PAPASH Syndrome: A Case Report and Lessons for Clinical Practice

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ABSTRACT

Introduction: PAPASH spectrum syndrome is a rare autoinflammatory condition encompassing psoriatic arthritis, pyoderma gangrenosum, acne, and hidradenitis suppurativa. Despite the individual prevalence of these conditions, their concurrent manifestation poses a diagnostic challenge that requires high clinical suspicion. This case illustrates the consequences of delayed recognition of this condition and underscores the crucial need for a multidisciplinary approach to optimize management.

Case presentation: We report the case of a 34-year-old African American man with a prior diagnosis of rheumatoid arthritis who developed migratory arthritis, pustular acne, and hidradenitis suppurativa. Despite suggestive clinical features, delayed access to biologic therapy contributed to disease progression and resulted in hospitalization. After extensive genetic and clinical evaluation, he was diagnosed with PAPASH syndrome.

Discussion: PAPASH syndrome is linked to mutations in the *PSTPIP1* gene and the overexpression of specific chemokines, which dysregulate interleukin-1 signaling and cause persistent inflammation. Although tumor necrosis factor-α inhibitors remain first-line therapy, limited literature exists on comprehensive treatment strategies, and further research is needed. This case demonstrates how ongoing diagnostic ambiguity and the absence of clear treatment guidelines can complicate the management of PAPASH syndrome.

Conclusions: This case emphasizes the importance of prompt identification of PAPASH syndrome in patients presenting with overlapping inflammatory conditions and highlights the need for clinical vigilance, timely initiation of biologic agents, and coordinated care to improve outcomes in this rare but serious disorder.

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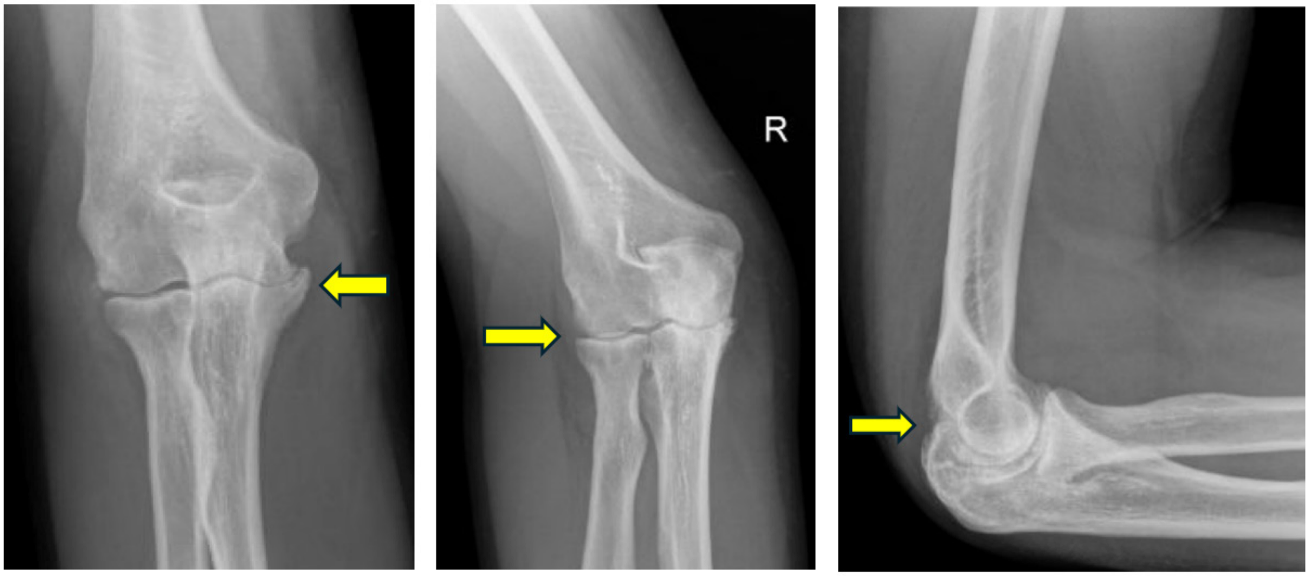
INTRODUCTION

PAPASH spectrum syndrome is a rare autoinflammatory condition that requires a high degree of clinical suspicion for accurate diagnosis and evaluation. It encompasses a diverse range of conditions including psoriatic arthritis, pyoderma gangrenosum, acne, and hidradenitis suppurativa (HS), each contributing to a complex clinical picture.[1] Although each of these conditions is individually common, their simultaneous occurrence poses a diagnostic and therapeutic challenge requiring individualized care. PAPASH syndrome has been linked to mutations in the *PSTPIP1* gene, which increase affinity to pyrin and upregulate caspase-1 and interleukin-1, producing a neutrophil-mediated inflammatory response.[2] We present the case of a man diagnosed with PAPASH syndrome in the setting of psoriatic arthritis, acne, and HS, highlighting the importance of recognizing overlapping symptoms to guide effective treatment.

CASE PRESENTATION

We report the case of a 34-year-old African American man with a history of rheumatoid arthritis diagnosed 6 years earlier. He had intermittently received steroid injections in both shoulders and was treated with oral prednisone at the time of diagnosis. He had received follow up from orthopedic surgery for some time due to chronic right elbow pain the previous few years. Previous management included activity modification, nonsteroidal anti-inflammatory drugs (NSAIDs), physical therapy, and bracing–none of which adequately relieved his symptoms. He was referred for fur-

Figure 1. X-ray of Right Elbow Showing Arthritis With Moderate Joint Space Narrowing, Subchondral Sclerosis, Small Osteophytes, and Subchondral Cysts/Erosions



ther imaging, and x-ray of the elbow showed "arthritis with moderate joint space narrowing, subchondral sclerosis, small osteophytes, and subchondral cysts/erosions (Figure 1).

Magnetic resonance imaging showed severe arthritis with thinning cartilage and synovitis, prompting referral to rheumatology for evaluation of inflammatory arthritis and consideration of biologic therapy to further manage pain. At presentation, the patient reported symptoms beginning approximately 7 years earlier, initially with bilateral knee pain, followed by midfoot swelling, shoulder pain, elbow pain, and edema of the left fifth finger. He had previously established care with an outside hospital at that time and was treated with corticosteroid injections and prednisone. However, he was lost to follow-up due to his move out of state and then presented to establish care with our team.

Along with migratory arthritic pain, the patient reported frequent scaly rashes on his scalp, leading to a formal diagnosis of psoriatic arthritis. He also reported a significant smoking history (1 pack per day) and heavy alcohol use (6 drinks per day on weekends). Laboratory evaluation in anticipation of biologic therapy revealed an elevated erythrocyte sedimentation rate (ESR) of 50 mm/hour, C-reactive protein (CRP) level of 2.3 mg/dL, and cyclic citrullinated peptide (CCP) antibody IgG of 1.2 units.

Around the same time, the patient developed erythematous papules and nodules on his face, groin, and in his armpits, prompting dermatology referral. He was diagnosed with HS (Hurley stage II) and pustular inflammatory acne. Treatment included topical clindamycin lotion to his affected areas, oral doxycycline 100 mg twice a day, and over-the-counter benzoyl peroxide wash in the shower.

Given the constellation of symptoms – including the pyogenic and psoriatic arthritis (with dactylitis, enthesitis, and synovitis), pustular acne, and HS – he was diagnosed with PAPASH syndrome by his rheumatologist. He was prescribed adalimumab 40 mg/0.4 mL subcutaneous injections every 2 weeks, prednisone for polyarthritis pain (tapered 40-30-20-10-5 mg in 5-day intervals), and continued on doxycycline. Despite urgent prior authorization for adalimumab, he was unable to obtain this medication or attend follow-up appointments. A few months later, he presented to the emergency department with worsening HS flare (Figure 2). He was admitted for evaluation, and inpatient rheumatology and dermatology were consulted. It was discovered that adalimumab had been approved by insurance but required dispensing through a specialty pharmacy, which is why he did not receive it. Rheumatology re-prescribed adalimumab and meloxicam 15 mg daily for arthritic pain. Dermatology recommended doxycycline 100 mg twice daily for 3 months, topical clindamycin, and benzoyl peroxide body wash. Soon after, he was discharged with outpatient follow-up arranged with both specialties.

DISCUSSION

Psoriatic arthritis, acne, and HS are all individual conditions that together define PAPASH syndrome, a rare disorder within the spectrum of autoinflammatory diseases characterized by genetic mutations and pathophysiologic changes.[3] In terms of genetics, various mutations – including those in the *PSTPIP1* gene – affect proteins of the inflammasome complex, which triggers autoinflammation, or proteins that regulate inflammasome function.[3] These conditions also share a common pathogenesis involving

Figure 2. Worsening Flare of Hidradenitis Suppurativa

the overactivation of the innate immune system, with abnormal interleukin (IL)-1 signaling leading to sterile, neutrophil-rich cutaneous inflammation.[4] The overexpression of chemokines such as IL-8, Fas/Fas ligand, and cluster of differentiation 40 (CD40) ligand systems also contribute to inflammation and tissue damage.[5]

Several clinically different syndromes have been described in the literature, including pyoderma gangrenosum, acne, and pyogenic arthritis (PAPA); pyoderma gangrenosum, acne, and HS (PASH); pyoderma gangrenosum, acne, and spondylarthritis (PASS); pyoderma gangrenosum, acne, pyogenic arthritis, and HS (PAPASH); psoriatic arthritis, pyoderma gangrenosum, acne, and HS (PsAPASH); and pyoderma gangrenosum, acne, and ulcerative colitis (PAC).[6] The underlying clinical features include painful arthritis and skin lesions consistent with HS and acne, as is seen in this patient. These manifestations are often accompanied by elevated systemic inflammatory markers,[6] such as an elevated ESR and CRP, which were present in this case.

Effective treatment of PAPASH syndrome requires recognition of its intersecting features–psoriatic arthritis, acne, and HS–to move beyond symptomatic relief and address underlying mechanisms. Understanding that these conditions are autoinflammatory in origin is imperative for timely initiation of biologic therapy. Tumor necrosis factor (TNF)-α is a proinflammatory cytokine, plays a pathogenetic role in many immune-mediated diseases, including psoriatic arthritis, HS, and pyoderma gangrenosum.[7] Thus, TNF-α inhibitors such as adalimumab are typically considered first-line therapy.[7] Although adalimumab has demonstrated efficacy and safety in psoriatic arthritis, evidence for its off-label use in HS and related skin disorders is limited, prompting the use of adjunctive therapies, such as antibiotics, isotretinoin, and dapsone.[7]

Emerging research on anti-IL-1 therapies for PAPASH syndrome reflects the role of IL-1 dysregulation in these disorders. Preliminary studies have shown promising results with IL-1 antagonists, including canakinumab and anakinra, in improving skin lesions such as HS, acne, and pyoderma gangrenosum.[8,9]

Although rare, it is important for clinicians to maintain awareness of PAPASH syndrome and related disorders–particularly when patients present with only some of the component conditions. Asking targeted questions about associated symptoms is critical, as patients may not volunteer what they fear may seem irrelevant. In this case, psoriatic scalp lesions were identified only through history-taking, leading to the diagnosis of psoriatic arthritis. Early recognition enables timely diagnostic evaluation and planning for biologic therapy. Along with medical management, studies support a multidisciplinary approach–including the use of systemic biologic agents, weight reduction, smoking cessation, and supportive wound care–as the most effective strategy for treating this disorder.[10,11]

CONCLUSIONS

PAPASH syndrome is a relatively rare condition with diverse presentations, typically including psoriatic arthritis, pyoderma gangrenosum, acne, and HS. The simultaneous presence of these autoinflammatory conditions challenges diagnosis and requires a nuanced management approach. Clinicians should remain attentive to the constellation of symptoms that may indicate an underlying syndrome rather than isolated conditions. The complexity of PAPASH necessitates multidisciplinary care, combining rheumatologic, dermatologic, and pharmacologic expertise. Comprehensive management and ongoing patient engagement are essential. Further research is needed to refine treatment protocols and develop new therapeutic options to better address the unique challenges posed by PAPASH syndrome.

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