Renal involvement as a potential feature of pyogenic arthritis, pyoderma gangrenosum, and acne syndrome with E250K mutation of PSTPIP1 gene

Raymond Zhao, BS,[a] Taylor Novice, MD, MBA,[b] and Sasank Konda, MD[b]

Key words: acne; E250K; PAPA syndrome; pyoderma gangrenosum; pyogenic sterile arthritis.

INTRODUCTION

Pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome is a rare, autosomal dominant disease associated with mutations in the proline-serine-threonine phosphatase-interacting protein (*PSTPIP1*) gene, also known as CD2 (cluster of differentiation 2)-binding protein 1 (*CD2BP1*), located on chromosome 15q24.3. PAPA syndrome classically presents in childhood with recurrent sterile arthritis followed by development of nodulocystic acne and recurrent nonhealing ulcers resembling pyoderma gangrenosum (PG).[1] The rarity and phenotypic heterogeneity associated with PAPA syndrome can lead to delayed diagnoses with resulting considerable morbidity. We present the seventh published case of PAPA syndrome secondary to the E250K mutation.[2] Notably, our patient was not formally diagnosed until adulthood and exhibited findings to suggest that renal disease may represent a clinical manifestation of the E250K mutation variant.

Abbreviations used:

CD2BP1:	CD-2 binding protein 1
FSGS:	focal segmental glomerulosclerosis
PAC:	pyoderma gangrenosum, acne and ulcerative colitis
PAPA syndrome:	pyogenic sterile arthritis, pyoderma gangrenosum, and acne syndrome
PAMI syndrome:	*PSTPIP1*-associated myeloid-related proteinemia inflammatory syndrome
PAID:	*PSTPIP1*-associated inflammatory disease
PAPASH:	pyoderma gangrenosum, acne, pyogenic arthritis and hidradenitis suppurativa
PASH:	pyoderma gangrenosum, acne and hidradenitis suppurativa
PASS:	pyoderma gangrenosum, acne and spondyloarthritis
PG:	pyoderma gangrenosum
PsAPASH:	psoriatic arthritis, pyoderma gangrenosum, acne and hidradenitis suppurativa
PSTPIP1:	proline-serine-threonine phosphatase-interacting protein

CASE REPORT

A 43-year-old man with a history of kidney transplantation received 9 years prior due to end-stage renal disease, a presumed diagnosis of juvenile idiopathic arthritis, and quiescent PG of the lower extremities presented to the emergency department with a 3-week history of malaise and an exquisitely painful cutaneous eruption on the scalp, face, chest, and back. Of note, he also described a decade-long history of recurrent, painful acneiform eruptions but felt that his current episode was distinct in nature.

The patient's transplant immunosuppressive regimen consisted of mycophenolate mofetil 1000 mg twice daily and tacrolimus 1.5 mg daily. A kidney biopsy performed for proteinuria prior to transplantation revealed features compatible with focal segmental glomerulosclerosis (FSGS). His renal failure was deemed multifactorial due to nephrolithiasis complicated by hydronephrosis, hypertension,

From the University of Michigan Medical School, Ann Arbor, Michigan[a]; and Department of Dermatology, Henry Ford Health, Detroit, Michigan.[b]

Funding sources: None.

IRB approval status: Not applicable.

Patient consent: Formal patient consent was obtained.

Correspondence to: Sasank Konda, MD, Department of Dermatology, 3031 W. Grand Blvd, STE 800, Detroit, MI 48202. E-mail: skonda1@hfhs.org.

JAAD Case Reports 2023;32:48-51.

2352-5126

https://doi.org/10.1016/j.jdcr.2022.11.030

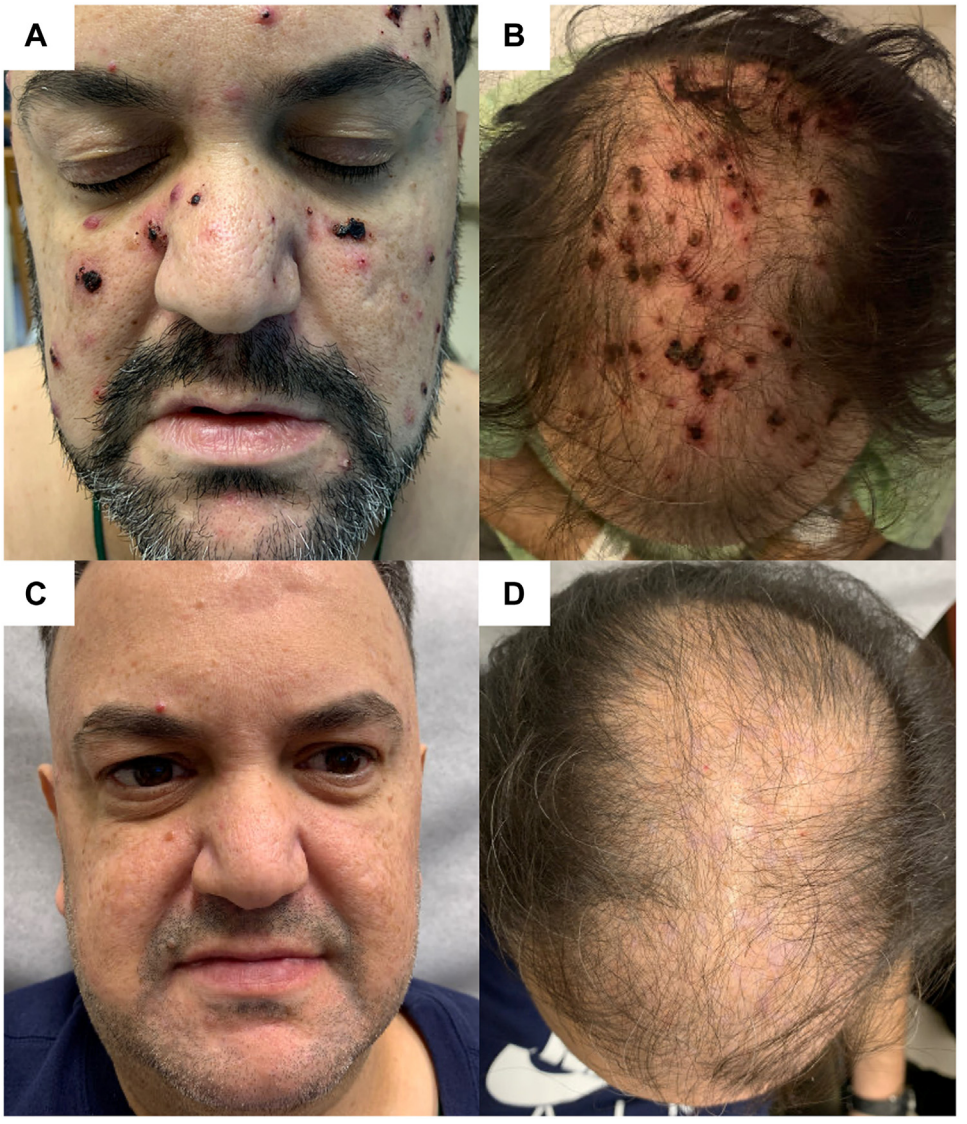

Fig 1. On the face (**A**) and scalp (**B**) as well as the chest and back (not pictured), there are numerous scattered erythematous papules and pustules with overlying hemorrhagic crusts. **C** and **D,** After 3 months of canakinumab, there is near resolution of all prior lesions without scarring.

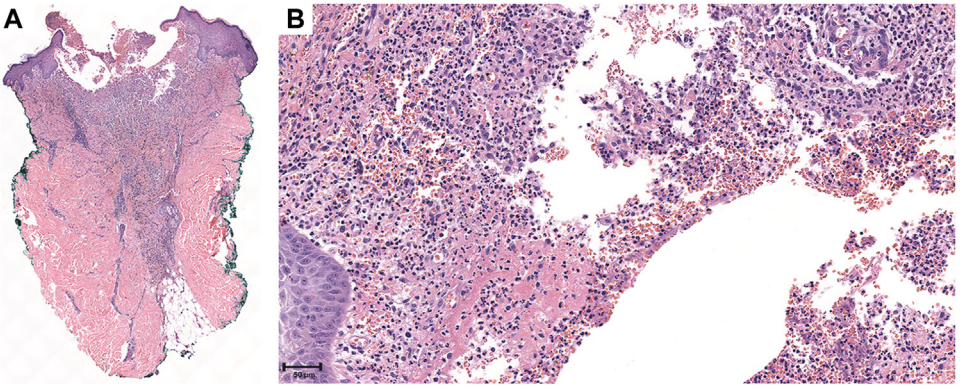

Fig 2. **A** and **B,** On histologic examination, there is a wedge-shaped, neutrophil-rich infiltrate in the dermis with loss of the overlying epidermis.

Table I. Pyogenic sterile arthritis, pyoderma gangrenosum, and acne syndrome patients with E250K mutations in the PTSPIP1 gene

Author (y)	Age (y), Sex	Clinical features	Effective treatment(s)
Demidowich et al, 2012[4]	Unknown, female	PG, arthritis, splenomegaly, thrombocytopenia, and pharyngeal papillomatosis	Cyclosporine and tacrolimus
Lee et al, 2012[5]	26, male	PG, arthritis, and acne	Corticosteroids and adalimumab
Lindwall et al, 2015[6]	25, male	PG, arthritis, acne, osteomyelitis, and hepatosplenomegaly	None
Omenetti et al, 2016[7]	12, male	PG	Canakinumab
Kanameishi et al, 2017[8]	25, male	PG, arthritis, acne, and splenomegaly	Corticosteroids, adalimumab, anakinra, methotrexate, and cyclosporine

PG, Pyoderma gangrenosum; *PSTPIP1* gene, proline-serine-threonine phosphatase-interacting protein gene.

sepsis with acute tubular necrosis, and chronic cyclosporine use for PG.

Physical examination revealed numerous tender erythematous, folliculocentric papules, and pustules with overlying hemorrhagic crusts scattered on the scalp, face, and trunk (Fig 1). Lesional swabs for herpes simplex virus and varicella zoster virus polymerase chain reaction testing were negative.

Two punch biopsies were performed for histopathologic examination as well as tissue culture. Pathology revealed a wedge-shaped neutrophil-rich infiltrate in the dermis with loss of the overlying epidermis (Fig 2). Gram, Fite, and periodic acid-Schiff with diastase stains were all negative. No bacterial (including mycobacterial) or fungal organisms were isolated on the tissue culture. He was treated empirically with vancomycin followed by linezolid, acyclovir, and prednisone with minimal improvement observed.

Given his clinical course, the patient's overall constellation of findings was deemed highly suspicious for a possible autoinflammatory syndrome. Further discussion with the patient revealed that his infant son was also being treated for a possible autoinflammatory syndrome by pediatric rheumatology outside of our hospital system. Genetic testing confirmed that the patient as well as his son were both heterozygous for a pathogenic missense E250K mutation in the *PSTPIP1* gene, specifically c.748 glycine to adenine in exon 11. Both father and son were formally diagnosed with PAPA syndrome. Canakinumab, an interleukin-1β inhibitor, was initiated with near complete resolution of the patient's acneiform lesions and significant improvement in his arthritis.

DISCUSSION

The markedly delayed diagnosis of PAPA syndrome in our 43-year-old patient highlights the importance of clinicians being aware of this condition and its protean manifestations. PAPA syndrome, first described in 1997, is classically associated with the triad of recurrent sterile arthritis, PG, and inflammatory nodulocystic acne.[1] However, in a recent review of the literature, only 16 of 63 patients (25.4%) exhibited the classically reported triad, and 24 of 63 patients (38.1%) demonstrated only one major disease finding.[2] Cutaneous lesions of PG and acne in this syndrome both clinically and histopathologically often resemble their classic standalone forms, further complicating the diagnosis.[3]

Only 3 of the 6 previously reported patients with the E250K mutation of the *PSTPIP1* gene displayed all 3 classic symptoms as seen in our patient (Table I).[4-8] Additional features present in other cases with the E250K mutation include splenomegaly, bleeding diathesis, and serious cutaneous and pulmonary infections.[6]

There has been increasing evidence that PAPA syndrome exists on a spectrum with other *PSTPIP1*-associated inflammatory diseases (PAIDs), namely PSTPIP1-associated myeloid-related inflammatory (PAMI) syndrome; pyoderma gangrenosum, acne and hidradenitis suppurativa (PASH); pyoderma gangrenosum, acne, pyogenic arthritis and hidradenitis suppurativa (PAPASH); psoriatic arthritis, pyoderma gangrenosum, acne and hidradenitis suppurativa (PsAPASH); pyoderma gangrenosum, acne and ulcerative colitis (PAC); and pyoderma gangrenosum, acne and spondyloarthritis (PASS).[2,9,10] Identical genotypes can manifest with variable phenotypic expression patterns ranging from joint and cutaneous symptoms in PAPA syndrome to severe multi-organ involvement and growth failure in *PSTPIP1*-associated myeloid-related (PAMI) syndrome.[2] While PAPA and PAMI syndromes may share similar dermatologic presentations, PAMI syndrome is most commonly

distinguished by associated vasculitis, cytopenia, and lymphoproliferation.[2] Renal disease has not been reported in previous cases of E250K PAPA syndrome; however, renal involvement is a characteristic of *PSTPIP1*-associated myeloid-related PAMI syndrome, which is most often associated with the E250K or E257K mutations.[10] In contrast, PAPA syndrome is most often associated with A230T or E250Q mutations.[2] Our patient, who received a kidney transplant at 34-years of age for end-stage renal disease with biopsy features of FSGS, had multiple other risk factors for renal disease apart from his genetic mutation. The presence of these mitigating factors makes the association between PAPA syndrome and renal disease difficult to ascertain; however, the presence of FSGS in a previously reported E250K *PSTPIP1* gene mutation patient highlights the need for further studies of PAPA or other *PSTPIP1*-associated inflammatory disease patients with renal dysfunction.[10] While PAMI syndrome was considered in this patient, PAPA syndrome was deemed more likely given his classic clinical triad as well as the absence of other PAMI features such as hepatosplenomegaly, pancytopenia, and growth failure.[10] Additional reports of renal disease in PAPA syndrome with the E250K mutation will be needed to establish it as an authentic finding.

PSTPIP1 mutations appear to interfere with the ability of its encoded protein to phosphorylate targets including proinflammatory pyrin domains, resulting in increased interleukin-1 activity.[6] In one review, clinical improvement was noted in 18 of 21 PAPA patients treated with interleukin-1 inhibitors.[2] Other treatments include tumor necrosis factor-alpha inhibitors, glucocorticoids, and immunosuppressants (eg, methotrexate).[2] PAPA-syndrome related acne may also be treated with the aforementioned therapeutic options unlike classic acne vulgaris; however, isotretinoin and other conventional acne treatments can also be beneficial.[11]

Our case may expand the phenotype of E250K-associated PAPA syndrome, a rare disorder that is diagnostically challenging but can be responsive to interleukin-1 inhibitors as well as other biologic and immunosuppressive treatments.

Conflicts of interest

None disclosed.

REFERENCES

1. Lindor NM, Arsenault TM, Solomon H, et al. A new autosomal dominant disorder of pyogenic sterile arthritis, pyoderma gangrenosum, and acne: PAPA syndrome. *Mayo Clin Proc*. 1997;72:611-615.
2. Wang Y, Wu N, Yu K, Shen M. Case report: pyogenic arthritis, pyoderma gangrenosum, and acne: a single-center experience and literature review. *Front Immunol*. 2021;12:735851.
3. Smith EJ, Allantaz F, Bennett L, et al. Clinical, molecular, and genetic characteristics of PAPA syndrome: a review. *Curr Genomics*. 2010;11:519-527.
4. Demidowich AP, Freeman AF, Kuhns DB, et al. Brief report: genotype, phenotype, and clinical course in five patients with PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum, and acne). *Arthritis Rheum*. 2012;64:2022-2027.
5. Lee H, Park SH, Kim SK, et al. Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome (PAPA syndrome) with E250K mutation in CD2BP1 gene treated with the tumor necrosis factor inhibitor adalimumab. *Clin Exp Rheumatol*. 2012;30:452.
6. Lindwall E, Singla S, Davis WE, Quinet RJ. Novel PSTPIP1 gene mutation in a patient with pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome. *Semin Arthritis Rheum*. 2015;45:91-93.
7. Omenetti A, Carta S, Caorsi R, et al. Disease activity accounts for long-term efficacy of IL-1 blockers in pyogenic sterile arthritis pyoderma gangrenosum and severe acne syndrome. *Rheumatology (Oxford)*. 2016;55:1325-1335.
8. Kanameishi S, Nakamizo S, Endo Y, et al. High level of serum human interleukin-18 in a patient with pyogenic arthritis, pyoderma gangrenosum and acne syndrome. *J Eur Acad Dermatol Venereol*. 2017;31:e115-e116.
9. Boursier G, Piram M, Rittore C, et al. Phenotypic associations of PSTPIP1 sequence variants in PSTPIP1-associated autoinflammatory diseases. *J Invest Dermatol*. 2021;141:1141-1147.
10. Borgia P, Papa R, D'Alessandro M, et al. Kidney involvement in PSTPIP1 associated inflammatory diseases (PAID): a case report and review of the literature. *Front Med (Lausanne)*. 2021;8:759092.
11. Maitrepierre F, Marzano AV, Lipsker D. A unified concept of acne in the PAPA spectrum disorders. *Dermatology*. 2021;237:827-834.