PASS Syndrome: An IL-1-Driven Autoinflammatory Disease

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Introduction

Autoinflammatory diseases are characterized by a dysregulation of the innate immunity. They differ from autoimmune or allergic disease, because they are not characterized by circulating autoantibodies or autoreactive T cells \textsuperscript{[1]}. Their most prominent manifestation is a recurrent sterile inflammation. Typically, autoinflammatory diseases respond to anti-interleukin (IL)-1 or anti-IL-1 receptor (IL-1R) therapy.

In recent years, many genetic mutations have been discovered, involving in particular the inflammasome, a molecular platform responsible for the activation of caspase-1 which will cleave pro-IL-1\(\beta\) into functionally active IL-1\(\beta\) \textsuperscript{[1]}. IL-1\(\beta\) is a proinflammatory cytokine whose action seems to play a central role in the autoinflammatory process. It is expressed by monocytes, tissue macrophages, dendritic cells, B lymphocytes, NK cells and epithelial cells. Their signal transduction happens through the binding to receptors such as IL-1R1 and IL-1R2 and is antagonized by the IL-1Ra.

A main clinical feature of autoinflammatory skin disorders is neutrophilic infiltration of the skin in the absence of infection \textsuperscript{[2]}. There are several autoinflammatory disorders of the skin including the PAPA and the PASH syndrome: the PAPA syndrome (pyogenic arthritis, pyoderma gangrenosum and acne) is a hereditary au-
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...toinflammatory autosomal dominant disorder resulting from mutations in the PSTPIP1 gene located on chromosome 15. Such mutations cause a hyperphosphorylation of the protein PSTPIP1 which will promote the assembly and activation of the inflammasome [3]. The PASH syndrome described in 2012 by Braun-Falco et al. [3] is closely related to the PAPA syndrome. Specific manifestations include pyoderma gangrenosum, acne and hidradenitis suppurativa, but, in contrast to PAPA, joint involvement is absent. Interestingly a mutation in the PSTPIP1 gene itself has not been found, but an increased number of microsatellite repeats in the GTCC region of the PSTPIP1 promoter has been reported [3].

Case Report

A 32-year-old man of Congolese origin presented to our clinic with recurrent painful ulceration of both legs. The patient reported a history of recurrent nodules on the face, inguinal folds and scalp for which a skin graft was performed. In his medical history, the patient reported a prior hepatitis B infection and α-thalassemia. His familial medical history was negative.

The leg lesions had started as painful swellings 5 days prior and were paralleled by malaise and high fever (>39°C; fig. 1d). Due to the pain, the patient was unable to walk. A few days after the initial manifestation, the lesion spontaneously ulcerated and released purulent material. A detailed history revealed that the patient had suffered from similar outbreaks 4, 6 and 9 months previously, without any obvious trigger factor being identified. No vascular abnormalities were found.

The patient also reported episodes of severe hip and back pain. He had previously consulted a rheumatologist who diagnosed a seronegative axial spondylarthritides based on the finding of a spondylitis with bilateral sacroilitis on CT scan along malleolar periostitis. No osteitis or hyperostosis was detected. Rheumatoid factors, antinuclear antibodies in the serum and HLA-B27 genotype were negative. During the investigation, the patient had a colonoscopy which demonstrated no sign of inflammatory bowel disease. The patient was put on anti-tumor necrosis factor treatment (etanercept, Enbrel®), which was discontinued after 6 weeks due to the lack of a clinical response. HIV status was negative.

On physical examination, the patient had boils in the scalp region consistent with dissecting cellulitis of the scalp (fig. 1a). He also showed acne nodules and pustules on the face and the...
upper trunk in the absence of typical comedos (fig. 1c). In his inguinal folds, the patient presented with purulent inflammatory nodules consistent with his hidradenitis suppurativa (fig. 1b). A skin biopsy of the leg lesions revealed a dense neutrophilic infiltrate in the upper and lower dermis. No signs of vasculitis, arteriosclerosis or microthrombosis were detected on histology, and calcium stains were negative. Stains for infectious agents including Gram, Grocott, Ziehl-Neelsen and PAS were all negative along with sterile tissue cultures. No pathergy phenomenon was seen after the biopsy. The clinical aspect along with the abundant neutrophilic infiltrate in the absence of infections allowed us to diagnose pyoderma gangrenosum. This diagnosis was confirmed by laboratory tests which showed elevated white blood cell counts (14.2 × 10^9/l with 81% neutrophils), an increased sedimentation rate (82 mm/h) and elevated C-reactive protein levels (110 mg/l).

The patient presented right sternoclavicular, sacroiliac and back pain with synovitis in the sternoclavicular joint. A puncture of the right sternoclavicular joint revealed a sterile nonsuppurative inflammatory process consistent with the previously diagnosed ankylosing spondylarthritis. The association of pyoderma gangrenosum, acne vulgaris, hidradenitis suppurativa and ankylosing spondylitis led us to the diagnosis of PASS syndrome [4].

The periodic recurrence of the sterile neutrophilic skin lesions in association with a seronegative spondylarthritist was highly suggestive of an autoinflammatory process. Accordingly, we found high levels of IL-1β and IL-1Ra in the serum of the patient during periods of disease flares (8.82 and 8,611 pg/ml, respectively). Because a recombinant IL-1R antagonist (anakinra) is a treatment of the PAPA syndrome, which shares many features with the PASS syndrome, we chose to adopt this treatment modality (100 mg once/day) in our patient. Anakinra has the advantage to block both IL-1α and IL-1β signaling and may further support high levels of endogenous IL-1Ra produced in the patient’s serum.

A spectacular response of the skin lesions and the associated pain was observed starting on day 4 of treatment and lasted during the entire 1-month treatment. A complete clearance of the facial acne lesion and a remission of subcutaneous nodules of the leg were achieved. We also observed a clear improvement of the hidradenitis suppurativa lesions (decrease in Hurley stage from III to II and Sartorius scale from 59 to 45 points). The patient also noted a significant improvement of his joint pain (the numeric pain rating scale improved from 8 to 4 after only 4 days of treatment; fig. 2). After 1 month of inpatient treatment, the patient was discharged from hospital. Anakinra treatment was stopped because the patient left the country. Unfortunately, skin lesions relapsed after only 3 days, in particular the hidradenitis suppurativa and the dissecting cellulitis lesions of the scalp along with debilitating joint pain.

**Discussion**

We describe here a patient with the PASS syndrome. PASS has been recently reported in the literature as a new clinical entity characterized by pyoderma gangrenosum, acne vulgaris, hidradenitis suppurativa and ankylosing spondylitis [4]. Clinically this syndrome is distinct from the PAPA syndrome (pyogenic arthritis, pyoderma gangrenosum and acne) and the PAPASH syndrome (pyogenic arthritis, pyoderma gangrenosum, acne and hidradenitis suppurativa) because of the presence of a nonpyogenic joint involvement [5]. Also a PASH syndrome (pyoderma gangrenosum, acne and suppurative hidradenitis) is excluded as it does not have joint involvement.
The finding of a periodic recurrence of the disease along with elevated circulating IL-1β levels and clinical responses to IL-1β signaling blockade demonstrates that PASS belongs to the group of IL-1-driven autoinflammatory diseases, which include PAPA, PAPASH and PASH [3, 6, 7]. Whereas PAPA syndrome is a monogenic disorder with a well-described phenotype, this is not the case for the other entities. The similarities in the clinical presentation with overlapping manifestations raise the question whether PAPA, PAPASH, PASH and PASS are really truly distinct diseases or whether they simply represent distinct clinical expressions of the same disease characterized by aberrant IL-1 expression.

There is some evidence that distinct genetic mutations may underlie the specific disease manifestations of these autoinflammatory diseases. PAPA is associated with mutations of the PSTPIP1 gene, an enzyme that activates pyrin involved in the inflammasome assembly [3]. This mutation has not been found in PASH, which has however been associated with an increased number of GTCC microsatellite repeats in the PSTPIP1 promoter region [3], suggesting a similar pathogenic mechanism. PASH has been recently linked to a loss-of-function gene mutation of nicastrin (NCSTN), a γ-secretase gene involved in the notch signaling pathway, which appears to specifically determine the presence of hidradenitis suppurativa [8]. Whether a distinct gene mutation is present in PASS is currently unknown. Although mutations of the PSTPIP1 were not detected in our patient with PASS syndrome, it would be interesting to determine whether other mutations in the IL-1 activation or signaling pathway exist. In particular IL-1RN appears to be a good candidate as IL-1RN single-nucleotide polymorphisms have been found in ankylosing spondylitis [9].

Many different combinations of clinical entities belonging to these autoinflammatory syndromes have been reported. For example, acne vulgaris, which has an IL-1-driven autoinflammatory component as *Propionibacterium acnes* can directly trigger the assembly of the NLRP3 inflammasome [10–12], can be associated with spondylarthropathies [2]. The SAPHO syndrome describes a spectrum of inflammatory bone disorders including spondylarthropathies and skin manifestations including acne, pyoderma gangrenosum and hidradenitis suppurativa. However, the SAPHO syndrome is typically associated with ostitis, hyperostosis and palmpoplantar pustulosis, all of which were absent in our patient. The association between hidradenitis suppurativa and spondylarthriti has also been described in 59 patients [13]. Moreover, associations between hidradenitis suppurativa or dissecting cellulitis of the scalp with pyoderma gangrenosum are not infrequent [14]. A recent study demonstrated the association between hidradenitis suppurativa and the inflammatory bowel disease, especially Crohn’s disease [15].

In conclusion, the PASS syndrome is a distinct clinical entity that belongs to the spectrum of autoinflammatory diseases, which include PAPA, PAPASH and PASH syndromes (table 1). Like these other autoinflammatory diseases, PASS is associated with an aberrant expression of IL-1β and a striking clinical response to IL-1 signaling blockade. However, in contrast to PAPA, PAPASH and PASH, the genetic mutations underlying PASS are still elusive.

### Statement of Ethics

The patient has given written consent to publish his case.

### Disclosure Statement

The authors report no conflicts of interest or financial support.
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