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Pyoderma gangrenosum and its syndromic forms: Evidence for a link with autoinflammation

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SUMMARY

Pyoderma gangrenosum is a rare inflammatory neutrophilic dermatosis manifesting as painful ulcers with violaceous, undermined borders on lower extremities. It may occur in the context of classic syndromes like PAPA (pyogenic arthritis, pyoderma gangrenosum and acne) and SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndromes as well as in a recently described entity named PASH (pyoderma gangrenosum, acne and suppurative hidradenitis).

Pyoderma gangrenosum has recently been included within the spectrum of autoinflammatory diseases, which are characterized by recurrent episodes of sterile inflammation, without circulating autoantibodies and autoreactive T-cells. In PAPA syndrome, different mutations involving the PSTPIP1 (proline-serine-threonine phosphatase-interacting protein 1) gene, via an increased binding affinity to pyrin, induce the assembly of inflammasomes. These are molecular platforms involved in the activation of caspase 1, a protease which cleaves inactive pro-interleukin (IL)-1 beta to its active isoform IL-1 beta. The overproduction of IL-1 beta triggers the release of a number of proinflammatory cytokines and chemokines which are responsible for the recruitment and activation of neutrophils, leading to a neutrophil-mediated inflammation. In SAPHO syndrome, the activation of the PSTPIP2 inflammasome has been suggested to play a role in inducing the dysfunction of the innate immune system. PASH

patients have recently been reported to present alterations of genes involved in well known autoinflammatory diseases, such as PSTPIP1, MEFV (mediterranean fever), NOD2 (nucleotide-binding oligomerization domain-containing protein 2) and NLRP3 (NOD-like receptor family, pyrin domain containing 3). Pyoderma gangrenosum and its syndromic forms can be regarded as a single clinicopathological spectrum in the context of autoinflammation.

What's already known about this topic?

- Pyoderma gangrenosum is a rare neutrophilic dermatosis usually manifesting as painful ulcers with violaceous, raised and undermined borders on the legs.
- It presents alone or in the context of syndromic forms like PAPA (pyogenic arthritis, pyoderma gangrenosum and acne), PASH (pyoderma gangrenosum, acne and suppurative hidradenitis) and SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis).

What does this study add?

- Pyoderma gangrenosum and its syndromes have a peculiar immunologic profile suggesting autoinflammation.
- IL-1 β is crucial in the pathophysiology of autoinfllammatory/neutrophilic dermatoses, and its crosstalk with IL-17 may contribute to neutrophil recruitment and activation.
- IL-1 blockade represents the most selective treatment for pyoderma and its syndromes but, in the next future, also IL-17 antagonists could be considered.

Keywords

Pyoderma gangrenosum, PAPA syndrome, PASH syndrome, SAPHO syndrome, autoinflammation.

Introduction

Pyoderma gangrenosum (PG) is a rare inflammatory skin disease which, in its classical presentation (Figure 1), manifests as single or multiple painful ulcers with violaceous, raised, undermined borders on the legs.[1] PG can be associated with different conditions, notably inflammatory bowel diseases, haematological malignancies and rheumatological disorders, or can be idiopathic. It may precede, coexist or follow the different systemic diseases[1]. PG may occur in the context of syndromes like PAPA (pyogenic arthritis, PG and acne)[2,3] and SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis)[4] as well as in the recently described entity named PASH (PG, acne and suppurative hidradenitis).[5,6] PG represents the prototype of the neutrophilic dermatoses, which encompass a wide spectrum of conditions that are hallmarked by an accumulation of neutrophils in the skin and, rarely, internal organs.[7] The cutaneous manifestations of neutrophilic dermatoses are polymorphic, including pustules, abscesses, papules, nodules, plaques and ulcers, and almost any organ system can be involved, giving rise to the term "neutrophilic disease".[8] The definition of neutrophilic dermatoses is closely similar to that of autoinflammatory diseases, which are a heterogeneous group of disorders clinically characterized by recurrent episodes of sterile inflammation in the affected organs, in the absence of high titres of circulating autoantibodies or autoreactive T cells.[3] The classic monogenic autoinflammatory syndromes like PAPA are due to mutations of single genes regulating the innate immune response;[2,3] however, there is increasing evidence that mutations in different genes involved in autoinflammation are associated with other neutrophilic dermatoses.[9,10,11]

Here, we review the pathophysiology, clinical aspects and management of the syndromic forms of PG, focusing on their genetic profile as well as the expression of cytokines and other effector molecules involved in autoinflammation, in order to support the inclusion of PG and neutrophilic dermatoses in general in the spectrum of autoinflammatory diseases. This inclusion may provide the rationale for treatment aimed at blocking the cytokines crucially involved in autoinflammation.

Recent advances in pyoderma gangrenosum

Recent studies aimed at assessing cell and cytokine expression profile in lesional skin of PG by both immunochemistry and protein array methods have contributed to clarify some pathomechanisms of this disease.[12] The pivotal finding in the definition of the pathogenic pathways of PG is the over-expression of interleukin-1β (IL-1β) and its receptors in PG compared to healthy controls, linked theoretically to dysregulation of inflammasome function. This highly active pleiotropic cytokine is a leading actor in the autoinflammation[3,13-15] and plays a key role in triggering the neutrophilic inflammation of the skin. IL-1 is produced mainly by macrophages, T lymphocytes, endothelial cells, fibroblasts, and also by activated keratinocytes.[16,17] It is a well-known inducer of cytokines, notably proinflammatory cyotokines and chemokines, forming a network of cytokine-induced cytokines.[15] IL-1 promotes the production and release of both classic proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ), and a number of chemokines, notably IL-8 and RANTES (regulated on activation, normal T cell expressed and secreted).[15] Consistent with this, TNF-α, which also acts as a key regulator of other proinflammatory cytokines and chemokines, including the same IL-1β and IL-8,[18] was found to be over-expressed in lesional skin of PG. This finding provides the rationale for the use of

anti-TNF-α therapy in refractory PG or in PG associated with inflammatory bowel diseases (IBD).[19]

Several chemokines, such as IL-8, CXCL1,2,3 (Chemokine (C-X-C motif) ligand 1,2,3 [C=cysteine, X=any amino acid]), CXCL16 and RANTES, were over-expressed in PG lesional skin, promoting neutrophil transendothelial migration into the site of inflammatory process, which was also favoured by the up-regulation of L-selectin (leukocyte-selectin).[12]

Interestingly, an over-expression of IL-17 and its receptor in PG seemed to confirm the hypothesized role for this T helper type 17-related cytokine in the pathophisiology of the whole spectrum of neutrophilic dermatoses, similarly to psoriasis and other autoimmune diseases.[20-22] IL-17 amplifies the recruitment of neutrophils and monocytes by increasing the local production of chemokines, most notably IL-8,[23] and synergizing with various other cytokines, in particular with TNF-α.[24] At the same time, a reduced proportion of regulatory T cells (Tregs) in PG skin may be responsible for an impairment of suppressive activity, leading to the development of lesions and conditioning their severity.[25] In agreement with this cutaneous scenario, also peripheral blood from patients with PG showed an expression of chemokines and dendritic cell subsets supporting a definite lymphocyte polarization towards a Th1/Th17 phenotype with a Th2 and Tregs down-regulation.[26]

IL-17, together with IL-1 and TNF-α, induces the production of metalloproteinases (MMPs),[27] such as MMP-2 and MMP-9, synthesized by inflammatory cells, mainly neutrophils. An improper activity of MMPs causes tissue damage via degradation of the extracellular matrix and stimulates the production of chemokines, promoting neutrophil accumulation in the affected organs, including the skin.[20,28] The over-expression of MMP-9,

found in the inflammatory infiltrate of PG lesions, suggests that this proteinase and, to a lesser degree, MMP-2 may be significantly involved in inducing tissue damage in the whole spectrum of neutrophilic dermatoses. Interestingly, an overproduction of tissue inhibitor of metalloproteinase 1 (TIMP-1) and TIMP-2, which represents an inhibitory pathway of MMP-mediated inflammation, was found as well. Other important inhibitory signals that attenuate immune responses and dampen inflammation in PG, and in autoinflammation in general, are probably carried by Siglec 5 (sialic acid-binding immunoglobulin-type lectin-5) and Siglec 9, both over-expressed in PG lesional skin. In fact, Siglecs are inhibitory receptors expressed mainly by cells of the innate immune system that regulate inflammation mediated by damage-associated and pathogen-associated molecular patterns (DAMPs and PAMPs, respectively).[29]

Two other important systems, the Fas/FasL system and the CD40/CD40L system, may contribute to tissue damage and inflammation in PG. The Fas/FasL system belongs to the TNF/TNF receptor superfamily and to date is the best-known pathway mediating apoptosis.[30] The CD40/CD40L system also belongs to the TNF/TNF receptor superfamily. It represents a co-stimulatory system that amplifies the immune response and can promote inflammation via up-regulation of adhesion molecules and inducing the production of various cytokines and chemokines such as IL-1, TNF-α, IL-8 and RANTES.[31]

Overall, these data, showing high values of proinflammatory cytokines, chemokines and tissue damage effector molecules in patients with PG, support the view that the disease has an important autoinflammatory component in its patyhogenesis. Moreover, although a specific genetic background has not been proven for PG alone, mutations in genes involved in classic autoinflammatory diseases have been found, particularly in PSTPIP1,[9] and familial cases of

PG have been reported, further supporting the close links between this disease and autoinflammation.

Pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome

Pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome is a rare autosomal dominant disease first reported by Lindor et al. in 1997.[32] Clinically, PAPA syndrome is characterized by aseptic inflammation of the skin and joints.[33] Painful, recurrent, sterile monoarticular arthritis with prominent neutrophilic infiltrate usually occurs in childhood and may be the presenting sign of disease.[34] Elbows, knees and ankles are most often involved. Traumatic events may precipitate episodes of arthritis but recurrences can occur spontaneously. Persistent disease can cause joint erosions and destruction, even if in young adults joint symptoms tend to decrease while cutaneous symptoms become more prominent. Skin involvement is variable. Pathergy is common and pustule formation followed by ulceration may be induced early in life upon vaccination or minimal trauma. Severe nodulocystic acne and PG (Figure 2) tend to develop around puberty and may persist into adulthood.[2,33-35] Other dermatologic manifestations described in the setting of PAPA include rosacea and psoriasis.[34] Standard laboratory findings reflect systemic inflammation with leukocytosis and elevated acute phase reactants, but are otherwise non-diagnostic. Elevated production of IL-1β and TNFα in peripheral blood leukocytes has been reported.[36-37]

PAPA syndrome is the result of different mutations on chromosome 15q affecting the PSTPIP1 (proline-serine-threonine phosphatase-interacting protein 1) gene, previously known as CD2-binding protein 1 (CD2BP1).[37,38] PSTPIP1 mutations may interfere with its ability to phosphorylate targets including proinflammation pyrin domains.[2,35] The PAPA mutations originally identified in PSTPIP1, A230T and E250Q, are located in the F-BAR

domain.[2,39] These mutations cause assembly and activation of the inflammasome and consequent release of IL-1β.[2] The overproduction of IL-1β triggers the release of a number of proinflammatory cytokines and chemokines which are responsible for the recruitment and activation of neutrophils, leading to a neutrophil-mediated inflammation.[2,15] In addition, other PSTPIP1 adaptor functions may play a role in the pathogenesis of PAPA syndrome, such as WASP (Wiskott-Aldrich syndrome protein) and PTP-PEST (protein tyrosine phosphatase-proline [P], glutamic acid [E], serine [S], and threonine [T] sequence) which are regulators of the cytoskeleton and cell migration.[40-42] Indeed, mutations in PSTPIP1 that disrupt the interaction with PTP-PEST, such as A230T and E250Q, have been found to result in impaired chemotaxis and migration of macrophages, by negatively regulating podosome formation.[43] As podosomes also have extracellular matrix (ECM) degrading capabilities through the activity of matrix MMPs,[44] these same PSTPIP1 mutations do not correlate with matrix degradation. On the contrary, a PSTPIP1-R405C mutation recently identified in a patient with aggressive PG was shown both to regulate a transition from podosome formation to filopodia formation in macrophages, regulating in turn an invasive macrophage migration, and to correlate with increased matrix degradation.[45]

Medications targeting IL-1 and TNFα are usually successful in managing the manifestations of PAPA syndrome[46-48] Response to the IL-1 receptor antagonist anakinra appears to be particularly effective in the management of PAPA joint manifestations.[49] Other two currently available anti-IL-1 drugs may also be considered, namely canakinumab, a fully human monoclonal IgG1anti-IL-1β antibody, and rilonacept, a dimeric fusion protein that binds and neutralizes IL-1.[50] Topical and systemic retinoids have been effective in combination with biologic agents for the management of severe acne.

Synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO)

SAPHO is an acronym for synovitis, acne, pustulosis, hyperostosis and osteitis.[4] There are several published diagnostic criteria for this entity, the most frequently mentioned of whom are those proposed by Kahn and Khan in 1994 as i) multifocal osteitis with/without skin symptoms, ii) sterile acute/chronic joint inflammation with either pustules/psoriasis of palms/soles, or acne or hidradenitis suppurativa (HS), and iii) sterile osteitis and any one of the above skin manifestations, with any one of the criteria being sufficient for the diagnosis.[51]

SAPHO syndrome is generally considered to be a rare condition, possibly due to being underdiagnosed. Clinical features occur mostly in young and middle-aged persons. Sex ratio is thought to be equal, though a slight female preponderance has been noted in some series.[52,53] The disease is mostly self-limiting, lasting about 4–5 years on average. Female gender, elevated erythrocyte sedimentation rate and C-reactive protein values, anterior chest wall involvement, peripheral synovitis and skin involvement at the onset are associated with a chronic course.[4]

The clinical features are heterogeneous and overlaps with other disease entities, due to which, diagnosis can be hard to establish. In general, the association of non-infectious, inflammatory osteitis with palmoplantar pustulosis (PPP) skin lesions is a finding of key importance for diagnosis. Skin and bone lesions may present at different times. The cutaneous manifestations are those of different neutrophilic dermatoses. The most common one is PPP, including pustular psoriasis, representing 50% to 75% of all dermatologic manifestations and affecting close to 60% of patients with extended follow-up.[54] Psoriasis vulgaris may also be included among the dermatologic manifestations of SAPHO. Severe acne, namely acne conglobata and fulminans, affects approximately one fourth of patients with SAPHO syndrome, with men

clearly predominating.[52,53] Men also predominate among the cases of SAPHO syndrome that have been reported in association with HS.[52,53,55]

Other rare cutaneous manifestations of the SAPHO syndrome include PG, Sweet's syndrome and Sneddon–Wilkinson disease.[51-56] Associations of SAPHO syndrome and IBD seem to be not rare, especially in Crohn's disease.[57]

There are no laboratory tests that are diagnostic of SAPHO. They can be normal or may show elevated inflammatory markers and elevated levels of components of complements C3 and C4. Mild leukocytosis and mild anemia were observed as well. Compared to healthy controls, patients can have elevated levels of immunoglobulin A.[58]

Although its pathogenesis is still elusive, there is increasing understanding that SAPHO shares similarities with other AIDs. Proinflammatory cytokines, such as IL-1β and TNFα as well as the chemokine IL-8 are deemed to be important in the pathogenesis of SAPHO.[58-60] The dysregulation of P2X7–IL1β axis is hypothesized to lead to an increased release of IL1β, as found in other AIDs.[61] Increasing evidence points to the P2X7R as a main player in Th17 differentiation and IL-17 secretion too.[62] In line with these findings, Th17 were recently found to be increased in peripheral blood of SAPHO subjects.[63]

Hereditary basis of SAPHO has been supported by the finding of familial clustering cases,[64] but no specific mutations have been found in SAPHO patients. Proline-serine-threonine-phosphatase-interacting protein 2 (PSTPIP2), which is involved in macrophage activation, neutrophil motility and osteoclast differentiation, has been recently supposed to play a role in innate immunity and development of autoinflammatory bone disorders, including SAPHO

syndrome. Other genes potentially involved in the SAPHO syndrome are located in the chromosome 18: LPIN2 (Lipin 2) and NOD2 (nucleotide-binding oligomerization domain-containing protein 2).[65] Furthermore, SAPHO syndrome is supposed to be associated with mutations of IL1RN causing deficiency of the interleukin-1 receptor antagonist. Finally, different types of pathogens have been isolated from different bone sites and pustules in the skin, mostly *Propionibacterium acnes (P. acnes).*[66,67] At present, *P. acnes* is regarded as an antigenic trigger for autoinflammatory responses, inducing a sclerotic and hyperostotic reaction as well as neutrophilic skin disorders.

To date, no randomized controlled clinical trials have been conducted to evaluate the efficacy of individual therapeutic modalities. Intra-articular or systemic corticosteroids are effective in the majority of patients.[68] Disease modifying antirheumatic drugs (DMARDs) such as methotrexate, sulfasalazine, cyclosporine and leflunomide have been widely used obtaining variable results.[54,69] Considering the hypothesized role of *P. acnes* in the pathogenesis of SAPHO syndrome, antibiotic treatment, in particular doxycycline, can be another treatment option.[52-54,66] Bisphosphonates, especially pamidronate, which act by inhibiting bone resorption and turnover, and by possible anti-inflammatory activity, have rapid but transient activity of pain relief in a part of these patients and may lead to partial or complete sustained remission over time.[70] Various case series and reports stated the use of anti-TNF-α agents as a therapeutic option for SAPHO cases unresponsive or refractory to conventional drugs.[71] In resistant SAPHO cases, the IL-1 antagonist anakinra has also been successfully used.[72]

Pyoderma gangrenosum, acne and suppurative hidradenitis (PASH)

The clinical triad of PG, acne, and suppurative hidradenitis (PASH) has been recently described and proposed to be an autoinflammatory syndrome.[10] Absence of pyogenic sterile arthritis (PA) distinguishes PASH syndrome from PAPA syndrome. Both PG and hidradenitis suppurativa (HS) (Figure 3) are prototypic neutrophilic dermatoses that are themselves diseases nowadays regarded as autoinflammatory in origin.[73-75] HS is an inflammatory chronic skin disease involving the folliculopilosebaceous units characterized by nodules, cysts, abscesses, draining sinuses and secondary retracting scars in apocrine gland-bearing sites.[76] Acne is a clinically polymorphic disease characterized by a complex pathophysiology in which there is a disorder of keratinization with abnormal sebaceous stem cell differentiation. However, in its pathogenesis, an autoinflammatory component induced by *P. acnes* via inflammasome activation has been recently demonstrated,[77-79] linking acne to classic autoinflammatory diseases (AIDs).

Whether PASH is a monogenic disorder and involves pleiotropic mutations in a single gene leading to all clinical manifestations, or corresponds to combined different diseases remains to be determined. PASH patients are characterized by a polymorphic profile with genetic alterations previously described in other well-known AIDs. In detail, a number of genetic alterations involving the innate immunity have been found in PG, HS, and their syndromic forms, in particular mutations of the PSTPIP1 gene in PG and impaired Notch–MKP-1 (mitogen-activated protein kinase phosphatase-1) signaling and loss-of-function mutations in the γ-secretase genes, Nicastrin (NCSTN), Presenilin Enhancer-2 (PSENEN), and Presenilin-1 (PSEN1), in HS.[2,11,37,79-84] Involvement of innate immunity dysfunction in both PG and HS is also supported by immunological studies.[12,37,81,85,86]

In the two first reported PASH patients an increased number of CCTG repeats (>5) in the PSTPIP1 promoter was described.[5] The presence of alleles carrying higher number of the repeats of CCTG motif close to the PSTPIP1 promoter likely deregulates PSTPIP1 expression and may also predispose to forms of neutrophilic inflammation as in aseptic abscesses with/without Crohn disease.[87,88] Thus, this microsatellite may be involved in these inflammatory disorders and act as a modifier gene, although it is probably not causal since it is found in controls.[87]

In a recent observational study conducted by some of us on 5 patients with PASH syndrome,[10] 9 gene mutations found in these case series were already reported in the single-nucleotide polymorphism (dbSNP) database (http://www.ncbi.nlm.nih.gov/snp/), and 7 of them are additionally present in the registry of hereditary autoinflammatory disorders mutations (INFEVERS; http://fmf.igh.cnrs.fr/ISSAID/infevers/). Overall, 4 out of these 5 PASH patients presented genetic alterations typical of well-known AIDs, including IBDs, and the only patient lacking genetic changes had a clinically evident Crohn disease. In particular, mutations, of the MEFV (mediterranean fever) gene have already been associated with typical symptoms of recessive familial Mediterranean fever (FMF) and mutations of the NOD2 (nucleotide-binding oligomerization domain-containing protein 2) gene were found to be intermittently associated with susceptibility to Crohn disease.[27,89]

Concerning the neutrophilic inflammation pathways of PASH syndrome, a recent study analyzed the expression profile of cytokines, chemokines, and other effector molecules in both PG ulcerative lesions and peripheral blood of PASH patients by means of a protein array method and enzyme linked immunosorbent assay (ELISA), respectively.[10] As in idiopathic PG, the overexpression of IL-1β and its receptors was the main finding. As previously

emphasized, this highly active pleiotropic cytokine is a leading actor in the AIDs[3,15] and plays a pivotal role in triggering the neutrophilic inflammation of the skin by promoting the production and release of proinflammatory cytokines and chemokines. Accordingly, TNF-α and several chemokines such as IL-8, CXCL 1/2/3, CXCL16, and RANTES were found to be overexpressed in PG lesions of PASH patients.[10]

An overexpression of IL-17 and its receptor was documented too, confirming the previously hypothesized role for this T-helper 17-related cytokine in the pathophysiology of the whole spectrum of neutrophilic dermatoses.[20-22] IL-17 amplifies the recruitment of neutrophils and induces tissue damage via MMPs production.[27] Two further important systems, the Fas/Fas L system and the CD40/CD40 ligand system, seem to contribute to tissue damage and inflammation in PASH. Taken together, these findings show that the same profile of cytokines and other effector molecules, demonstrated in PASH, was also previously found in PG occurring outside syndromic forms,[12] supporting the autoinflammatory nature of PASH.

In peripheral blood, the serum levels of the main proinflammatory cytokines, that is, IL-1β, TNF-α, and IL-17, were within the normal range, suggesting that in PASH syndrome the inflammatory process is mainly localized into the skin.[10]

Treatment of PASH patients can be problematic and challenging. Classic immunosuppressive regimens, such as systemic glucocorticosteroids and azathioprine, dapsone, and isotretinoin can fail to obtain a satisfactory control of the disease.[5] The TNF-α blockers infliximab and adalimumab were found to provide a remarkable clinical improvement of cutaneous picture, mostly of PG and acne lesions.[5,6,90,91] Anakinra, even combined with cyclosporine, can be of great benefit, too.[5,92]

Pathophysiology of autoinflammation

The term ‘‘autoinflammatory syndrome’’ was initially introduced after the identification of the genetic causes of the most prevalent monogenic autoinflammatory disease worldwide, the autosomal recessive disease, familial Mediterranean fever (FMF), and the discovery of TNF receptor mutations in the autosomal dominant disorder, TNF receptor associated periodic syndrome (TRAPS) in 1999.[93] Since then, the number of identified autoinflammatory diseases has increased substantially. Several of the mutations associated with autoinflammatory disorders occur in the IL-1β pathway.[94] IL-1β is a proinflammatory cytokine and can induce tissue damage when levels reach a critical threshold.[95] Inflammasomes are molecular platforms involved in the activation of the caspase 1, a protease which cleaves the functionally inactive pro-IL-1β to its active isoform IL-1β.[96] The first event leading to inflammasome activation is the presence in the extracellular environment of either molecules associated to cell damage or pathogen infections, recognized by specific receptors.[97] The overproduction of IL-1β triggers the release of a number of proinflammatory cytokines and chemokines which are responsible for the recruitment and activation of neutrophils, leading to a neutrophil-mediated inflammation (Figure 4).[15,20,92]

Other autoinflammatory diseases mediated by IL-1 overproduction which are worthy of mention because of their skin involvement, namely urticarial lesions, are cryopyrin-associated periodic syndromes (CAPS).[98,99] CAPS, also called cryopyrinopathies, are classified as three distinct entities, namely familial cold autoinflammatory syndrome (FCAS), Muckle-Wells Syndrome (MWS) and chronic infantile neurological cutaneous and articular syndrome (CINCA), also known as NOMID (neonatal-onset multisystem inflammatory disease). The three entities of CAPS group represent a clinical spectrum of autosomal dominant disorders caused by different mutations in a single gene, NLRP3, encoding for

cryopyrin, a crucial inflammasome protein that directly activates IL-1β. Another severe, early-onset entity named ‘‘deficiency of the interleukin-1 receptor antagonist’’ (DIRA) is characterized by homozygous mutations in the IL1RN (interleukin 1 receptor antagonist) gene, which encodes a circulating antagonist to IL-1ß signaling.[99,100] The secretion of a nonfunctional anti-IL-1ß antagonist leads to hyperresponsiveness of inflammatory cells to IL-1ß stimulation. From a clinical point of view, DIRA is characterized by generalized pustulosis, periostitis, and osteomyelitis with negative bone-tissue culture. DITRA is an acronym for “deficiency of the IL-36 receptor antagonist (IL-36Ra)”. Interleukin 36Ra is an IL-1 family member that antagonizes the proinflammatory signals of IL-36α, IL-36β, and IL-36γ in a manner analogous to the effect of IL-1Ra inhibition on IL-1 responses.[101] Mutations in the gene encoding the IL-36 receptor (IL-36R) antagonist, IL-36RN, are responsible for familial and sporadic cases of generalized pustular psoriasis, high fever, and systemic inflammation.

An important contributing role in autoinflammation is played by IL-17 which is also a leading actor in neutrophil recruitment and activation.[102] As such, therapeutics that target IL-1β or antagonize the IL-1β receptor are effective in the treatment of PG and its syndromic forms as well as a number of other autoinflammatory diseases.[92,103,104] Targeting IL-17 may also be considered in future perspectives.

Conclusions

All the autoinflammatory syndromes described above, including PAPA, SAPHO and PASH, may be regarded as variants belonging to a single clinicopathological spectrum having abnormal activation of innate immunity as the crucial pathogenetic event (Figure 5). The evidence that autoinflammation-associated cytokines like IL-1β and IL-17 are upregulated in

the lesional skin of these syndromic forms of PG supports their autoinflammatory origin. Similarly, IL-1β and IL-17 overexpression has been detected in PG occurring outside the context of these autoinflammatory syndromes as well as in other neutrophilic dermatoses like Sweet's syndrome,[12] amicrobial pustulosis of the folds[105] and hidradenitis suppurativa.[102] Thus, with respect to the involvement of the innate immune response, it seems justified to assign neutrophilic dermatoses to the growing family of autoinflammatory diseases.

Disease-based gene discovery and basic research continue to go hand in hand in deciphering the molecular mechanisms that lead to excessive innate immune responses and cause autoinflammatory phenotypes. Future research is expected to identify environmental and intrinsic sources of variation, identify new inflammatory mediators, and examine the basis for organ-specific inflammation. Growing insights into autoinflammatory syndromes' pathogenesis will provided us with novel therapeutic targets that allow us to effectively treat these conditions.

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FIGURE LEGENDS

Figure 1. Ulcers of pyoderma gangrenosum (panel A and B). In panel B, a healing pyoderma gangrenosum ulcer is evident.

Figure 2. Pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome presenting with acne (panel A) and ulcerative pyoderma gangrenosum (panel B).

Figure 3. Pyoderma gangrenosum, acne and suppurative hidradenitis (PASH) syndrome. Hidradenitis suppurativa lesions involving the intermammary flexure (panel A), anogenital region (panel B) and axillary fold (panel D). Ulcerative pyoderma gangrenosum on the leg (panel C).

Figure 4. Pathophysiological model of autoinflammation. Mutations of a gene regulating the innate immunity like PSTPIP1 (proline-serine-threonine phosphatase-interacting protein 1) induce, via an increased binding affinity to pyrin, an activation of the inflammasome. This molecular platform is responsible for the activation of caspase-1, an enzyme which

proteolitically cleaves pro-IL-1β (pro-interleukine-1β) to its active isoform IL-1β. This pivotal cytokine is thus overproduced, leading to an uncontrolled release of a number of proinflammatory cytokines (particularly IL-17), chemokines and other effector molecules responsible for the neutrophil-mediated autoinflammation. Inhibitory signals carried by molecules like TIMP-1 (tissue inhibitor of metalloproteinase-1), TIMP-2, Siglec-5 (sialic acid-binding immunoglobulin-type lectin-5) and Siglec-9 represent an attempt to dampen inflammation. L-selectin = leukocyte selectin; E-selectin = endothelial selectin; MCP-1 = monocyte chemotactic protein 1; RANTES = regulated on activation, normal T cell expressed and secreted; CXCL = Chemokine (C-X-C motif) ligand [C=cysteine, X=any amino acid]; MMP = matrix metalloproteinase; Fas = Fas protein also known as CD95; FasL = Fas ligand also known as CD178; CD40 = cluster of differentiation 40; CD40 L = CD40 ligand.

Figure 5. Spectrum of the syndromic forms of pyoderma gangrenosum (PG) in the context of autoinflammation. SS = Sweet's syndrome; HS = hidradenitis suppurativa; APF = amicrobial pustulosis of the folds; PAPA = pyogenic arthritis, pyoderma gangrenosum and acne; SAPHO = synovitis, acne, pustulosis, hyperostosis, osteitis; PASH = pyoderma gangrenosum, acne and suppurative hidradenitis.

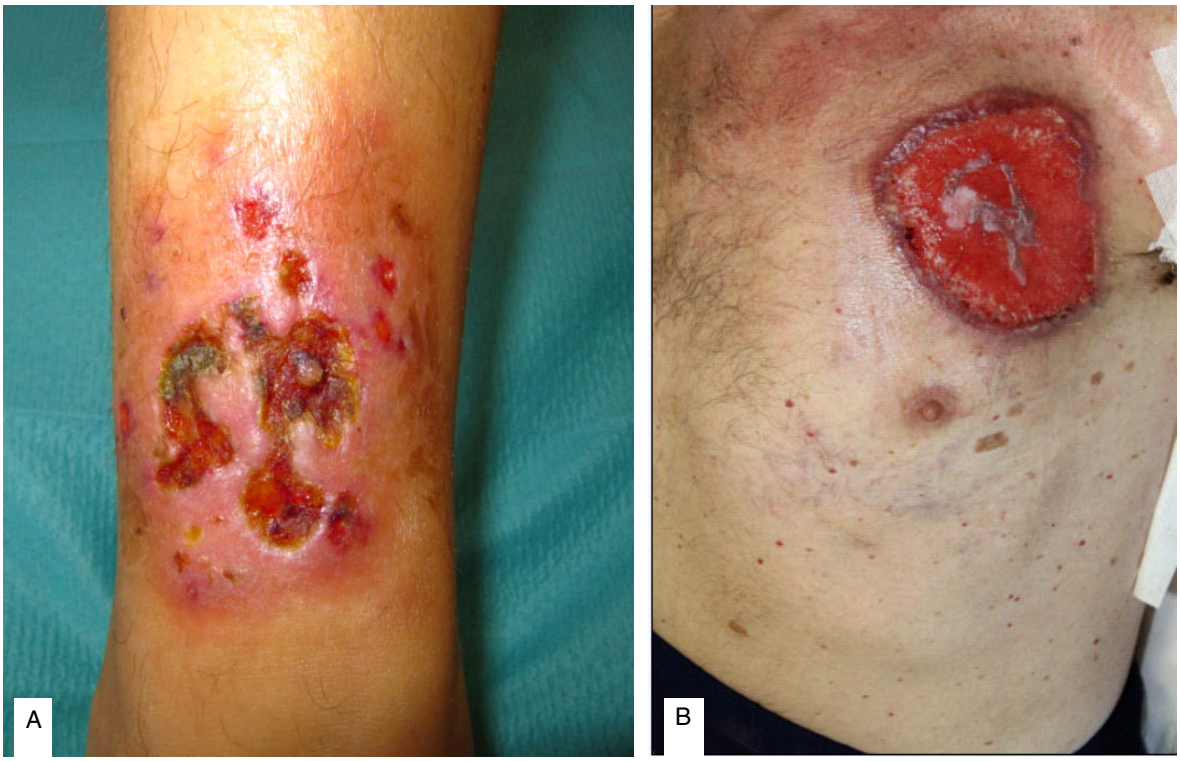


Figure 1

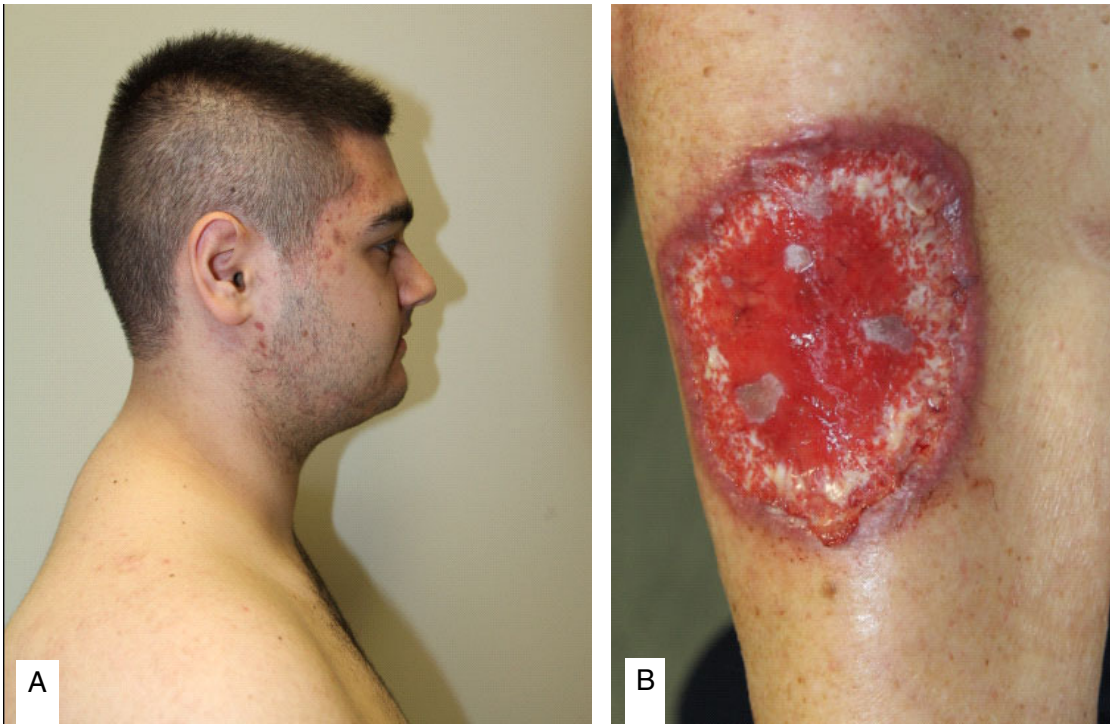
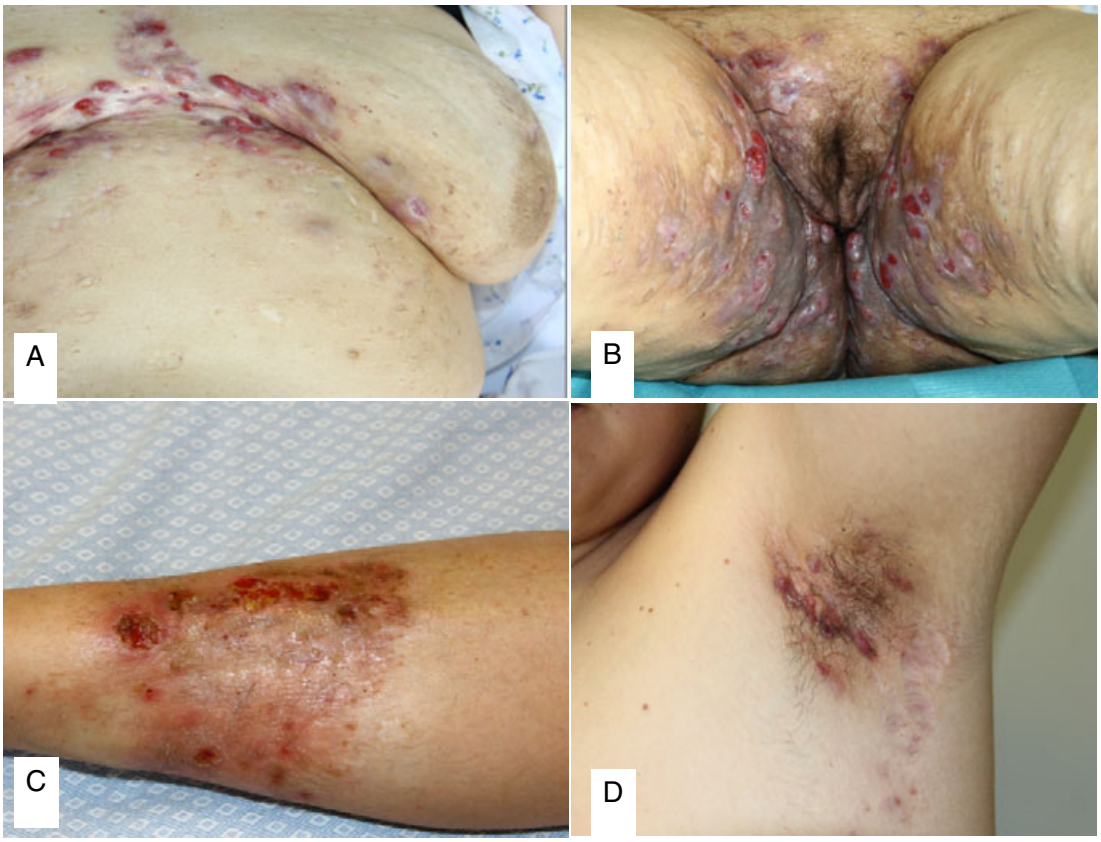


Figure 2



Figure

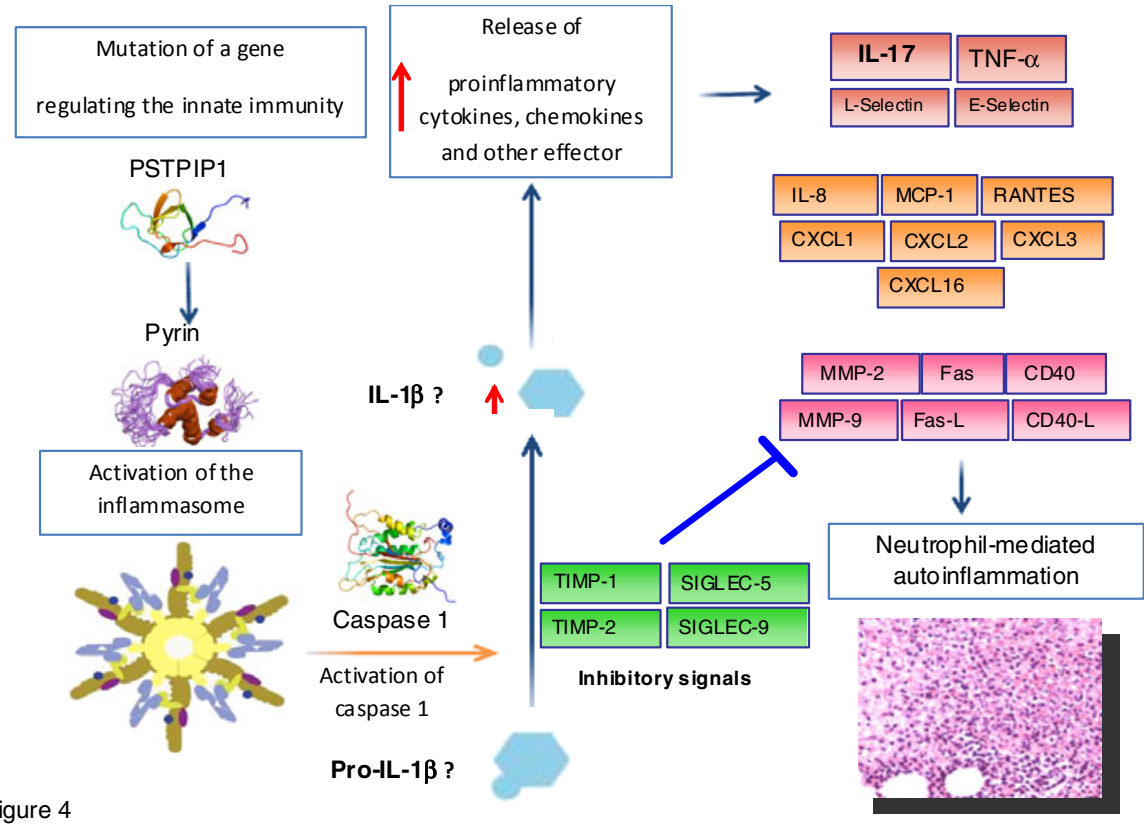


Figure 4

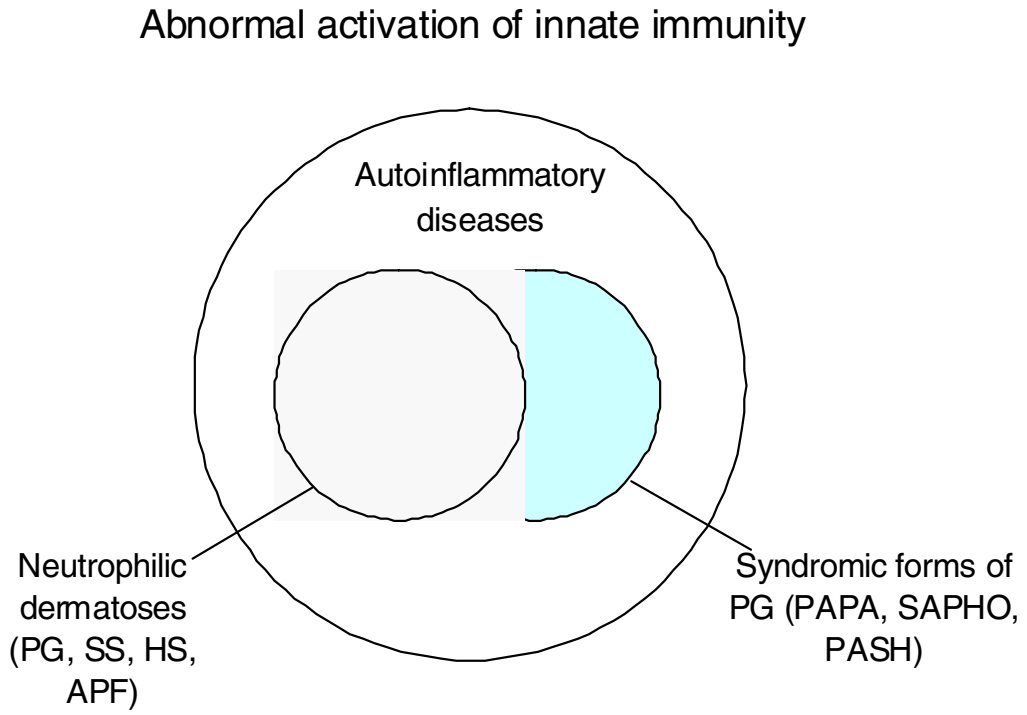


Figure 5