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Case-based Review

A pediatric case of SAPHO-CNO syndrome with clinical correlation between cutaneous and osteoarticular features

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Abstract

Synovitis acne pustulosis hyperostosis osteitis (SAPHO) and chronic nonbacterial osteomyelitis (CNO) represent overlapping osteoarticular autoinflammatory syndromes, with a minority displaying neutrophilic skin features at the time of diagnosis. The pathophysiological link and chronological timeframe between skin and osteoarticular findings remain ambiguous, which in turn can manifest in diagnostic delay. We present a rare pediatric case of SAPHO-CNO with a clear association between cutaneous and osteoarticular symptoms, treated with nonsteroidal anti-inflammatory medications, corticosteroids, and intravenous pamidronate. By raising physician awareness of these syndromes, we hope that appropriate management will be initiated in a more timely fashion avoiding unnecessary investigations and treatment.

Keywords: SAPHO, CRMO, CNO, osteomyelitis, pustulosis, neutrophilic dermatoses

Introduction

In 1972 Giedion et al. (1) detailed a syndrome of acquired, aseptic, multifocal osteomyelitis of insidious onset and chronic course, characterized by unpredictable episodes of exacerbation and relapse in a pediatric population. The terminology, chronic recurrent multifocal osteomyelitis (CRMO), was coined in 1986 and in 1987, the rheumatologist Chamot described a comparable disease process characterized by coexisting skin and osteoarticular manifestations in an otherwise healthy individual (2, 3). He subsequently termed this the synovitis acne pustulosis hyperostosis osteitis (SAPHO) syndrome. A coexisting pseudonym is chronic nonbacterial osteomyelitis (CNO), taking into account the understanding that culture-negative osteomyelitis can either be unifocal or multifocal, acute (lasting less than 6 months) or chronic, and with a disease course that is not always relapsing (4). In some instances, multifocal disease is only uncovered through imaging, with some bone lesions remaining clinically asymptomatic.

Both SAPHO and CNO, and the spectrum of disease they represent, are regarded as rare, though robust data on their true prevalence remains elusive because of diagnostic delay and clinical uncertainty at the time of presentation. Historically, SAPHO affects a middle-aged population, but it is more prevalent in females diagnosed under the age of 30. Whereas some clinicians regard SAPHO and CNO as unique entities, others regard them as the same disease, with CNO considered the pediatric manifestation of SAPHO, presenting in patients at a median age of 10 years, and with a female preponderance (5). Historically, inflammation favors the extremities in pediatric CNO, whereas in SAPHO the axial skeleton and sternoclavicular site are more commonly the focus (2). Despite this, a number of isolated cases have been published describing SAPHO in children and adolescents with the youngest documented case being only 15 months old, in addition to reports of CNO presenting in adults (2, 6). The interchangeable use of these descriptive terms in the literature highlights the comparable disease features.

Before a diagnosis of SAPHO or CNO is made, preliminary imaging might suggest inflammatory changes in keeping with bacterial osteomyelitis with metaphyseal lucency, yet subsequent gram staining and cultures invariably fail to identify an infectious source. Skin lesions arise concurrently or in the future in both diseases, and classically manifest as neutrophilic pustular eruptions (including acne fulminans, neutrophilic eccrine hidradenitis, psoriasis, palmoplantar pustulosis, acute febrile neutrophilic dermatosis aka Sweet's syndrome, and pyoderma gangrenosum) (7).

For both SAPHO and CNO, the clinical picture can vary widely; and therefore, patients present to numerous specialties including dermatology, rheumatology, orthopedics, and pediatrics. Knowledge of these rare

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conditions which tie together atypical musculoskeletal inflammation with atypical cutaneous lesions is paramount to avoid diagnostic delay and to initiate appropriate and timely treatment.

Case Presentation

A 9-year-old Caucasian female presented to the dermatology department in April 2018 with a 6-month history of a pruritic inflammatory rash affecting her lower legs (Figure 1). The rash failed to respond to oral antibiotics or 2 weeks of topical steroids, including Fucidin-H (LEO Laboratories Limited, Dublin, Ireland) or Eumovate (GlaxoSmithKline, Middlesex, UK) and was progressing despite this treatment regimen. Family and past medical history were unremarkable apart from bilateral congenital dislocation of the hip. A month later, she was assessed by a dermatology specialist nurse who noted keratosis pilaris on the upper arms, and discrete areas of inflammatory papules and pustules on the legs, associated with intermittent pain. Daktacort and Balneum emollients were prescribed, and she was subsequently referred to a consultant led dermatology clinic where she was assessed in July 2018. During this attendance, multiple crops of inflammatory papules and pustules were noted on her legs, with a differential of folliculitis, follicular eczema, or Sweet's syndrome considered. A trial of potent topical steroids combined with an antifungal (Lotriderm) twice daily for 2 weeks was prescribed, and she was reviewed 4 weeks later.

Prior to this review, she was admitted to hospital under the orthopedic team with a 5-day history of swelling, pain, and reduced range of movement in her left wrist. There was no history of trauma, and the patient was afebrile and systemically well. Despite a normal C-reactive protein level (-3.5 mg/L) and white cell count (-8.8 10^9/L), erythrocyte sedimentation rate was raised (-34 mm/hr) and X-rays, followed by magnetic resonance imaging (MRI) favored a diagnosis of osteomyelitis of the left wrist. The patient was commenced on intravenous penicillin-based antibiotics for 1 week, with subsequent switch to oral antibiotics to complete a 4-week course at home. Two weeks later she presented again with pain in and swelling of the right knee and ankle. A full body MRI revealed multiple areas of abnormal signal within the distal femoral metaphyses, distal tibial metaphyses, and the distal left radial and ulnar metaphyses, raising the suspicion of CNO (Figure 2). This, along with the concurrent pustular eruption, led to a combined review by the rheumatology and dermatology departments, following which a diagnosis of SAPHO/CNO was made in the context of a growing body of literature defining the association between sterile (multisite) osteomyelitis and neutrophilic dermatoses in children. She was commenced on once daily piroxicam and intravenous pamidronate twice weekly with initial good clinical response and discharged home with an ongoing follow-up by both specialties. Despite an initial turbulent recovery period, necessitating oral corticosteroids (tapering dose of prednisolone 1 mg/kg), an increase in her analgesia, and with extended periods of time spent off school, she ultimately responded well to treatment. The ongoing pamidronate regimen has been coupled with input from both clinical psychology and physiotherapy/hydrotherapy, with a resultant increase in physical activity, reduction in pain, and a return to school full-time. She is currently looking forward to resuming all of her previous sporting activities.

Informed and written parental consent was acquired for publication.

Main Points

- SAPHO and CNO represent overlapping osteoarticular autoinflammatory syndromes, with a minority manifesting neutrophilic skin features at the time of diagnosis.
- Disease course is typically chronic, and treatment options include nonsteroidal anti-inflammatories with corticosteroids, colchicine, dapsone, bisphosphonates, and disease-modifying agents as second-line treatment.
- Bisphosphonates (pamidronate) are emerging as an effective therapeutic option.
- This case describes a rare pediatric presentation of SAPHO-CNO syndrome with a clear temporal relationship between dermatological and subsequent osteoarticular features.

Discussion

Owing to the relevant paucity of literature in the pediatric population on both SAPHO and CNO as disease entities, coupled with ambiguity as to whether they represent separate or overlapping autoinflammatory syndromes with osseous manifestation, they remain a diagnostic challenge. One recent multicenter retrospective study on CNO reported a mean diagnostic delay of 8 months, in which skin lesions were apparent in only 6 out of the 41 children evaluated (17%) (4). As such, where an atypical neutrophilic or pustular eruption coexists with or predates a non-infective osteomyelitis clinical picture, this should prompt the clinician to consider the diagnosis of SAPHO or CNO more readily, as evidenced by our case where the time from first presentation to the dermatology department to diagnosis was comparatively shorter, at only 4 months. Overall, the pathophysiology underlying the link between skin and osteoarticular lesions remains poorly understood, with some authors postulating that it may be secondary to an autoimmune response triggered by a micro-organism (molecular mimicry) (5). In a review of 7 pediatric cases, Tlougan et al. (7) found only 1 patient to have a clear temporal relationship between skin lesions and bone lesions. In the patient presented in this case, not only was there a direct correlation between dermatological presentation and bone pathology, but both these features improved once appropriate therapy was initiated, negating the need for skin or bone biopsy.

Aside from the potential lack of dermatological signs to confound timely diagnosis, initial radiological investigation (particularly plain radiographs) may either lack the sensitivity to identify osteomyelitis, or unifocal lesions may be erroneously diagnosed as infective osteomyelitis leading to inappropriate antibiotic use. This was evidenced by Kaiser et al. (4), who reported that 46% of patients subsequently diagnosed with CNO were initially treated with antibiotics; a feature replicated by the patient described here. Where diagnostic ambiguity persists or when symptoms progress, bone biopsy is advisable because multifocal bone lesions in children can be the presenting features of a multitude of pathologies, including neuroblastoma, Langerhans cell histiocytosis, or leukemia.

The histological features of CNO and SAPHO are in keeping with osteomyelitis, but cultures and staining are typically negative for an infectious pathogen. The inflammatory infiltrate initially has a neutrophilic predominance, which progresses to become lymphocytic. Multinucleated giant cells, noncaseating granulomas, necrotic bone fragments, and sites of new bone formation have also been reported (7). Significant histopathological variation has been demonstrated both within and between samples, making pathognomonic criteria difficult to define. However, major and minor criteria for nonbacterial osteitis have been established on the basis of a combination of clinical, radiological, and histopathological features, whereby a diagnosis can be made if 2 major or 1 major criterion and 3 minor criteria are met (7, 8).

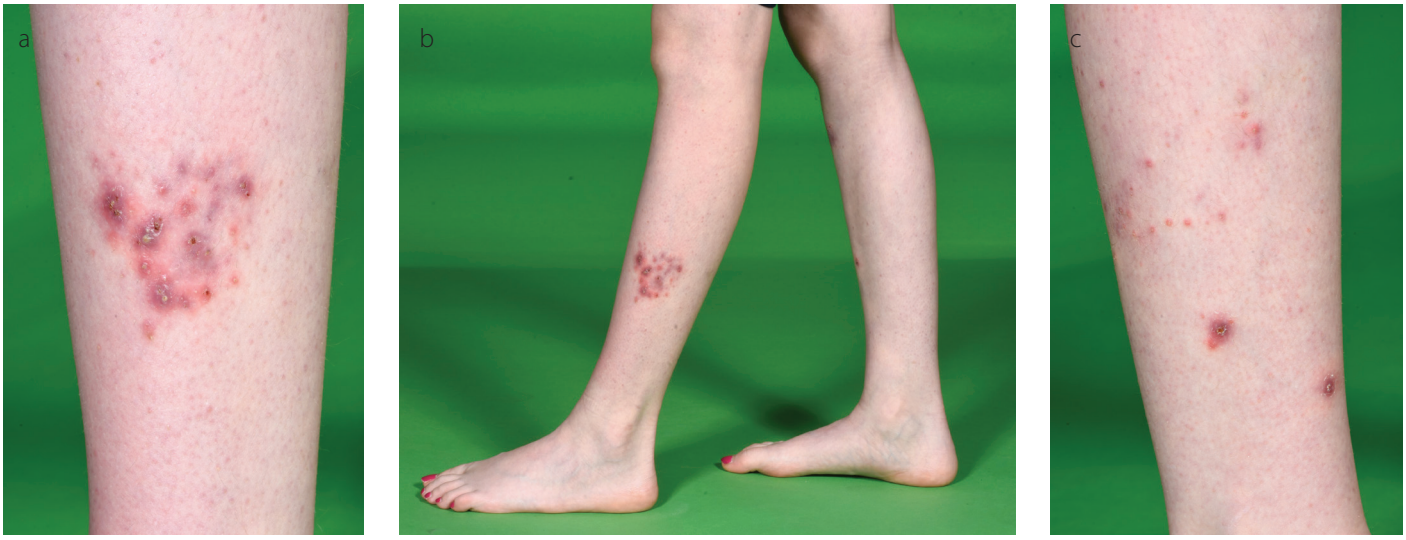

Figure 1. a-c. Images showing a coalescing pustular eruption affecting the lower legs bilaterally.

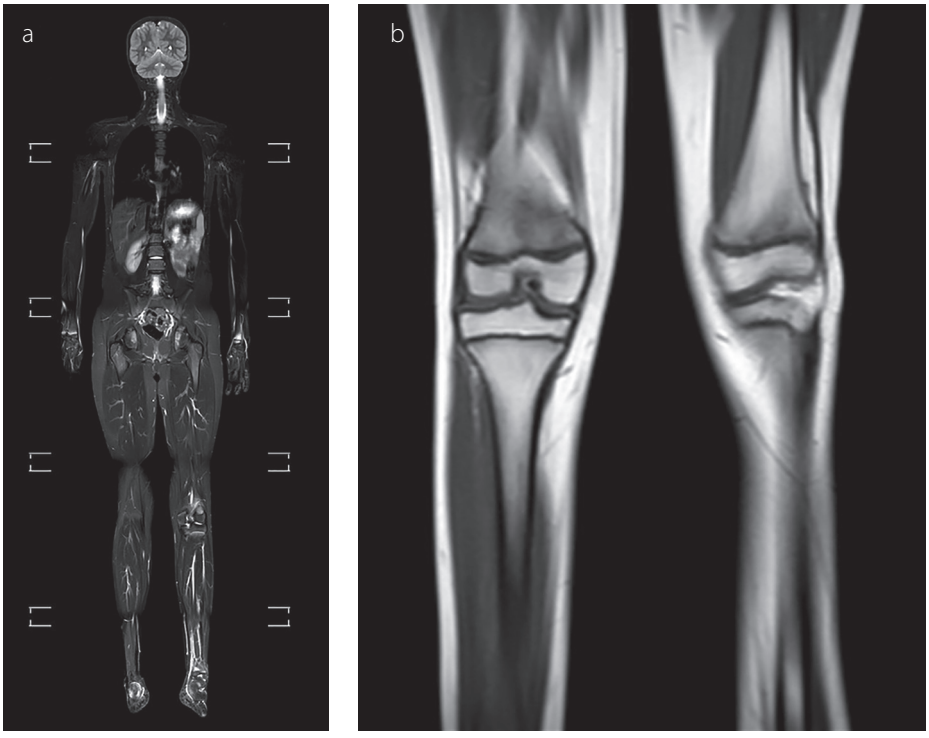

Figure 2. a, b. Axial T1-weighted MR image showing abnormal signal within the distal femoral metaphyses (a). Coronal T1-weighted MR images showing abnormal signal within the distal femoral metaphyses, distal tibial metaphyses, and distal left radial and ulnar metaphyses (b).

The clinical course of autoinflammatory osseous syndromes such as SAPHO and CNO is typically either relapsing-remitting or chronic and indolent. Female sex, anterior chest wall involvement, peripheral arthritis, cutaneous findings, and elevated inflammatory markers at time of presentation have been cited as predictors of a chronic course (9). Treatment options include nonsteroidal anti-inflammatory drugs as first-line, with second-line options including corticosteroids; colchicine; dapsone; and disease-modifying agents such as methotrexate, sulfasalazine, and anti-TNFα therapy (2). In a review of 7 pediatric patients with SAPHO syndrome, Kerrison et al. (10) reported all to benefit from the use of pamidronate, a bisphosphonate which not only inhibits bone turnover and resorption, but also has pain-modifying and anti-inflammatory effects. Historically, there have been concerns regarding the use of bisphosphonates in children, yet the authors from this study concluded it to be well tolerated, with no significant adverse effects. They recommend future cases of pediatric osteoarticular autoinflammatory syndromes should be reported to determine optimal dosing regimens and long-term outcomes.

This case represents a pediatric presentation of the SAPHO-CNO constellation of symptoms and highlights the need for a unifying term in the literature, with the aim of reducing ambiguity in a condition which already represents a diagnostic challenge owing to its variable presentation. As previous authors have highlighted, it is the heterogenous features of these syndromes that may lead to patients presenting to a variety of specialties, and as such this case also reflects an attempt to raise physician awareness so that appropriate therapy can be initiated sooner, thereby reducing the risk of long-term sequelae.

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