteoarticular manifestations, including osteitis, hyperostosis, and synovitis, are the primary distinguishing features of SAPHO. Cutaneous manifestations include palmoplantar pustulosis (PPP), which affects over 60% of patients with SAPHO, and other neutrophilic skin conditions like nodulocystic, hidradenitis suppurativa, pyoderma gangrenosum, Sweet syndrome, and generalized pustular disorders, which are less common.[2] Inflammatory bowel disease and uveitis may also occur. These and other associated disorders are characterized, at least in the early stages, by neutrophilic infiltration.[2] As SAPHO and CNO are rare, efforts to develop diagnostic and classification criteria and to establish treatment algorithms have evolved slowly, but they are gaining consensus as a result of global collaborative efforts. At the Group for Research and Assessment for Psoriasis and Psoriatic Arthritis (GRAPPA) 2023 annual meeting, a 3-part presentation provided (1) an overview of current efforts at establishing consensus on diagnosis/classification, treatment, and core outcome sets for SAPHO and CNO; (2) an overview of PPP in SAPHO and as a standalone condition; and (3) an overview of the role of the neutrophil in these disorders.

SAPHO/CNO diagnosis and classification

Like many complex rare immune-mediated disorders, there are no clinical markers or widely accepted response or classification criteria, limiting the ability to conduct prospective and observational studies. In response, several international working groups have been established to address these gaps.

Core domain set. The Outcome Measures in Rheumatology (OMERACT) CNO/SAPHO working group was created to develop a core domain set for CNO and SAPHO that fulfills OMERACT requirements and can ultimately be used in clinical trials and observational studies. The OMERACT working group is led by Melissa Oliver from Indiana University in the United States. This group had its first face-to-face meeting at the OMERACT 2023 Conference. Several stages of the

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OMERACT process have been completed, the aim being to develop a core outcome set for clinical trials involving people with SAPHO and/or CNO. To date, the group has completed a scoping review, created online discussion boards, conducted focus groups of patients and their caregivers, and completed a Delphi consensus exercise aimed at narrowing down candidate core domains.[3]

Classification/diagnostic criteria and treatment guidelines. In the last 5 years, surveys of expert clinicians and researchers led by Leerling and Dekker (Center for Bone Quality at Leiden University) and members of GRAPPA have laid the groundwork for establishing classification, diagnostic, and therapeutic considerations.[4] An in-person consensus meeting was held in Leiden, the Netherlands in October 2023 to advance consensus on nomenclature and guidelines on assessment and treatment of these disorders. In parallel, work done by the American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) has resulted in the development of new ACR/EULAR classification criteria for childhood CNO.[5]

The treatment for SAPHO/CNO is largely empirical as they are orphan diseases; thus, carrying out sufficiently powered randomized controlled trials remains a challenge. The most commonly used therapies for the musculoskeletal manifestations of SAPHO are bisphosphonates, followed by biologics, particularly tumor necrosis factor inhibitors (TNFi). Use of biologics targeting interleukin 17 (IL-17) and new classes of oral therapies are reported to have efficacy,[6] but these agents remain to be tested in clinical trials.

PPP

PPP is the most common cutaneous manifestation of SAPHO and CNO.[2,7] As a standalone condition, it is also considered rare, with a prevalence of 5-12/10,000 and presenting more commonly in women.[7,8] It typically manifests as sterile white or yellow pustules primarily affecting the palms and soles. Smoking, stress, infection, and contact allergy are considered aggravating features, and some treatments (eg, biologics such as TNFi and systemic steroids) may trigger PPP.[9]

The European classification working group, European Rare and Severe Psoriasis Expert Network (ERASPEN), considers PPP to be synonymous with PPP psoriasis (PsO), and 20% of patients present with overlapping plaque-type PsO.[10] As a result, there is a large collective experience with therapeutic agents that could inform an approach to the treatment of SAPHO/CNO. Topical corticosteroids can be efficacious and are often used first-line for PPP.[11] The conventional systemics methotrexate, cyclosporine, and acitretin have been the cornerstones of treating PPP because of the risk of paradoxical flaring that may occur with biologics.[9] Apremilast, approved for plaque PsO for nearly a decade, has been shown effective for PPP vs placebo in a Japanese study population.[12] The Janus kinase inhibitor upadacitinib, approved for psoriatic arthritis and atopic dermatitis, has been reported to be efficacious for PPP in over 8 published cases.[13-15]

Biologics are often used for PPP, but their efficacy in PPP is not equivalent to that in plaque PsO. A 2023 network meta-analysis evaluated 7 randomized, placebo-controlled clinical trials of apremilast and 4 different biologics (imsidolimab, guselkumab, spesolimab, and ustekinumab).[16] In secondary fixed effects modeling, apremilast and guselkumab were more effective than placebo. Unfortunately, the IL-36 receptor antagonist spesolimab, approved in many countries for generalized pustular PsO, did not meet its phase IIb clinical trial primary endpoint for PPP.[17]

Role of the neutrophil

The main immunologic feature of bone, skin, and other overlapping conditions associated with SAPHO syndrome is a neutrophil-predominant, inflammatory response.[18] The neutrophil is important in many aspects of the immune system and is becoming more commonly recognized as a sophisticated regulatory innate immune cell of crucial importance for immune homeostasis. Neutrophils make up 50% to 70% of leukocytes in humans, acting to provide the frontline innate immunity host defense against invading pathogens.[19] Neutrophils circulate in the blood awaiting active recruitment to tissue sites of infection where they phagocytize and eliminate pathogens.[20] Homing to specific tissues is normally dependent on the interaction with endothelial cells of blood vessels and adhesion molecules, such as selectins and integrins, for a smooth extravasation and migration into specific tissues.[21]

SAPHO and its associated neutrophilic conditions are thought to be autoinflammatory, where overexpression of proinflammatory cytokines like IL-1β, IL-17, and TNF and the dysregulation of genes lead to aberrant neutrophil recruitment and tissue damage.[22] Sun et al previously demonstrated that 442 genes are differentially expressed in patients with SAPHO.[23] Genes encoding the receptors for TNF, IL-6, IL-17, and IL-18 were upregulated in peripheral blood neutrophils of the patients with SAPHO studied, and other genes with expression enriched in cell migration and cell adhesion were identified.[23] For example, 1 overexpressed gene was *C-C chemokine receptor-like 2* (*CCRL2*), which has previously been shown to play an important role in neutrophil recruitment.[24]

Neutrophils have several receptors that recognize microbial structures as well as specific complement receptors that facilitate the phagocytosis of pathogens. Triggering receptors expressed on myeloid cells (TREMs) are a family of cell-surface receptors mainly expressed by neutrophils, monocytes, and tissue macrophages.[25] These receptors have been implicated in inflammation (including the skin), bone remodeling, metabolic syndrome, neurologic conditions, and atherosclerosis. A better understanding of the role of TREMs in SAPHO and related conditions may provide insight into future targets allowing modulation of neutrophil recruitment and function.

In summary, neutrophils play a central role in SAPHO syndrome, PPP, and numerous other related autoinflammatory disorders, but it remains unclear what precise mechanisms underlie the diverse presentations of these neutrophilic disorders. International collaborations are making progress on disease classification, assessment, and treatment of SAPHO and CNO in both pediatric and adult populations.

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