Pyoderma gangrenosum (PG), acne, and hidradenitis suppurativa (HS) (PASH) syndrome is a recently identified disease process within the spectrum of autoinflammatory diseases (AIDs), which are distinct from autoimmune, infectious, and allergic syndromes and are gaining increasing interest given their complex pathophysiology and therapeutic resistance. Autoinflammatory diseases are defined by a dysregulation of the innate immune system in the absence of typical autoimmune features, including autoantibodies and antigen-specific T lymphocytes. Mutations affecting proteins of the inflammasome or proteins involved in regulating inflammasome function have been associated with these AIDs. Many AIDs have cutaneous involvement, as seen in PASH syndrome. Pyoderma gangrenosum is a neutrophilic dermatosis presenting as skin ulcers with undermined, erythematous, violaceous borders. It can be isolated, syndromic, or associated with inflammatory conditions (eg, inflammatory bowel disease, rheumatologic disorders, hematologic disorders). Acne vulgaris develops because of chronic obstruction of hair follicles as a result of disordered keratinization and abnormal sebaceous stem cell differentiation. Propionibacterium...
Acnes can reside and replicate within the biofilm community of the hair follicle and activate the inflammasome. Hidradenitis suppurativa, a chronic relapsing neutrophilic dermatosis, is a debilitating inflammatory disease of the hair follicles involving apocrine gland–bearing skin (ie, the axillary, inguinal, and anogenital regions). Onset often occurs between the ages of 20 and 40 years, with a 3-fold higher incidence in women compared to men. Patients experience painful, deep-seated nodules that drain into sinus tracts and abscesses. The condition can be isolated or associated with inflammatory conditions, such as inflammatory bowel disease.

PASH syndrome has been described as a polygenic autoinflammatory condition that most commonly presents in young adults, with onset of acne beginning years prior to other manifestations. A study analyzing 5 patients with PASH syndrome reported an average age of 32.2 years at diagnosis with a disease duration of 3 to 7 years. Pathophysiology of this condition is not well understood, with many hypotheses calling upon dysregulation of the innate immune system, a commonality this syndrome may share with other AIDs. Given its poorly understood pathophysiology, treating PASH syndrome can be especially difficult. We report a novel case of disease remission lasting more than 4 years using adalimumab and cyclosporine. We also discuss prior treatment successes and hypotheses regarding etiologic factors in PASH syndrome.

Case Report
A 36-year-old woman presented for evaluation of open draining ulcerations on the back of 18 months’ duration. She had a 16-year history of scarring cystic acne of the face and HS of the groin. The patient’s family history was remarkable for severe cystic acne in her brother and son as well as HS in her mother and another brother. Her treatment history included isotretinoin, doxycycline, and topical steroids.

Physical examination revealed 2 ulcerations with violaceous borders involving the left upper back (greatest diameter, 5×7 cm)(Figure 1). Evidence of papular and cystic acne with residual scarring was noted on the cheeks. Scarring from HS was noted in the axillae and right groin. A biopsy from the edge of an ulceration on the back demonstrated epidermal spongiosis with acute and chronic inflammation and fibrosis (Figure 2). The clinico-pathologic findings were most consistent with PG, and the patient was diagnosed with PASH syndrome, given the constellation of cutaneous lesions.

After treatment with topical and systemic antibiotics for acne and HS for more than 1 year failed, the patient was started on adalimumab. The initial dose was 160 mg subcutaneously, then 80 mg 2 weeks later, then 40 mg weekly thereafter. Doxycycline was continued for treatment of the acne and HS. After 6 weeks of adalimumab, the PG worsened and prednisone was added. She developed tender furuncles on the back, and cultures grew Pseudomonas aeruginosa and methicillin-sensitive Staphylococcus aureus that responded to ciprofloxacin and cephalaxin.

Due to progression of PG on adalimumab, switching to an infliximab infusion or anakinra was considered, but these options were not covered by the patient’s health insurance. Three months after the initial presentation, the patient was started on cyclosporine 100 mg 3 times daily (5 mg/kg/d) while adalimumab was continued; the ulcers started to improve within 2.5 weeks. After 3 months (Figure 3), the cyclosporine was reduced to 100 mg twice daily, and adalimumab was continued. She had a slight flare of PG after 8 months of treatment when adalimumab was unavailable to her for 2 months.
After 8 months on cyclosporine, the dosage was tapered to 100 mg/d and then completely discontinued after 12 months.

The patient has continued on adalimumab 40 mg weekly with excellent control of the PG (Figure 4), although she did have one HS flare in the left axilla 11 months after the initial treatment. The patient’s cystic acne has intermittently flared and has been managed with spironolactone 100 mg/d for 3 years. After 4 years of management, the patient’s PG and HS remain well controlled on adalimumab.

**Comment**

Our case represents a major step in refining long-term treatment approaches for PASH syndrome due to the 4-year remission. Prior cases have reported use of anakinra, anakinra-cyclosporine combination, prednisone, azathioprine, topical tacrolimus, etanercept, and dapsone without sustainable success. The case studies discussed below have achieved remission via alternative drug combinations.

Staub et al found greatest success with a combination of infliximab, dapsone, and cyclosporine, and their patient had been in remission for 20 months at time of publication. Their hypothesis proposed that multiple inflammatory signaling pathways are involved in PASH syndrome, and this is why combination therapy is required for remission. In 2018, Lamiaux et al demonstrated successful treatment with rifampicin and clindamycin. Their patient had been in remission for 22 months at the time of publication—this time frame included 12 months of combination therapy and 10 months without medication. The authors hypothesized that, because of the autoinflammatory nature of these antibiotics, this pharmacologic combination could eradicate pathogenic bacteria from host microbiota while also inhibiting neutrophil function and synthesis of chemokines and cytokines.

More recently, reports have been published regarding the success of tildrakizumab, an IL-23 antagonist, and ixekizumab, an IL-17 antagonist, in the treatment of PASH syndrome. Ixekizumab was used in combination with doxycycline, and remission was achieved in 12 months. However, tildrakizumab was used alone and achieved greater than 75% improvement in disease manifestations within 2 months.

Marzano et al conducted protein arrays and enzyme-linked immunosorbent assay to analyze the expression of cytokine, chemokine, and effector molecule profiles in PASH syndrome. It was determined that serum analysis displayed a normal cytokine/chemokine profile, with the only abnormalities being anemia and elevated C-reactive protein. There were no statistically significant differences in serum levels of IL-1β, tumor necrosis factor (TNF) α, or IL-17 between PASH syndrome and healthy controls. However, cutaneous analysis revealed extensive cytokine and chemokine hyperactivity for IL-1β and IL-1β receptor; TNF-α; C-X-C motif ligands 1, 2, and 3; C-X-C motif ligand 16; regulated on activation, normal T cell expressed and secreted; IL-17 and IL-17R; Fas/Fas ligand; and CD40/CD40L. This cutaneous profile of elevated cytokines and chemokines mirrors that of nonsyndromic PG and many other AIDs. These results demonstrate that the inflammation in PASH syndrome is localized mainly to the skin and further support the hypothesis that possibilities for alternative treatment options are diverse.

Ead et al presented a unique perspective focusing on cutaneous biofilm involvement in PASH syndrome. Microbes within these biofilms induce the migration and proliferation of inflammatory cells that consume factors normally utilized for tissue catabolism. These organisms deplete necessary biochemical cofactors used during...
healing. This lack of nutrients needed for healing not only slows the process but also promotes favorable conditions for the growth of anerobic species. In conjunction, biofilm formation restricts bacterial access to oxygen and nutrients, thus decreasing the bacterial metabolic rate and preventing the effects of antibiotic therapy. These features of biofilm communities contribute to inflammation and possibly the troubling resistance to many therapeutic options for PASH syndrome.

Each component of PASH syndrome has been associated with biofilm formation. As previously described, PG manifests in the skin as painful ulcerations, often with slough. This slough is hypothesized to be a consequence of increased vascular permeability and exudative byproducts that accompany the inflammatory nature of biofilms. Acne vulgaris has well-described associations with *P. acnes*. Ead et al. described *P. acnes* as a component of the biofilm community within the microcomedone of hair follicles. This biofilm allows for antibiotic resistance occasionally seen in the treatment of acne and is potentially the pathogenic factor that both impedes healing and enhances the inflammatory state. Hidradenitis suppurativa has been associated with biofilm formation.

In further pursuit of PASH syndrome pathophysiology, many experts have sought to uncover the relationship between PASH syndrome and the previously described pyogenic arthritis, PG, and acne (PAPA) syndrome, another entity within the AIDS spectrum (Table). This condition was first recognized in 1997 in a 3-generation family with 10 affected members. It is characterized by PG and acne, similar to PASH; however, PAPA syndrome includes PG arthritis and lacks HS. Pyogenic arthritis manifests as recurrent aseptic inflammation of the joints, mainly the elbows, knees, and ankles. Pyogenic arthritis commonly is the presenting symptom of PAPA syndrome, with onset in childhood. As patients age, the arthritis symptoms decrease, and skin manifestations become more prominent.

PAPA syndrome has autosomal-dominant inheritance with mutations on chromosome 15 in the proline-serine-threonine phosphatase interacting protein 1 (*PSTPIP1*) gene. This mutation induces hyperphosphorylation of *PSTPIP1*, allowing for increased binding affinity to pyrin. Both *PSTPIP1* and pyrin are co-expressed as parts of the NLRP3 inflammasome in granulocytes and monocytes. As a result, pyrin is more highly bound and loses its inhibitory effect on the NLRP3 inflammasome pathway. This lack of inhibition allows for uninhibited cleavage of pro-IL-1β to active IL-1β by the inflammasome.

Elevated concentrations of IL-1β in patients with PAPA syndrome result in a dysregulation of the innate immune system. IL-1β induces the release of proinflammatory cytokines, namely TNF-α, interferon γ; IL-8; and regulated on activation, normal T cell expressed and secreted (RANTES), all of which activate neutrophils and induce neutrophilic inflammation. IL-1β not only initiates this entire cascade but also acts as an antiapoptotic signal for neutrophils. When IL-1β reaches a critical threshold, it induces enough inflammation to cause severe tissue damage, thus causing joint and cutaneous disease in PAPA syndrome. IL-1 inhibitors (anakinra) or TNF-α inhibitors (etanercept, adalimumab, infliximab) have been used many times to successfully treat PAPA syndrome, with TNF-α inhibitors providing the most consistent results.

Another AIDS entity with similarities to both PAPA syndrome and PASH syndrome is pyogenic arthritis, PG, acne, and HS (PA-PASH) syndrome. First identified in 2012 by Bruzzese, genetic analyses revealed a p.E277D

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### Comparison of PASH, PAPA, AND PA-PASH Syndromes

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Abbreviations: CRP, C-reactive protein; CXCL16, C-X-C motif ligand 16; FasL, Fas ligand; MEFV, Mediterranean fever gene; NCSTN, gamma-secretase gene Nicastrin; NOD2, nucleotide-binding oligomerization domain-containing protein 2; PAPA, pyogenic arthritis; pyoderma gangrenosum, and acne; PA-PASH; pyogenic arthritis; pyoderma gangrenosum, acne, and hidradenitis suppurativa; PASH, pyoderma gangrenosum, acne, and hidradenitis suppurativa; RANTES, regulated upon activation, normal T cell expressed and secreted; TNF, tumor necrosis factor.
missense mutation in PSTPIP1 in PA-PASH syndrome. Research has suggested that the key molecular feature is neutrophil activation by TLR17 cells and the TNF-α axis. This syndrome has not been further characterized, and little is known regarding adequate treatment for PA–PASH syndrome.

Although it is similar in phenotype to aspects of PAPA and PA–PASH syndromes, PASH syndrome has distinct genotypic and immunologic abnormalities. Genetic analysis of this condition has shown an increased number of CCTG repeats in proximity to the PSTPIP1 promoter. It is hypothesized that these additional repeats predispose patients to neutrophil inflammation in a similar manner to a condition described in France, termed aseptic abscess syndrome. Other mutations have been identified, including those in IL-1N, PSMB8, MEFV, NOD2, NCSTN, and more. However, it has been determined that the majority of these variants have already been filed in the Single Nucleotide Polymorphism Database or in the Registry of Hereditary Auto-inflammatory Disorders. The question remains regarding the origin of inflammation seen in PASH syndrome; the potential role of biofilms; and the relationship between PASH, PAPA, and PA–PASH syndromes. Much work remains to be done in refining therapeutic options for PASH syndrome. Continued biochemical research is necessary, as well as collaboration among dermatologists worldwide who find success in treating this condition.

Conclusion

There are genotypic and phenotypic similarities between PASH, PAPA, and PA–PASH syndromes, with various mutations within or near the PSTPIP1 gene; however, their genetic discrepancies seem to play a major role in the pathophysiology of each syndrome. Much work remains to be done in PA–PASH syndrome, which has not yet been well described. Meanwhile, PAPA syndrome has been well characterized with mutations affecting proteins of the NLRP3 inflammasome, resulting in elevated IL-1β and excess neutrophil inflammation. In PASH syndrome, the importance of increased repeats near the PSTPIP1 promoter is yet to be elucidated. It has been shown that these abnormalities predispose individuals to neutrophil inflammation, but the mechanism by which they do so is unknown. In addition, consideration of biofilms and their predisposition to inflammation within the pathophysiology of PASH syndrome is a possibility that must be considered when discussing therapeutic options. Based on our case study and previous successes in treating PASH syndrome, it is clear that a multidrug approach is necessary for remission. It is likely that the etiology of PASH syndrome is multifaceted and involves hyperactivity in multiple arms of the innate immune system.

Patients with PASH syndrome have severely impaired quality of life and often experience social withdrawal due to the disfiguring sequelae and limited treatment options available. To improve patient outcomes, it is essential for physicians and scientists to report on successful treatment strategies and advances in immunologic understanding. Improved understanding of PASH syndrome calls for further genetic exploration into the role of additional genomic repeats and how these affect the PSTPIP1 gene and inflammasome activity. As medical advances improve understanding of the pathophysiology of this disease entity, it will likely become clear which mechanisms are most important in disease progression and how clinicians can best optimize treatment.

REFERENCES