P(A)SH Syndrome: Case Presentation and Short Update of Related Disorders

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ABSTRACT

Hidradenitis suppurativa (HS) is a chronic inflammatory disease that is frequently associated with syndromes, such as those within the PAPA spectrum. Syndromic HS presents unique management challenges, as it often shows resistance to conventional therapies. Pyoderma gangrenosum is a rare inflammatory neutrophilic dermatosis that is often seen in association within the spectrum of autoinflammatory diseases.

The PAPA spectrum disorders include a group of autoinflammatory diseases characterized by mutations in the PSTPIP1 gene or by clinical manifestations that closely resemble or overlap with those of PAPA syndrome. Each syndrome (PASH, PAPASH, PsAPASH, PASS, PAC, and PAMI syndrome) in this spectrum highlights specific inflammatory pathways and symptoms, providing insight into targeted therapeutic approaches.

Here, we present a rare case of incomplete PASH (pyoderma gangrenosum and hidradenitis suppurativa) syndrome successfully managed with a standard combination of antibiotics (ceftriaxone and metronidazole) and corticosteroids (methylprednisolone), followed by immunosuppressant (azathioprine) and corticosteroids (dexamethasone). We review both novel and established/standard treatment options, with an emphasis on treatment outcomes. Conventional therapies remain both effective and affordable, providing valuable alternatives for patients.

KEYWORDS

PAPA syndrome; PASH syndrome; pyoderma gangrenosum; hidradenitis suppurativa; antibiotics; azathioprine; corticosteroids

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INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic inflammatory disease affecting the major skin folds, marked by recurrent suppurative lesions that lead to progressive tissue destruction and fibrosis (1). Its association with other complex clinical syndromes, though uncommon, adds a layer of therapeutic complexity, making effective management challenging (1). Patients with syndromic HS often exhibit signs of systemic inflammation, atypical cutaneous involvement, and resistance to conventional therapies (1).

Pyoderma gangrenosum is a rare inflammatory neutrophilic dermatosis that manifests as painful ulcers with violaceous, undermined edges, particularly on the lower extremities (2). Both pyoderma gangrenosum and its syndromic forms can be observed within the spectrum of autoinflammatory diseases (2).

"Autoinflammatory diseases" is a term used in the literature to describe a group of disorders caused by tissue damage resulting from overactivation of the innate immune system, occurring in absence of autoreactive T cells or antibodies (3).

Pyoderma gangrenosum (PG), pyogenic arthritis and acne (PAPA) syndrome is a rare autosomal dominant autoinflammatory disease caused by mutations in proline-serine-threonine phosphatase interacting protein 1 (PSTPIP1) gene (4). PAPA spectrum disorders represent a group of autoinflammatory diseases caused by mutations in the PSTPIP1 gene or marked by clinical findings that are similar to or overlap with those of PAPA syndrome (4). These disorders include PASH (PG, acne and hidradenitis suppurativa), PAPASH (involves all clinical findings of PASH plus pyogenic sterile arthritis), PsA-PASH (includes the features of PASH along with psoriatic arthritis), PASS (defined by PG, acne, ankylosing spondylitis, with or without hidradenitis suppurativa), PAC (involves PG, acne and ulcerative colitis), and PAMI syndrome (PSTPIP1-associated myeloid-related-proteinemia inflammatory syndrome) (4).

Incomplete PASH syndrome was discussed within the broader context of the PAPA spectrum syndromes, that was successfully managed with standard therapeutic combination of antibiotics (ceftriaxone, metronidazole), immunosuppressant (azathioprine) and corticosteroids (methylprednisolone, dexamethasone). With this case report we will explore PAPA, PASH, and PAPASH syndromes, focusing on their complex pathogenesis and reviewing the currently available treatment options. While acknowledging the effectiveness of conventional therapies, we aim to highlight the additional benefits that newer treatment strategies may offer to patients.

CASE REPORT

A 61-year old male presented in October 2024 to the dermatology department with primary complaints of painful, non-healing wounds on both lower legs. These wounds first appeared in 2018, and although local treatment with antiseptics and antibiotics initially led to improvement, the wounds reappeared.

The patient also reported a history of acne inversa (hidradenitis suppurativa), which began in the axillary region in 2016 as abscesses with purulent discharge. A year later, similar lesions developed in the genital area. Antibiotic therapy and local disinfection were used with satisfactory results.

In 2021, the patient underwent treatment with adalimumab 40 mg, starting with once-a-month injections administered for three months, followed by once a week injections for another three months. He observed slight improvement in his skin during this period. The patient also reported chronic back, knee, and ankle pain since 2018, along with endoscopic ligation for Mallory-Weiss syndrome in 2023, colon surgery for benign tumor in 2023, and surgery for postoperative ventral hernia in 2024.

At the time of the consultation the patient requested a physical examination and further therapeutic approach to be established.

Routine evaluations included blood and urine tests, biochemical analysis, and serum protein electrophoresis analysis (Table 1).

Tab. 1 Routine evaluations: blood and urine tests, biochemical analysis, and serum protein electrophoresis analysis.

Test	Result	Status
Routine Blood Tests		
WBC (white blood count)	18.2 × 10^9/l	Elevated
HGB (Hemoglobin)	118.0 g/l	Decreased
HCT (Hematocrit)	0.37 l/l	Decreased
MCV (Mean Corpuscular Volume)	75.0 fL	Decreased
MCH (Mean Corpuscular Hemoglobin)	23.9 pg	Decreased
RDW-CV (Red Cell Distribution Width)	15.8%	Elevated
PLT (Platelet Count)	513.0 × 10^9/l	Elevated
PDW (Platelet Distribution Width)	8.3%	Decreased
Granulocytes %	80.9%	Elevated
Lymphocytes %	15.2%	Decreased
ESR (Erythrocyte Sedimentation Rate)	72 mm/h	Elevated
Urine Tests		
Red Blood Cells (RBCs)	24.0 u/l	Elevated
WBC (White Blood Cells)	25.0 u/l	Elevated
Squamous Cells	49.0 u/l	Elevated
Hyaline Casts	4.0 u/l	Elevated
Granular Casts	24.0 u/l	Elevated
Biochemical Analysis		
HDL (High-Density Lipoprotein)	1.26 mmol/l	Elevated
Urea	1.8 mmol/l	Decreased
Uric Acid	470.0 micromol/l	Elevated
Total Protein	92.0 g/l	Elevated
C-Reactive Protein (CRP)	84.1 mg/l	Elevated
Iron Levels	1.4 micromol/l	Decreased

Albumin Levels	26.0 g/l	Decreased
Serum Protein Electrophoresis		
Albumin Fraction	36.20%	Decreased
Alpha 1 Fraction	6.30%	Elevated
Alpha 2 Fraction	12.30%	Elevated
Beta 1 Fraction	7.50%	Slightly elevated
Beta 2 Fraction	10.30%	Elevated
Gamma Fraction	27.40%	Elevated
Albumin Electrophoresis	27.04 g/l	Decreased
Alpha 1 Globulins	4.71 g/l	Elevated
Alpha 2 Globulins	9.19 g/l	Elevated
Beta 1 Globulins	5.60 g/l	Slightly elevated
Beta 2 Globulins	7.69 g/l	Elevated
Gamma Globulins	20.47 g/l	Elevated
C3 Complement	0.84 g/l	Decreased
ANA Screening	Borderline	

The patient was diagnosed with secondary iron deficiency anemia and hypoalbuminemia. Iron III-hydroxide polymaltose complex 100mg/ folic acid 0.35 mg two chewable tablets a day was prescribed.

From the consultation with a rheumatologist, HLA-B27 testing resulted negative. X-ray findings indicated unilateral sacroiliitis, possible lumbar syndesmophytes, and a compression fracture of T12, with suspicion of inflammatory changes in the thoracic vertebrae. The patient has shown a relatively poor response over the years to methylprednisolone and sulfasalazine. From the orthopedic consultation, en face and lateral X-rays of both knee joints were obtained, revealing early osteoarthritic changes bilaterally. Therapy with etoricoxib 90 mg once daily after meal and esomeprazole 20 mg one tablet before meal was suggested.

The dermatological examination revealed multiple undermined ulcerative lesions on both lower legs (regio cruris), some of which were confluent and irregularly shaped, covered with purulent-hemorrhagic crusts. A violet halo and local erythema were noted around the lesions (Fig.1a–c). Additionally, cicatricial changes and numerous deep and superficial abscesses exuding pus-like material were present in the genital and gluteal areas (Fig. 2a). Additional multiple dysplastic nevi were noted on the trunk (Fig. 2b) and back regions (Fig. 2c). In the axillae, only cicatricial and fibrous changes were observed, with no active inflammatory process. Onychomycosis was also noted. Enlarged lymph nodes were not palpable.

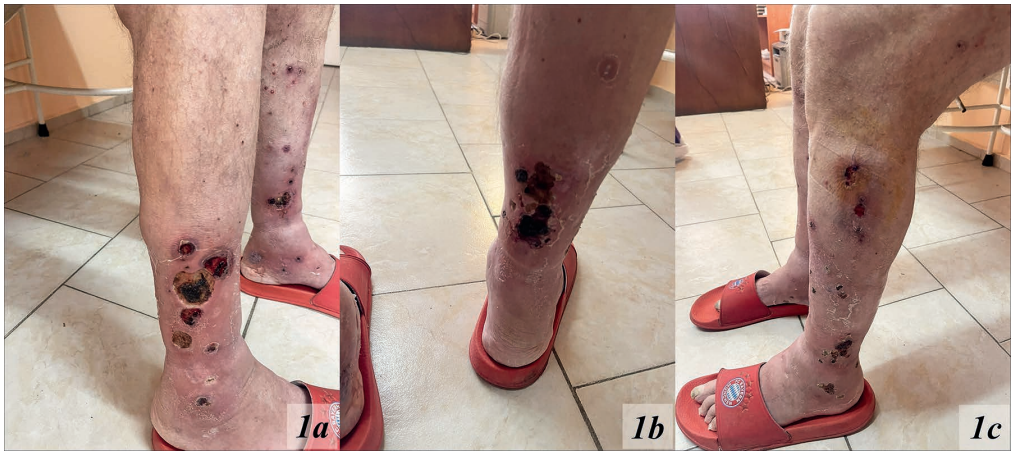

Fig. 1a–c Pyoderma gangrenosum: Multiple undermined ulcerative lesions on both lower legs (regio cruris), some of which were confluent and irregularly shaped, covered with purulent-hemorrhagic crusts. A violet halo and local erythema were also noted around the lesions. **1a** Lateral view of pyoderma gangrenosum lesions on the right lower leg. **1b** Posterior view of pyoderma gangrenosum lesions on the right lower leg. **1c** Lateral view of pyoderma gangrenosum lesions on the left lower leg.

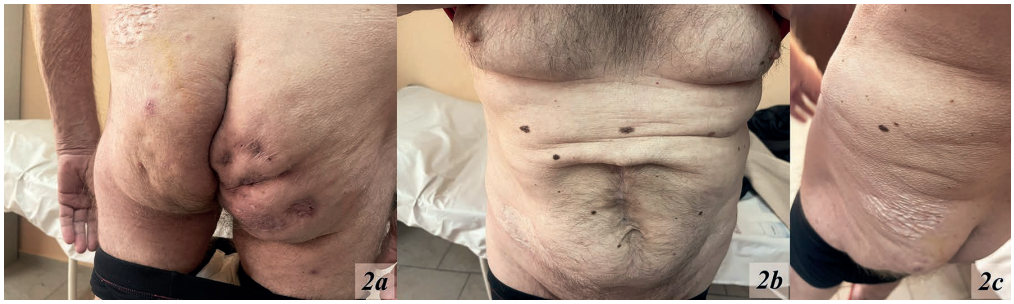

Fig. 2a–c Dermatological examination. **2a** Hidradenitis suppurativa: Cicatricial changes and numerous deep and superficial abscesses exuding pus-like material in the gluteal area. **2b** Multiple dysplastic nevi on the trunk region. **2c** Dysplastic nevus located in the lower left back region.

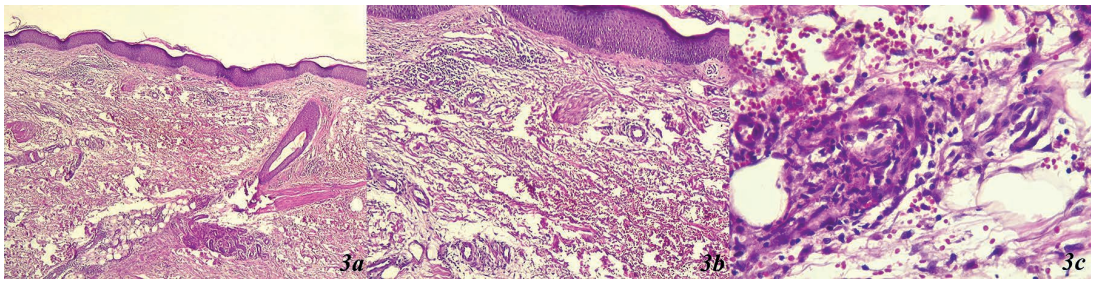

Fig. 3a–c Pyoderma gangrenosum: Orthohyperkeratosis, uneven acanthosis with smoothing of dermo-epidermal undulations, and a myxoid papillary dermis. There was also a moderate interstitial and perivascular round cell inflammatory infiltrate, with occasional eosinophils present in the upper and middle dermal layers. **3a** Pyoderma gangrenosum HEx40. **3b** Pyoderma gangrenosum HEx100. **3c** Pyoderma gangrenosum HEx200.

A biopsy was conducted from an erythematous-infiltrative ulcer with a raised edge and a fibrinous center located on the lower leg (regio cruris). The histological examination revealed orthohyperkeratosis, uneven acanthosis with smoothing of dermo-epidermal undulations, and a myxoid papillary dermis. There was also a moderate interstitial and perivascular round cell inflammatory infiltrate, with occasional eosinophils present in the upper and middle dermal layers. The histological findings were consistent with pyoderma gangrenosum (Fig. 3a–c).

Treatment was initiated with ceftriaxone 2 g i.v., metronidazole 500 mg i.v. twice daily, nadroparin calcium 0.4 ml subcutaneously, and metamizole sodium ampoules as needed. Local dressings with potassium permanganate were applied to the lower legs. Given the histologically confirmed diagnosis of pyoderma gangrenosum and the presence of hidradenitis suppurativa, a diagnosis of incomplete PASH syndrome was established, prompting the initiation of treatment with methylprednisolone 60 mg i.v. and famotidine 40 mg twice daily. Due to deviations in serum electrophoresis indicators, an immunofixation electrophoresis of serum proteins and urine was performed. Paraproteinemia was ruled out. Antibiotic and immunosuppressive therapies were administered, leading to a regression of the pyoderma gangrenosum lesions (Fig. 4a–d).

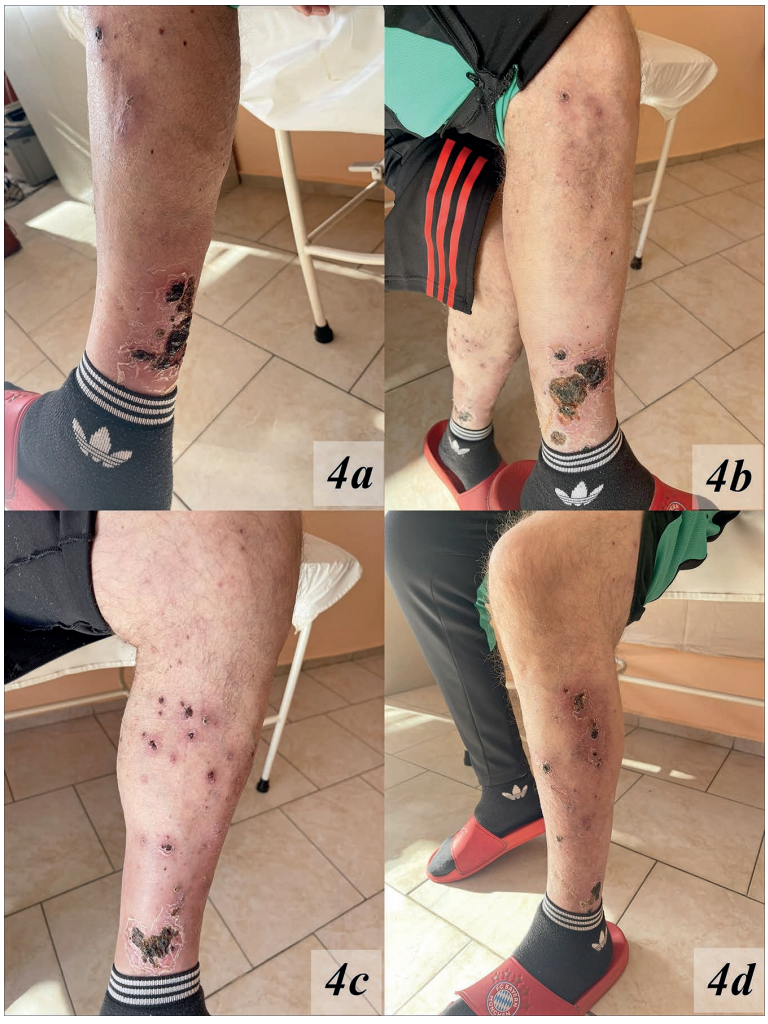

Fig. 4a–d Dermatological findings: Regression of pyoderma gangrenosum lesions following antibiotic and immunosuppressive therapies, with subsequent crust formation. **4a** Medial-posterior view of the lesions located on the right lower leg. **4b–c** Medial view of the lesions located on the left lower leg. **4d** Lateral view of the lesions located on the left lower leg.

Outpatient treatment included azathioprine 50 mg twice daily, to be taken after meals, and dexamethasone 4 mg after food, with a gradually reducing regimen: 1 tablet in the morning and half at lunch during the first week, followed by half a tablet in the morning and half at lunch during the second week. Esomeprazole 40 mg was prescribed twice before meals, along with bilastine 20 mg, to be taken at 5 p.m. For pain management, metamizole sodium was recommended, and local dressings with pale pink potassium permanganate solution were to be applied 2-3 times daily for 30 minutes. A hydrating intensive gel-cream was advised for the surrounding skin.

DISCUSSION

In 1975, a 14-year-old boy with "streaking leukocyte factor", arthritis, and pyoderma gangrenosum was documented as the first reported case in the literature, marking the initial description of what is now known as pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome (5).

PAPA syndrome is a rare, hereditary, autosomal dominant autoinflammatory disorder resulting from missense mutations in the proline-serine-threonine phosphatase interacting protein 1 (PSTPIP1)/CDBP1 gene located on chromosome 15q (6). These mutations lead to an overproduction of interleukin-1beta (IL-1beta) through hyperphosphorylated PSTPIP1 protein, which disrupts its role in the inflammasome activation, a key component in IL-1beta production (6). In addition to IL-1beta overproduction, PAPA syndrome has also been associated with elevated serum levels of tumor necrosis factor-alpha (TNF-alpha) (7). In the case of "streaking leukocyte factor", arthritis, and pyoderma gangrenosum (5), trauma or other stimuli may induce the accumulation of a serum factor that enhances the random leukocyte migration in vitro. This accumulation in certain tissues could lead, as suggested by the authors, to excessive leukocyte influx and increased local leukocyte activity in the inflammatory exudates (5). According to a study by Mistry et al. (8), neutrophils and low-density granulocytes exhibit increased formation of neutrophil extracellular traps (NET) compared with control neutrophils. The overproduction of NET formation and decreased degradation may contribute to prolonged or heightened inflammatory responses and overall immune dysregulation (8). Additionally, IL-17 and IL-6 have been suggested as potentially pathogenic cytokines in PAPA syndrome (8).

The clinical findings can vary, ranging from early onset, painful flares of recurrent sterile arthritis to skin ulcerations, pyoderma gangrenosum, and severe cystic acne (6). The initial sign is typically joint involvement, which presents as painful recurrent monoarticular arthritis that may be triggered by trauma or occur spontaneously (9). The cutaneous manifestations are generally more severe in adults compared to those in children (9). In children with recurrent or recurrent pyogenic arthritis/osteomyelitis, an underlying immunological disorder should always be considered (10). PAPA syndrome has been also linked with other disorders, including Crohn's disease and primary sclerosing cholangitis/autoimmune hepatitis overlap (11), as well as hypogammaglobulinemia (7).

While blood tests are not diagnostic for PAPA syndrome, they can reveal a non-specific elevation in acute phase reactants, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), particularly during episodes of arthritis (4). Additionally, increased levels of IL-1beta and TNF-alpha can be observed in peripheral blood mononuclear cells (4).

Interestingly, cases of suspected PAPA syndrome lacking the PSTPIP1 mutation have been identified (6). As summarized by Smith et al. (6), PSTPIP1 mutations were confirmed in only 3 out of 8 cases studied. Among the mutation-negative cases, three exhibited the full clinical characteristics of PAPA syndrome, one was presented with alleged pyoderma gangrenosum and severe bleeding that responded to corticosteroids, and another showed severe pauciarticular corticosteroid responsive arthritis and recurrent, destructive pyoderma gangrenosum (6). A homolog of PSTPIP1, known as proline-serine-threonine-phosphatase-interacting protein 2 (PSTPIP2), was found in both humans and mice (12). Although data is limited on whether PSTPIP1 and PSTPIP2 proteins share a common or distinct pathways, the possibility of PSTPIP2 mutations may be considered in cases of PAPA syndrome that lack identifiable mutations (6). Based on these findings, it can be concluded that not all cases of PAPA syndrome are associated with identifiable causative mutation. This implies that 1) genetic testing may not always provide a definitive diagnosis, and 2) cases of PAPA syndrome can occur without presenting the full spectrum of clinical symptoms.

A personalized therapeutic approach is advisable for effective disease management. In some instances, the response of pyoderma gangrenosum to systemic corticosteroids may be poor (13, 14), posing a challenge particularly when 1) only a partial response is achieved, or 2) alternative treatments are cost-restrictive or unavailable in some countries. A one month regimen of high-dose corticosteroid treatment with prednisone at 60 mg daily, combined with regular wound care, resulted in rapid progression of the patient's pyoderma gangrenosum ulcers (13). The combination of etanercept and vacuum-assisted closure devices ultimately proved to be an effective therapy for managing the patient's condition (13). A rapid and lasting response to pyoderma gangrenosum in a patient with PAPA syndrome was achieved through target therapy with anakinra, a recombinant human interleukin-1 receptor antagonist (14).

A 14-year-old patient with PAPA syndrome, previously unresponsive to multiple therapies, experienced dramatic improvement in pyoderma gangrenosum after one infusion of infliximab, a chimeric anti-TNF alpha monoclonal antibody (15). A second infusion subsequently led to resolution of the condition (15).

A table by Lu et al. (16) summarized the effective drugs based on their gene mutation sites. The following agents have demonstrated good efficacy: corticosteroids, azathioprine, sulfasalazine, leflunomide, tumor necrosis factor-alpha inhibitors, and interleukin-1beta antagonist (16). In the same study, a 9-year-old boy with PAPA syndrome was treated with tocilizumab, a humanized anti-IL-6 receptor monoclonal antibody (16). The symptoms subsided within a week of treatment but reappeared after

six months (16). Following this, adalimumab, a TNF-inhibitor, was administered and controlled the symptoms for six months before a relapse occurred (16). Rapid symptom relief was achieved with intra-articular triamcinolone hexacetonide (a corticosteroid) during one of the patient's episodes, with no subsequent cutaneous symptoms observed (16). Unfortunately, due to the high cost of this treatment plan, more cost-effective therapies will need to be considered (16). The initial treatment for a patient with PAPA syndrome involved adalimumab 40 mg every two weeks, which led to partial clinical improvement in the pyoderma gangrenosum lesions and acne (17). Subsequently, the treatment was modified to include tacrolimus, administered at a dose of 3 mg twice daily, in combination with adalimumab (17). This combination resulted in more significant improvement in the lesions (17). Rare onset of new pyoderma gangrenosum lesions was managed with topical dapsone and/or topical steroids (17).

A patient with a PAPA-like syndrome, primarily exhibiting cutaneous manifestations such as pyoderma gangrenosum and acne fulminans, was treated with canakinumab, leading to the resolution of the dermatological symptoms (18).

Given the high cost of biological agents, cost-effectiveness and accessibility are important considerations for patient care. Sardana et al. (19) reported a case of PAPA syndrome with accompanying arthritis and worsening ulcerations that was successfully managed using minocycline, dapsone, deflazacort and methotrexate (19). This approach resulted in complete healing of the ulcers and sustained results over a two-year-follow-up period (19).

PASH syndrome is a rare autoinflammatory condition that is clinically characterized by the triad of pyoderma gangrenosum, acne, and hidradenitis suppurativa (acne inversa) (9). The first documented cases of the disease appeared in 2012, involving two patients who exhibited no signs of inflammatory joint involvement (20). These cases presented with the characteristic triad of severe Hurley III hidradenitis suppurativa, cystic acne, and pyoderma gangrenosum, along with systemic inflammation indicated by elevated serum amyloid A and CRP levels (20). The initial manifestation of the disease is typically acne, with the onset of PASH generally observed in the third or fourth decade of life (4, 21). Although no triggering factors or associated conditions were noted in the initial description by Braun-Falco (20), PASH syndrome has since been reported as a potential complication following bariatric surgery for morbid obesity in one case and as associated with Crohn's disease in another (21).

The histopathological findings of pyoderma gangrenosum are considered nonspecific but can be further categorized according to its clinical subtypes (22). In the early stages, a characteristic neutrophilic infiltrate is typically observed (22). However, in cases of vegetative pyoderma gangrenosum, the histopathological presentation may include neutrophilic and eosinophilic histiocytic mixed infiltrate (22). Although systemic pyoderma gangrenosum is not typically associated with tissue eosinophilia, eosinophilia may still be observed peripherally, particularly in conditions such as idiopathic hypereosinophilic syndrome (23).

Some authors suggest that vasculitis may also be observed in pyoderma gangrenosum, making its histological findings generally "problematic" (22). In addition to neutrophilic infiltration, observed in all cases in the case series by Moxda Suresh Patel et al. (22), the following histological findings were also noted: vaculitis in 11 patients (57.89%), lymphoplasmacytic infiltrate in 6 patients (31.57%), pseudoepitheliomatous hyperplasia in 5 patients (26.31%), mixed inflammatory infiltrate in 4 patients (21%), epidermal ulceration in 4 patients (21%), and mitotic activity in 3 patients (15.78%). Given the complex histological findings in pyoderma gangrenosum, a comprehensive diagnostic approach is essential. This includes both clinical and histological evaluations, with particular emphasis on integrating detailed patient anamnesis to support precise diagnosis and personalized therapeutic approach.

Based on the information above, we diagnosed our patient with incomplete PASH syndrome, despite the absence of severe acne in the clinical presentation. This conclusion is further supported by: 1) the presence of pyoderma gangrenosum and hidradenitis suppurativa, 2) chronic inflammatory markers (elevated CRP, ESR, WBC) and systemic inflammatory complications (iron deficiency anemia and hypoalbuminemia), 4) partial response to immunosuppressive treatment (adalimumab), and a 5) history of endoscopic ligation for Mallory-Weiss syndrome. Although this condition is not directly associated with PASH syndrome, the frequent vomiting characteristic of Mallory-Weiss syndrome (24) could suggest underlying gastrointestinal issues, which might arise from conditions that cause chronic inflammation.

Genetic testing for mutations in the autoinflammatory genes MEFV, NLRP3, TNFRSF1A, and PSTPIP1, resulted negative, except for an increased number of CCCTG microsatellite repeats in the promoter region of the PSTPIP1 gene (1, 20). Similar to PAPA syndrome, PASH is associated with the overactivation of the innate immune system, resulting in an increased production of interleukins and "sterile" neutrophil-rich cutaneous inflammation (9). Mutations in the PSTPIP1 gene have also been documented (25). Additionally, mutations in MEFV, NOD2, and NLRP3 have been identified in seven patients diagnosed with PASH syndrome (1, 26). Despite the mutations presented above, the genetic basis of PASH syndrome remains shrouded in mystery (27). However, PASH has been associated with testicular cancer (28) and ulcerative colitis (29), suggesting a link between this neutrophilic dermatosis and conditions such as inflammatory bowel disease and certain malignancies (27).

In a study by Marzano et al. (21), serum levels of IL-1beta, TNF-alpha, and IL-17 – key proinflammatory cytokines – were found to be within the normal ranges in the peripheral blood of patients with PASH syndrome. However, in lesional skin, particularly in the ulcerative lesions of pyoderma gangrenosum, elevated levels of proinflammatory cytokines, chemokines, and tissue-damaging effector molecules were observed (21). This finding suggests that the inflammatory response in PASH syndrome is predominantly localized to the skin, with no detectable proinflammatory activity in the bloodstream (21).

In the management of each patient with PASH syndrome, it is essential to consider the potential hyperactivity of the innate immune system and to employ a combination of multimodal anti-inflammatory therapies (30).

Systemic corticosteroid therapy or antibiotics with anti-inflammatory properties, such as dapsone and tetracyclines, are considered as first-line treatment options for pyoderma gangrenosum (31). Furthermore, immunosuppressive agents like azathioprine, cyclosporine, and mycophenolate mofetil may also be regarded as initial therapeutic strategies (31). Anti-tumor necrosis factor-alpha agents, such as adalimumab and infliximab, are frequently used in clinical practice, exhibiting favorable outcomes in the majority of patients with PASH syndrome, although not in every case (32). These agents typically promote rapid remission of pyoderma gangrenosum; however, hidradenitis suppurativa lesions tend to be more resistant to treatment (32).

In a study by Yan et al. (33), hidradenitis suppurativa lesions appeared several years before the onset of pyoderma gangrenosum and the initial diagnosis of PASH syndrome. This pattern aligns with our case report, adding further support to our diagnostic conclusion. If adalimumab proves ineffective or if the patient has more severe clinical findings, high-dose infliximab can be used to achieve disease control (33). This approach is often paired with intralesional corticosteroids, systemic corticosteroids, and vitamin supplementation (33). In the study, three out of the eight patients with PASH syndrome were found to have deficiencies in either zinc, vitamin A, or both (33). Some studies suggest that low vitamin D levels may contribute to the pathogenesis of PASH and PAPASH syndromes, indicating that vitamin D supplementation could serve as a potential additional treatment option (34).

A multimodal treatment regimen with infliximab, cyclosporine, and dapsone was administered to a 22-year-old woman with PASH syndrome, leading to prolonged improvement in her clinical symptoms (35). Previously, her symptoms had proven resistant to treatment with etanercept, adalimumab, fumaric acid and the IL-1 receptor antagonist anakinra (35).

The IL-23 inhibitor tildrakizumab, a monoclonal antibody used for treating moderate to severe psoriasis (36), has been proposed as a promising new therapeutic option for managing PASH syndrome (37). Gul et al. (38) reported remission of refractory PASH syndrome with a treatment regimen consisting of ixekizumab, an IL-17A inhibitor, and doxycycline (38). Guselkumab, an IL-23 inhibitor used for the treatment of moderate to severe plaque psoriasis (39), has also been reported in the literature as a therapeutic option for PASH syndrome (40).

Partial improvement was achieved in a patient with various treatment modalities, including isotretinoin, cyclosporine, azathioprine, and adalimumab (41).

In addition to biologic therapies, the management of PASH syndrome involves managing pyoderma gangrenosum and hidradenitis suppurativa (27). Some of the treatment options include oral antibiotics such as doxycycline, rifampin, moxifloxacin, amoxicillin, linezolid, and metronidazole, as well as immunosuppressants like cyclosporine, sulfasalazine, and corticosteroids (27). Immunomodulators, including thalidomide and dapsone, may also be employed, along with surgery (27).

Ead et al. (42) highlighted the significance of antibiotic use and wound care, suggesting that PASH syndrome may be a bacterial biofilm disease – a dysregulation of the host microbiota that leads to a chronic inflammatory state (27).

Systemic corticosteroids, in combination with azathioprine, cyclosporine, or mycophenolate, have been described in the literature as effective treatments in some cases (20, 43). Four patients with refractory PASH syndrome have achieved remission using target antibiotic therapy, which included different regimens including ceftriaxone, metronidazole, ertapenem, amoxicillin and other antibiotics (4, 44).

Given the high cost of newer therapies and/or the lack of disease control with adalimumab in our patient, we developed a therapeutic regimen that included antibiotics (ceftriaxone and metronidazole) and corticosteroids (methylprednisolone) during hospitalization, which resulted to an improvement in the pyoderma gangrenosum lesions. For outpatient management, the regimen was continued with an immunosuppressant (azathioprine) and corticosteroid (dexamethasone) resulting in an improvement.

PAPASH syndrome is characterized by the presence of pyoderma gangrenosum, acne, suppurative hidradenitis and pyogenic sterile arthritis, and is classified within the PAPA spectrum disorders (45). This syndrome is associated with missense mutations found in exons 10 and 11 of the PSTPIP1 gene (4, 45). A study reported successful treatment outcomes in two cases of PAPASH syndrome using infliximab and methotrexate (4, 46). In addition to the pyogenic arthritis, the other manifestations of the syndrome have been addressed in terms of their management.

CONCLUSION

We are currently in an era where innovative treatments, such as the monoclonal antibodies, for rare diseases and syndromes are emerging at a rapid pace. However, older treatment modalities should not be overlooked as they remain effective and are often more affordable than newer alternatives. In fact, conventional therapies and their treatment combinations are gaining renewed recognition, often proving to be the primary treatment option that patients may require.

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