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Pyogenic Arthritis, Pyoderma Gangrenosum, Acne, Suppurative Hidradenitis (PA-PASH) Syndrome: An Atypical Presentation of a Rare Syndrome

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Conflict of interest: None declared

Patient: Male, 44
Final Diagnosis: PAPASH syndrome
Symptoms: Recurrent skin ulcers • diarrhea • inflammatory arthritis
Medication: Prednisone • anti-tumor necrosis factor
Clinical Procedure: N/A
Specialty: Rheumatology

Objective: Rare disease

Background: Pyogenic arthritis, pyoderma gangrenosum (PG), acne, and suppurative hidradenitis (PA-PASH) syndrome has been linked to an auto-inflammatory pathway. We report a case that is an atypical presentation of a rare syndrome, which supports literature suggesting that different phenotypes of PG-related syndromes may be a variation of the same pathogenic spectrum. Interestingly, our patient displayed a positive proteinase-3 antibody (PR-3). The clinical relevance of this is unclear. In recent literature, antineutrophil cytoplasmic autoantibodies (ANCA) positivity has been reported in various inflammatory conditions other than ANCA-associated vasculitis (AAV).

Case Report: A 44-year-old African American male with history of pyogenic arthritis, acne, suppurative hidradenitis, and chronic diarrhea presented for evaluation of painful ulcers located on the bilateral lower extremities, bilateral proximal interphalangeal joints, buttocks, and scrotum, and chronic diarrhea. Infectious etiologies for the ulcers were ruled out. Biopsy of an ulcer revealed PG. Colonoscopy revealed inflammation and ulceration with biopsy consistent with ulcerative colitis (UC). After treatment with prednisone, the ulcers healed within 4 weeks, and the chronic diarrhea resolved.

Conclusions: Our patient displayed a variation of PA-PASH syndrome and UC. Previously reported cases of similar phenotypes of PG-related syndromes have not presented in this fashion. Furthermore, the literature does not report cases of PG-related syndromes with an elevation in PR-3 antibody. Elevation in PR-3 has been reported in various inflammatory disorders aside from AAV. The relevance of this is currently unclear. It may be possible that the milieus of these various auto-inflammatory disorders may share pathogenic commonalities.

MeSH Keywords: Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis • Caspase 1 • Hereditary Autoinflammatory Diseases • Hidradenitis Suppurativa • Pyoderma Gangrenosum

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/898027

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Background

Pyogenic arthritis, pyoderma gangrenosum, acne, and suppurative hidradenitis (PA-PASH) syndrome, initially reported in 2012, has been linked to an auto-inflammatory pathway. PA-PASH syndrome has been linked to mutations in gene *PSTPIP1*, which encodes for proline/serine/threonine phosphatase-interacting protein that interacts with pyrin [1]. This mutation causes an increased affinity to pyrin leading to an up-regulation of caspase-1 and activation of interleukin-1, producing a neutrophil-mediated response [2–4]. Recent literature also suggests that syndromes of similar phenotypes (pyogenic arthritis, pyoderma gangrenosum, and acne [PAPA], pyoderma gangrenosum, acne, and suppurative hidradenitis [PASH], axial spondyloarthritis with the triad of PASH [PASS], pyoderma gangrenosum, acne, and ulcerative colitis [PAC]) may be part of the same pathogenic spectrum, given the association of *PSTPIP1* mutations found in PAPA, PASH, and PAC [5–7]. The presence of elevated levels of proteinase-3 (PR-3) antibody in the sera has commonly been associated with vasculitis that is associated with antineutrophil cytoplasmic autoantibodies (ANCA); however recent literature also reports the presence of these antibodies in various inflammatory conditions. Currently, the relevance of this ANCA positivity is unclear. It may be postulated that significant inflammation may lead to neutrophil priming and induction of ANCA positivity. Current literature review does not report an association of PA-PASH syndrome (or those of similar phenotypes) with an elevation in PR-3 antibody.

Case Report

A 44-year-old African American male presented to the emergency room for evaluation of worsening painful ulcers located in the bilateral lower extremities, bilateral proximal interphalangeal joints, and scrotum. As part of initial management, the patient was evaluated for infection and started on broad-spectrum antibiotics. The rheumatology service was consulted after an infectious etiology was felt to be unlikely; the infectious agents evaluated for included HIV, acute/chronic hepatitis, tuberculosis, syphillis, and fungal culture/stain – all which were found to be negative.

The past medical history included acne (Figure 1), suppurative hidradenitis, intermittent chronic diarrhea, recurrent skin ulcers (Figures 2, 3) complicated by soft tissue infections, and inflammatory arthritis involving bilateral knees, ankles, and the bilateral second and third proximal interphalangeal joints. Previous attempts to treat the cutaneous lesions with oral and intravenous clindamycin, doxycycline, and topical bacitracin failed to improve his symptoms. Furthermore, prior arthrocentesis of various joints to evaluate for septic arthritis or crystal-induced arthropathy yielded sterile inflammatory synovial fluid. The patient had no known family history of autoimmune disease.

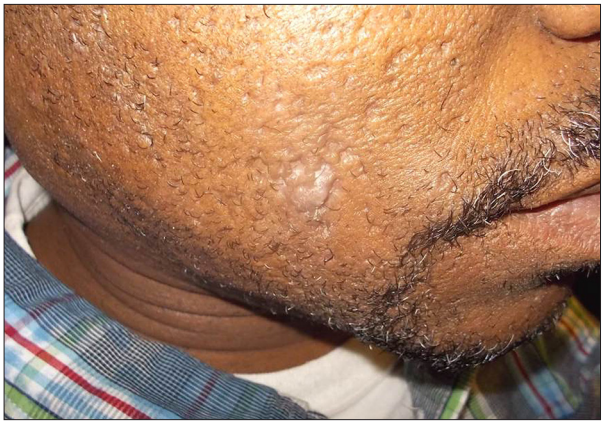


Figure 1. Skin acne.

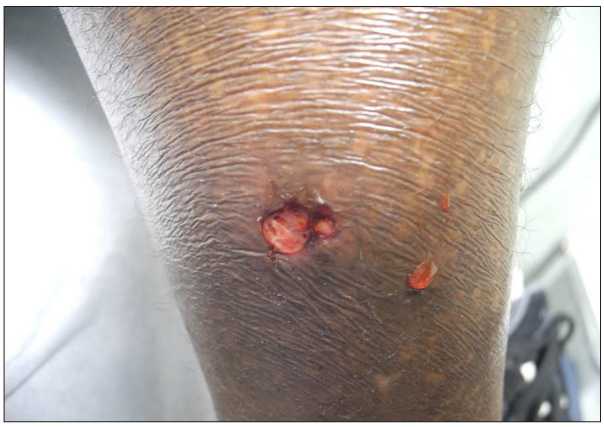


Figure 2. Pyoderma gangrenosum lesion on the right lower extremity prior to treatment with prednisone.

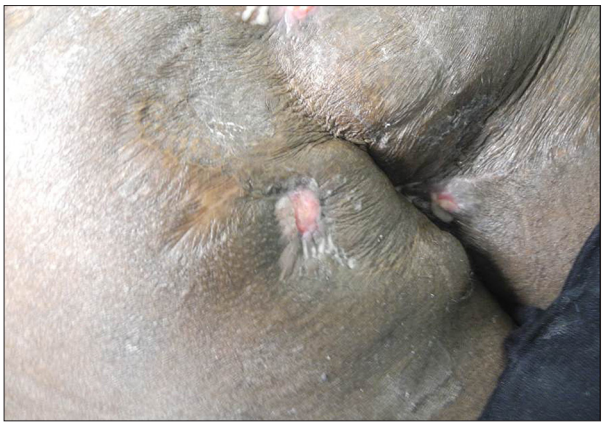
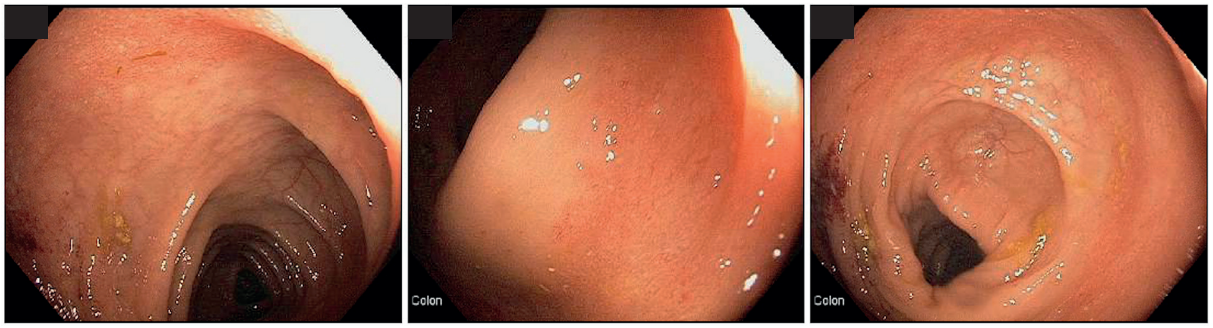


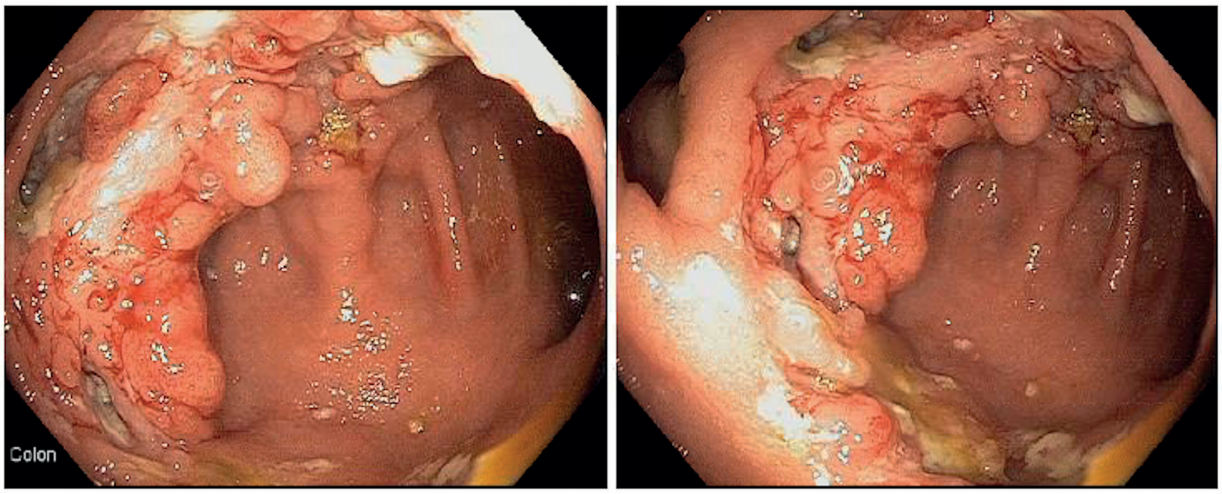
Figure 3. Pyoderma gangrenosum lesions displayed on the buttocks prior to treatment with prednisone.

During the hospital course, the patient underwent a punch biopsy of an ulcer on his right lower extremity. The biopsy was suggestive of pyoderma gangrenosum. Due to chronic



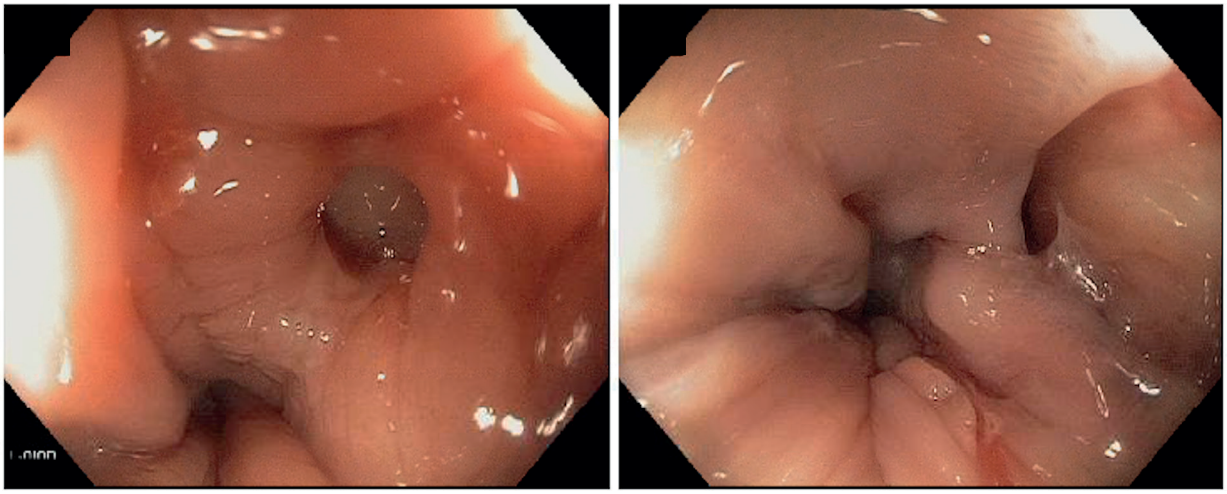
Erythematous mucosa-colon | Erythematous mucosa-colon | Erythematous mucosa-colon

Figure 4. Colonoscopy image displaying diffuse erythema in the rectum.



Anastomosis | Anastomosis

Figure 5. Colonoscopy image displaying anastomosis and ulceration of the colon at 25–27 cm.



Fistula-in-ano-colon | Fistula-in-ano-colon

Figure 6. Colonoscopy image displaying new fistula formation in the ano-rectal region.

nonbloody diarrhea, the patient underwent a colonoscopy, which revealed ulceration and fistula formation (Figures 4–6). The biopsy of the ulcerative lesions revealed transmural ulceration, acute cryptitis, crypt abscesses, and granulation tissue, consistent with ulcerative colitis.

Serologic testing revealed elevated C-reactive protein 33 mg/dL (normal <1 mg/dL), a positive rheumatoid factor 19.2 IU/mL (normal <13.9 IU/mL), negative cyclic citrullinated peptide, negative antinuclear antibody test, positive P-ANCA (<1:20 negative), positive C-ANCA (<1:20 negative) followed by a PR-3 level of 6.1 U/mL (normal range <3.5 U/mL), and negative myeloperoxidase. Furthermore, blood chemistry revealed normal renal function, and urinalysis showed the absence of proteinuria and hematuria.

Given that this patient had a long-standing history of acne, suppurative hidradenitis, pyoderma gangrenosum, and arthritis with no other family history of similar symptoms, the diagnosis of PA-PASH syndrome was made. The patient was managed initially with prednisone 1 mg/kg for 4 weeks, and the dose was tapered slowly thereafter. Subsequent to starting prednisone therapy, the patient reported significant improvement of skin ulcerations and resolution of diarrhea. Prednisone was tapered down to 5 mg daily five months postdischarge from the hospital, and therapy with adalimumab was discussed.

Discussion

PA-PASH is a rare auto-inflammatory syndrome initially described in 2012 [4]. The true etiology is unknown, but genetic analysis has shown associations with *PSTPIP1* mutations that ultimately lead to elevations in interleukin-1 activity. This mutation is similar to the PAPA syndrome and also found in PASH and other phenotypically related disorders such as PsAPASH (which exhibits psoriasis), PASS, and PAC [5–7].

Our patient varied from previously reported cases of this rare syndrome. Features consistent with an overlap of PA-PASH and PAC were displayed in this case, which have not been previously reported in the literature. Due to their similar phenotypic presentation and genotypic relation to the mutation of *PSTPIP1*, this leads us to believe that these syndromes may be within the same pathogenic spectrum. Similar to other patients with PA-PASH, PAPA, and PAC, this patient responded to prednisone with resolution of his symptoms. Literature supports the use of tumor necrosis factor inhibitors as steroid-sparing agents to induce remission, and this option was discussed with our patient.

Our patient did not display any clinical signs or symptoms of ANCA-associated vasculitis, but the serum PR-3 antibody level was elevated. Although the presence of PR-3 antibodies has been reported in non-ANCA vasculitis-associated inflammatory disorders, the clinical relevance of this serologic finding is unclear. It can be postulated that perhaps the inflammatory milieu induced by PA-PASH syndrome had led to development of ANCA positivity. Additionally, various medications, such as minocycline for acne, can cause a drug-induced ANCA-associated vasculitis; however, our patient denied use of such medications [8]. Close monitoring will be needed to assess the relevance of the PR-3 antibody in pyoderma gangrenosum-related auto-inflammatory syndrome.

Conclusions

Our patient displayed an interesting variation of a rare syndrome of pyogenic arthritis, pyoderma gangrenosum, acne, suppurative hidradenitis, and inflammatory bowel disease. Similar phenotypes of pyoderma gangrenosum – related syndromes have presented as isolated PA-PASH or PAC, but not as an overlap between the two, such as occurred in this case. Further studies are needed to understand the etiology and relationship between the various pyoderma gangrenosum – related syndromes, as genetic linkage is not consistent among the disorders. For example, PAPA appears to be autosomal dominant while others (PsAPASH, PAC, PASS) are not, although they all appear to be related to mutation in *PSTPIP1* [9,10]. Unique to our case is the presence of PR-3 antibody, which has not been described in cases reported in the literature. The significance of this ANCA antibody is unclear in the absence of true manifestations of ANCA-associated vasculitis.

Conflict of interest

The authors report no conflict of interest in this publication.

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