SHORT COMMUNICATION

PAPASH Syndrome with a Pathogenic *PSTPIP1* p.(Ala230Thr) Variant: A Case Report of Therapeutic Complexity

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PAPASH syndrome (pyogenic arthritis, pyoderma gangrenosum, acne, and suppurative hidradenitis) is a rare autoinflammatory condition for which no standardized treatment guidelines exist, and its pathophysiological basis remains unclear. We present a clinically challenging case to support early recognition and outline the therapeutic interventions applied in our patient.

CASE REPORT

A 30-year-old Finnish male was referred to the dermatology clinic in 2014 for a non-healing ulcer on the posterior thigh, which was clinically and histologically diagnosed as pyoderma gangrenosum (PG). His medical history included HLA-B27-positive arthritis, diagnosed at age 17, presenting as recurrent, severe, sterile oligoarthritis, primarily affecting the shoulder, hip, and knee. Based on his joint symptoms, he had been on adalimumab (40 mg every 2 weeks) for 1 year, along with intermittent prednisolone. He had also had acne vulgaris since adolescence, treated with isotretinoin and multiple antibiotic courses. Additionally, he had a history of psoriasiform scalp scaling, with mild facial and axillary lesions at presentation, leading to a diagnosis of psoriasis vulgaris. He was a smoker, had a normal bodyweight, and was employed full time.

The thigh PG lesion healed within 6 months with systemic corticosteroids. However, in subsequent years his acne worsened, and he developed recurrent draining abscesses on the face, back, limbs, and axillae (**Figs 1** and **2**). The inguinal region exhibited multiple draining fistulas, consistent with hidradenitis suppurativa (HS). His psoriasis remained almost asymptomatic.

In 2017, after 4 years of adalimumab therapy, oligoarthritis significantly worsened despite negative anti-adalimumab antibodies, while cystic and fistulizing acne on the face and back became more severe. A 6-month trial of etanercept (50 mg weekly) was attempted but proved ineffective, leading to its replacement with secukinumab (150–300 mg every 4 weeks). While secukinumab provided adequate control of joint symptoms for 3 years, acne and hidradenitis remained active. Surgical drainage was performed for individual abscesses; however, procedures in the inguinal region triggered new PG lesions and severe skin infections necessitated a 6-month pause in biologic treatment. The newly activated PG was treated with prednisolone and cyclosporine (4.3 mg/kg), but cyclosporine induced a rapid exacerbation of acne within weeks.

In 2021, 7 years after the patient's initial visit to the dermatology clinic, a detailed rheumatologic reassessment and literature review raised suspicion of an autoinflammatory syndrome, such as PAPASH (pyogenic arthritis, pyoderma gangrenosum, acne, and suppurative hidradenitis). Based on our clinical suspicion, single-gene analysis of *PSTPIP1*, including both sequence analysis and copy number variation (CNV) analysis, was performed. Genetic testing identified a heterozygous pathogenic variant in *PSTPIP1*: NM_003978.5:c.688G>A p.(Ala230Thr), confirming the PAPASH syndrome. The variant was suggested to be *de novo* based on the absence of similar symptoms in the patient's parents.

Following the PAPASH diagnosis, adalimumab was reintroduced at an intensified dose (80 mg every 10–14 days), leading to rapid PG improvement and reduced HS activity. However, arthritis flares increased after 2 years, prompting a switch to ixekizumab (80 mg every 3–4 weeks). While ixekizumab effectively controlled joint symptoms, inflammatory skin lesions and PG on the lower legs reactivated, necessitating a switch back to adalimumab (intensified dose) after 1 year. Methotrexate (5 mg weekly) was added to prevent anti-adalimumab antibody formation. Upon this third reintroduction of adalimumab, PG improved within months (**Fig. 3**), and abscess formation decreased, with only 1 or 2 active lesions at a time. Notably, in his early 20s, prior to biologic therapy, the patient was treated with methotrexate (15 mg weekly) without significant response. Due to severe nausea, methotrexate was discontinued and has been avoided since.

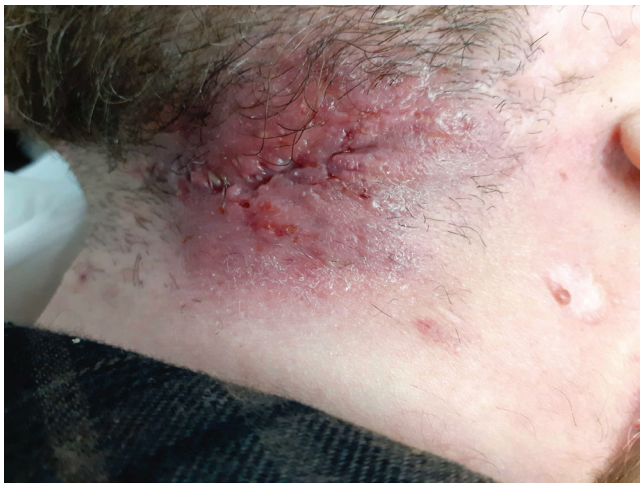

Fig. 1. Inflammatory lesion in the patient's submandibular area, associated with recurrent draining abscesses on the face.

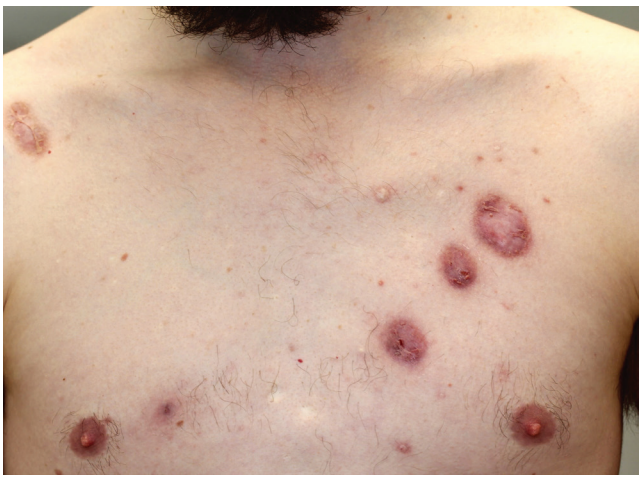

Fig. 2. Partially healed and scarring abscess lesions on the chest, following atypical acne and hidradenitis suppurativa.

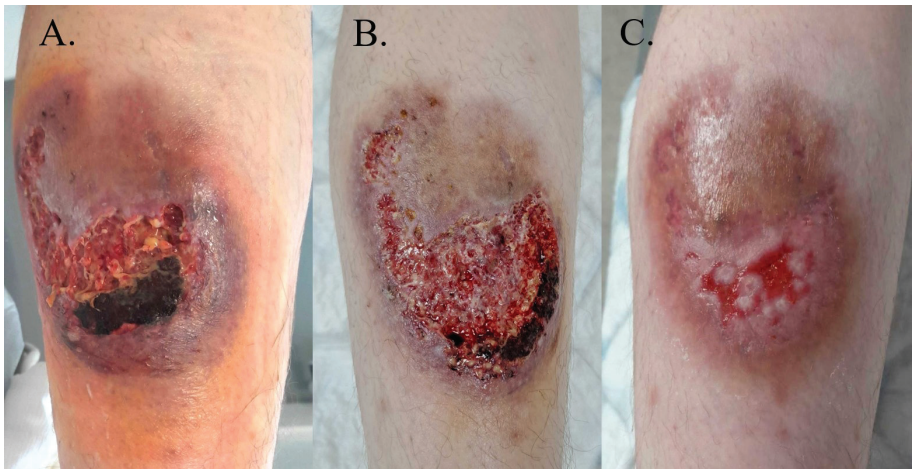

Fig. 3. Pyoderma gangrenosum ulcer on the posterior lower leg showed significant healing within 1 month following the third reintroduction of adalimumab therapy.

In addition to biologic therapies, the patient received multiple courses of systemic corticosteroids (prednisolone) and repeated antibiotic treatments. Other agents trialled alongside biologics included isotretinoin, acitretin, and dapsone; however, these either demonstrated limited efficacy or led to adverse effects and were therefore used only temporarily. Over the years, intermittent clindamycin and clobetasol applications have been the most effective topical management. During the latest follow-up in April 2025, the patient had been on adalimumab for over a year and reported overall stability with no joint symptoms. Several mild, flat, scaly plaques were observed on the lower extremities and on the lateral abdomen, probably indicating a newly developing psoriasiform lesion.

DISCUSSION

PAPASH syndrome was first recognized as a distinct entity within the autoinflammatory syndromes in 2013 (1), differentiating it from related conditions such as PAPA (pyogenic arthritis, pyoderma gangrenosum, and acne) and PASH (pyoderma gangrenosum, acne, and hidradenitis suppurativa). In the literature, only a dozen cases of PAPASH syndrome have been described (2). We identified 1 additional case report describing PAPASH syndrome coexisting with scalp psoriasis (3). Pustular psoriasis and psoriatic arthritis have also been reported with hidradenitis suppurativa-related autoinflammatory syndromes, highlighting the clinical overlap between these autoinflammatory conditions (2, 4, 5).

The genetic background of PAPASH remains poorly understood. The pathogenic *PSTPIP1* variant p.(Ala230Thr) identified in our patient is widely recognized in *PSTPIP1*-related autoinflammatory diseases, particularly PAPA syndrome (6, 7). Pathogenic variants in *PSTPIP1* have also been implicated in PAPASH, as well as in PASH and HS (5, 6). However, to our knowledge, this may represent the first published case of PAPASH syndrome with a confirmed p.(Ala230Thr) variant. Conversely, in some reported cases of PAPASH, no pathogenic variants in *PSTPIP1* have been identified (8). *PSTPIP1* plays a key role in cytoskeletal regulation. Its dysfunction leads to abnormal inflammatory responses, primarily through excessive IL-1β production, contributing to a spectrum of neutrophilic autoinflammatory diseases (6, 7, 9). Excessive IL-1β production can induce TNF-α expression, suggesting that targeting these cytokines with biologic therapy may be beneficial (1, 2, 9). PG and PASH lesions have elevated levels of IL-1β, IL-17, and TNF-α (3, 10), suggesting that IL-17 antagonists may also be effective.

Currently, there are no established treatment guidelines for PAPASH syndrome. Based on a review article (11) discussing the collective management of syndromic hidradenitis suppurativa, treatments included systemic antibiotics and oral retinoids; however, these typically showed limited efficacy. Classic immunosuppressants, such as cyclosporine and methotrexate, have also been used both as monotherapy and in combination. Among biologic agents, the most commonly used were infliximab and adalimumab, followed by anakinra. In some cases, combination therapy with immunosuppressive drugs and/or antibiotics may also be considered. These same biologics have also been reported in case reports of PAPASH syndrome, showing good or partial treatment responses (1, 2, 3, 11, 12).

The nosology of hidradenitis suppurativa-related autoinflammatory diseases remains without consensus (2). The pathogenic framework of these rare conditions is still fragmented, involving a wide spectrum of associated monogenic and polygenic backgrounds, and a robust genotype–phenotype correlation is currently lacking (2, 11, 12). In addition, new disease entities are increasingly being reported as research activity in the field continues to grow (5). Whole-exome sequencing (WES) has been proposed as a potentially useful diagnostic and research tool (12).

In this case report both the rheumatologist and dermatologist found the patient's symptoms atypical and dif-

ficult to treat. Resolving the case required familiarization with the limited number of recently published articles on hidradenitis suppurativa-related autoinflammatory syndromes, culminating in single-gene analysis of *PSTPIP1* to confirm the diagnosis. In our patient, secukinumab and ixekizumab effectively controlled joint symptoms, while an increased dose of adalimumab demonstrated the greatest efficacy for skin manifestations. This case report aligns with the current understanding of PAPASH as a therapeutically challenging syndrome.

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REFERENCES

1. Marzano AV, Trevisan V, Gattorno M, Ceccherini I, De Simone C, Crosti C. Pyogenic arthritis, pyoderma gangrenosum, acne, and hidradenitis suppurativa (PAPASH): a new autoinflammatory syndrome associated with a novel mutation of the PSTPIP1 gene. JAMA Dermatol 2013; 149: 762–764. https://doi.org/10.1001/jamadermatol.2013.2907
2. Maronese CA, Moltrasio C, Marzano AV. Hidradenitis suppurativa-related autoinflammatory syndromes: an updated review on the clinics, genetics, and treatment of pyoderma gangrenosum, acne and suppurative hidradenitis (PASH), pyogenic arthritis, pyoderma gangrenosum, acne and suppurative hidradenitis (PAPASH), synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO), and rarer forms. Dermatol Clin 2024; 42: 247–265. https://doi.org/10.1016/j.det.2023.12.004
3. Garzorz N, Papanagiotou V, Atenhan A, Andres C, Eyerich S, Eyerich K, et al. Pyoderma gangrenosum, acne, psoriasis, arthritis and suppurative hidradenitis (PAPASH)-syndrome: a new entity within the spectrum of autoinflammatory syndromes? J Eur Acad Dermatol Venereol 2016; 30: 141–143. https://doi.org/10.1111/jdv.12631
4. Nikolakis G, Kreibich K, Vaiopoulos A, Kaleta K, Talas J, Becker M, et al. Case report: PsAPSASH syndrome: an alternative phenotype of syndromic hidradenitis suppurativa treated with the IL-17A inhibitor secukinumab. F1000Res 2021; 10: 381. https://doi.org/10.12688/f1000research.52100.2.
5. Garcovich S, Genovese G, Moltrasio C, Malvaso D, Marzano AV. PASH, PAPASH, PsAPASH, and PASS: the autoinflammatory syndromes of hidradenitis suppurativa. Clin Dermatol 2021; 39: 240–247. https://doi.org/10.1016/j.clindermatol.2020.10.016
6. Satoh TK. Genetic mutations in pyoderma gangrenosum, hidradenitis suppurativa, and associated autoinflammatory syndromes: insights into pathogenic mechanisms and shared pathways. J Dermatol 2024; 51: 160–171. https://doi.org/10.1111/1346-8138.17028
7. Boursier G, Piram M, Rittore C, Sarrabay G, Touitou I. Phenotypic associations of PSTPIP1 sequence variants in PSTPIP1-associated autoinflammatory diseases. J Invest Dermatol 2021; 141: 1141–1147. https://doi.org/10.1016/j.jid.2020.08.028
8. Maitrepierre F, Marzano AV, Lipsker D. A Unified concept of acne in the PAPA spectrum disorders. Dermatology 2021; 237: 827–834. https://doi.org/10.1159/000509874
9. Cugno M, Borghi A, Marzano AV. PAPA, PASH and PAPASH syndromes: pathophysiology, presentation and treatment. Am J Clin Dermatol 2017; 18: 555–562. https://doi.org/10.1007/s40257-017-0265-1
10. Marzano AV, Damiani G, Ceccherini I, Berti E, Gattorno M, Cugno M. Autoinflammation in pyoderma gangrenosum and its syndromic form (pyoderma gangrenosum, acne and suppurative hidradenitis). Br J Dermatol 2017; 176: 1588–1598. https://doi.org/10.1111/bjd.15226.
11. Nikolakis G, Kaleta K, Vaiopoulos A, Wolter K, Baroud S, Wojas-Pelc A, et al. Phenotypes and pathophysiology of syndromic hidradenitis suppurativa: different faces of the same disease? A systematic review. Dermatology 2021; 237: 673–697. https://doi.org/10.1159/000509873
12. Marzano AV, Genovese G, Moltrasio C, Tricarico PM, Gratton R, Piaserico S, et al. Whole-exome sequencing in 10 unrelated patients with syndromic hidradenitis suppurativa: a preliminary step for a genotype-phenotype correlation. Dermatology 2022; 238: 860–869. https://doi.org/10.1159/000521263