

## CASE REPORT

# A case of pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome successfully treated with combination therapy of corticosteroids, cyclosporine, and colchicine

Hideo Hashizume<sup>1\*</sup>, Reiko Kageyama<sup>1,2</sup>, Takatsune Umayahara<sup>2</sup>, Tomohiro Morio<sup>3</sup>

<sup>1</sup> Department of Dermatology, Shimada Municipal Hospital, Shimada 427-8502, Japan

<sup>2</sup> Department of Dermatology, Hamamatsu University School of Medicine, Hamamatsu 431-3125, Japan

<sup>3</sup> Department of Developmental Biology and Pediatrics, Tokyo Medical and Dental University, Graduate School of Medical and Dental Science, Tokyo, Japan

## ABSTRACT

Pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome is an autoinflammatory disease characterized by destructive inflammation of the skin and joints in association with genetic mutation of the Pombe Cdc15 homology family member *PSTPIP1*. Because a therapeutic strategy specific to this disease has not been established, treatment is always challenging for clinicians. We herein describe a case of PAPA syndrome with typical clinical features successfully treated with combination therapy of traditional anti-inflammatory drugs. A 39-year-old man presented with painful plaques on his extremities that had been present for several years. Large brown plaques were observed on both arms and legs with numerous fistulae and ulcers. Cystic acne lesions subsequently appeared on his cheeks and upper back. We diagnosed the patient with PAPA syndrome based on the presence of typical clinical features; however, no genetic mutations of exon-1 to 15 of *PSTPIP1* were found. Although recent reports have emphasized the efficacy of biologics that target inflammatory cytokines such as antibodies to interleukin-1 $\beta$  and tumor necrosis factor- $\alpha$ , use of these agents remains uncovered by health insurance in Japan, showing unresolved discrepancy in practical use for clinicians. The present patient was successfully treated with combined therapy of a corticosteroid, colchicine, and cyclosporine A, encouraging the use of this combination therapy as a novel therapeutic option.

**Keywords:** pyogenic arthritis; pyoderma gangrenosum; acne syndrome; treatment; corticosteroids; cyclosporine A; colchicine

## ARTICLE INFO

Received: April 11, 2018

Accepted: May 19, 2018

Available online: June 19, 2018

## \*CORRESPONDING AUTHOR

Hideo Hashizume, Department of Dermatology, Shimada Municipal Hospital, 1200-5 Noda, Shimada 427-8502, Japan; hihashiz0001@mac.com

## CITATION

Hashizume H, Kageyama R, Umayahara T, *et al.* A case of pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome successfully treated with combination therapy of corticosteroids, cyclosporine, and colchicine. Trends Immunother 2018; 2(1): 719. doi: 10.24294/ti.v2.i2.719

## COPYRIGHT

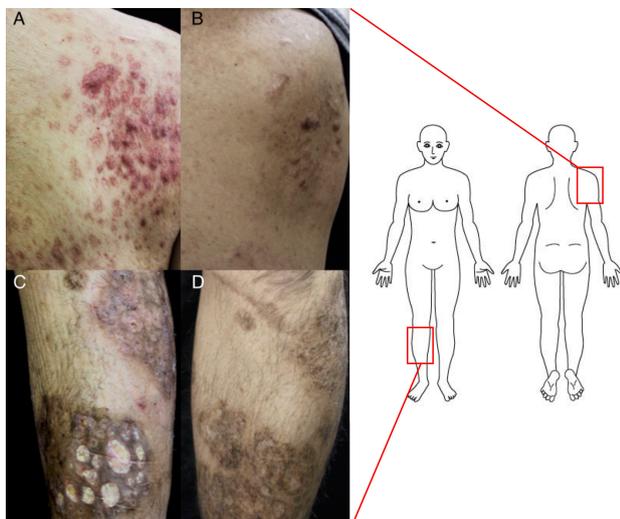
Copyright © 2018 by author(s) and EnPress Publisher LLC. This work is licensed under the Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0). <http://creativecommons.org/licenses/by/4.0/>

## Introduction

Pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome is an autoinflammatory disease characterized by destructive inflammation of the skin and joints<sup>[1]</sup> in association with genetic mutation of the Pombe Cdc15 homology family member *PSTPIP1*<sup>[2,3]</sup>. This is an extremely rare disease as the prevalence is estimated less than one per million. Because a therapeutic strategy specific to this disease has not been established except for anecdotal systemic administration of corticosteroids, treatment is always challenging for clinicians. We herein describe a case of PAPA syndrome with typical clinical features successfully treated with combination therapy of traditional anti-inflammatory drugs.

## Case Presentation

A 39-year-old man presented with painful plaques on his extremities that had been present for several years. He had no history of autoimmune disorders or hematological disorders and no family history of such skin lesions. Cystic acne lesions appeared on his cheeks and upper back (**Figure 1A**). Large brown plaques were observed on both arms and legs with numerous fistulae and ulcers (**Figure 1B**). A skin biopsy of an arm lesion revealed nonspecific inflammatory infiltrates comprising neutrophils and lymphocytes. The multiple cystic acne lesions later deteriorated with simultaneous emergence of a low-grade fever and arthralgia of both knees and ankles. Neither bacteria nor fungi



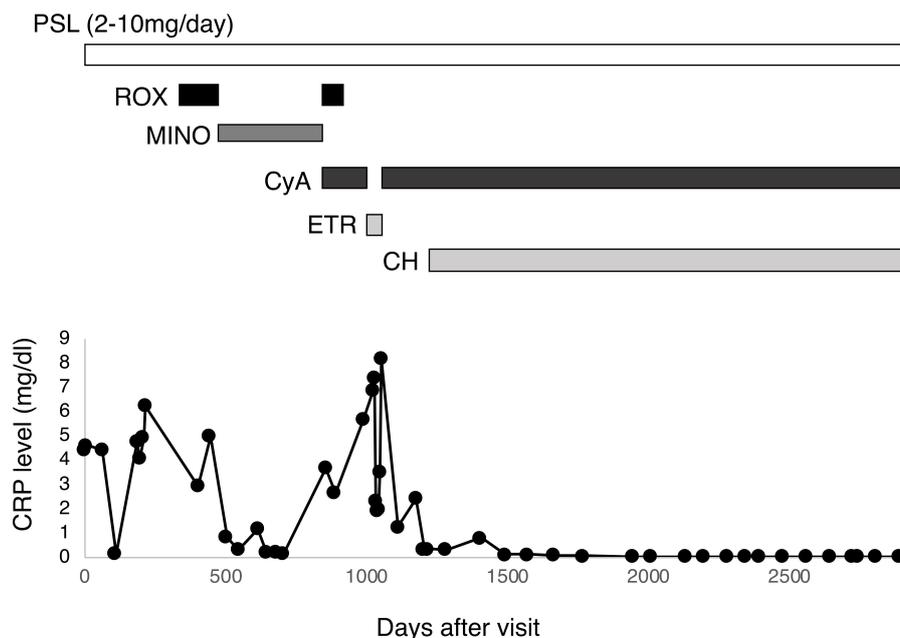
**Figure 1.** Clinical skin features before (A, C) and after the combination therapy (B, D). Acne formation of the right back (A, B) and pyoderma gangrenosum of the left leg (C, D).

grew in cultures of discharge from the arm lesions and serous fluid from a fine needle aspiration of the right knee joint. We diagnosed the patient with PAPA syndrome based on the presence of typical clinical features; however, no genetic mutations of exon-1 to 15 of *PSTPIP1* were found. Laboratory investigation revealed leukocytosis with neutrophilia and elevated levels of serum C-reactive protein in parallel with the disease severity (Figure 2). The serum interleukin-1 $\beta$  and tumor necrosis factor- $\alpha$  levels were within the normal range at different two time points (IL-1 $\beta$ , 0.4

pg/mL and <0.2 pg/mL, [normal range, <10 pg/mL]; TNF- $\alpha$ , 2.1 pg/mL and 0.8. pg/mL, [normal range, 0.6-2.8 pg/mL]). The activities of phagocytosis and reactive oxygen species production in neutrophils were lower than those in normal individuals. The natural killer cell activity, which was evaluated by Cr release assay 12 hours after co-culture of circulating mononuclear cells (as effector cells) and Cr-labeled K562 cell line (as target cells), was 5.9% (normal range, 8.9%–29.5%) and 8.6% (17.1%–48.7%) in 10:1 and 20:1 of effector cells:target cells, respectively. The patient was hospitalized for treatment; however, monotherapy with an anti-inflammatory agent (corticosteroid, cyclosporine A, etretinate, or minocycline) could not control the disease activity. Therefore, we tried various combinations of multiple anti-inflammatory agents. Finally, we found that the combination of a systemic corticosteroid (prednisolone at 10–15 mg/day) with cyclosporine A (100 mg/day) and colchicine (1 mg/day) achieved alleviation of the patient’s PAPA syndrome, resulting in complete resolution at least >4 years after initiation of this combination therapy (Figures 1B, 1D and 2).

## Discussion

Immunological aberrance associated *PSTPIP1* gene mutation-linked inflammasomes is considered the hallmark abnormality in most cases of PAPA syndrome<sup>[3]</sup>. However, four cases of PAPA syndrome without *PSTPIP1* gene mutations have been



**Figure 2.** CRP levels during the disease course. PSL, prednisolone; ROX, roxithromycin; MINO, minomycin; CyA, cyclosporine A; ETR, etretinate; CH, colchicine.

reported<sup>[4]</sup>, including the present case, suggesting that *PSTPIP1* gene mutations are not a prerequisite for the clinical manifestations of PAPA syndrome. Instead, we found defects in natural killer cell activity in the present case; such defects have not been previously found and might be involved in the pathogenesis of PAPA syndrome from a novel immunological viewpoint. However, further investigation is required. Although recent reports have emphasized the efficacy of biologics that target inflammatory cytokines such as antibodies to interleukin-1 $\beta$  and tumor necrosis factor- $\alpha$ <sup>[5,6]</sup>, use of these agents remains uncovered by health insurance in Japan, showing unresolved discrepancy in practical use for clinicians. Conversely, several trials of various treatments have been reported, including corticosteroids, immunosuppressant, and antibiotics, and the efficacy of the combination of corticosteroids and immunosuppressants remains equivocal. The present patient was successfully treated with combined therapy of a corticosteroid, colchicine, and cyclosporine A, encouraging the use of this combination therapy as a novel therapeutic option.

## Conclusion

The present case was successfully treated with combined therapy of a corticosteroid, colchicine, and cyclosporine A, suggestive of a novel treatment option for PAPA syndrome.

## Conflict of interest

The authors declare no potential conflicts of

interest.

## 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(7): 611–615. doi: 10.1016/S0025-6196(11)63565-9.
2. Wise CA, Gillum JD, Seidman CE, *et al.* Mutations in CD2BP1 disrupt binding to PTP PEST and are responsible for PAPA syndrome, an autoinflammatory disorder. *Hum Mol Genet* 2002; 11(8): 961–969. doi: 10.1093/hmg/11.8.961.
3. Shoham NG, Centola M, Mansfield E, *et al.* Pyrin binds the PSTPIP1/CD2BP1 protein, defining familial Mediterranean fever and PAPA syndrome as disorders in the same pathway. *Proc Natl Acad Sci USA* 2003; 100(23): 13501–13506. doi: 10.1073/pnas.2135380100.
4. Smith EJ, Allantaz F, Bennett L, *et al.* Clinical, molecular, and genetic characteristics of PAPA syndrome: A review. *Curr Genomics* 2010; 11(7): 519–527. doi: 10.2174/138920210793175921.
5. Caso F, Rigante D, Vitale A, *et al.* Monogenic autoinflammatory syndromes: State of the art on genetic, clinical, and therapeutic issues. *Int J Rheumatol* 2013; 2013(19): 513782. doi: 10.1155/2013/513782.
6. Kondo N, Tanifuji O, Mochizuki T, *et al.* SAPHO syndrome in which certolizumab pegol was effective: A case report. *Trends in Immunotherapy* 2017;1: 93–98. doi: 10.24294/ti.v1.i2.51.