

A dermatologic perspective on autoinflammatory diseases

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ABSTRACT

Autoinflammatory diseases (AIDs) encompass a heterogeneous group of disorders pathogenetically related to an abnormal activation of the innate immunity and clinically characterised by aseptic inflammation in the affected organs in the absence of high titre of circulating autoantibodies or autoreactive T cells. In classic monogenic AIDs, the skin is frequently involved with a wide range of cutaneous lesions. Monogenic AIDs result from different mutations in a single gene, which regulates the innate immunity. These mutations cause an uncontrolled activation of the inflammasome, leading to an overexpression of interleukin (IL)-1 β . IL-1 β is the pivotal cytokine which is responsible for the exaggerated production of cytokines and chemokines that induce the recruitment of neutrophils, key cells in autoinflammation. Paradigmatic autoinflammatory forms are the cryopyrin-associated periodic syndromes (CAPS), whose skin involvement consists of urticarial lesions. Similar IL-1 β -mediated autoinflammatory pathomechanisms also occur in deficiency of IL-1 receptor antagonist (DIRA) and deficiency of IL-36 receptor antagonist (DITRA), whose cutaneous appearance is characterised by pustular lesions, as well as in pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome. Pyoderma gangrenosum, which is the cutaneous hallmark of the PAPA syndrome, is a prototypic neutrophil-mediated skin disease, manifesting as single or multiple ulcers with undermined, raised erythematous to violaceous borders. This review is focused on the CAPS, DIRA/DITRA and PAPA syndromes with emphasis on their cutaneous manifestations, as well as their histology and pathophysiology.

Introduction

Autoinflammatory diseases (AIDs) are a heterogeneous group of disorders that are pathogenetically related to a dys-

regulation of the innate immunity and clinically characterised by recurrent episodes of sterile inflammation in affected organs in the absence of infection, allergy, and high titre of circulating autoantibodies or autoreactive T cells (1, 2). The skin is one of the major organs involved in classic monogenic AIDs, with a wide range of cutaneous lesions occurring. Monogenic AIDs, for which a typical example is the cryopyrin-associated periodic syndromes (CAPS), are due to different mutations involving a single gene regulating the innate immune response (3-8). In CAPS, these mutations cause an aberrant activation of the inflammasome, which is a molecular platform that plays a pivotal role in autoinflammation as it induces the overexpression of the key proinflammatory cytokine, interleukin (IL)-1 β (3-8). Excessive amounts of IL-1 β triggers the uncontrolled release of a number of cytokines and chemokines, which act synergistically with IL-1 β inducing the autoinflammatory process. The autoinflammatory process is mainly mediated via the recruitment and activation of neutrophils, which are central mechanistic components of the AIDs (3-8). Urticarial lesions, which present alongside periodic fever and other systemic symptoms and signs characteristic of CAPS, may be regarded as the skin hallmark of these conditions (9). A similar inflammatory scenario occurs as a consequence of inherited gain-of-function mutations in genes encoding the IL-1 receptor antagonist (IL-1RA) (10) and the IL-36 receptor antagonist (IL-36RA); these mutations give rise to two disorders known as deficiency of the interleukin-1 receptor antagonist (DIRA) and deficiency of interleukin thirty-six-receptor antagonist (DITRA), respectively (11). Similar to CAPS, the cutaneous picture of DIRA and DITRA is monomorphic but is characterised by a pustular presentation (10, 11). There is an increasing body of evidence that autoinflammation is the physiopatho-

logical explanation of many polygenic cutaneous diseases, and in particular neutrophilic dermatoses. These are a spectrum of disorders hallmarked by an accumulation of neutrophils in the skin and rarely in internal organs, which are clinically characterised by polymorphic skin lesions (12-14). Pyoderma gangrenosum (PG), the prototype of neutrophilic dermatoses, also occurs in the context of syndromic forms, one of which, namely pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA), is a well-known monogenic autoinflammatory syndrome (15-18). In this review, we will focus on CAPS, DIRA/DITRA and syndromic PG, with emphasis on cutaneous manifestations as well as their histopathological features and pathophysiological mechanisms.

Cryopyrin-associated periodic syndrome (CAPS)

CAPS is an umbrella term for three phenotypes that increase in severity from familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome to chronic infantile neurological, cutaneous and articular syndrome (CINCA), which is also known as neonatal-onset multisystem inflammatory disease (NOMID) (3-7, 19-22). These three entities of the CAPS group represent a clinical continuum of autosomal dominant disorders caused by a number of different mutations in a single gene, *NLRP3* (nucleotide-binding oligomerisation domain [NOD]-like receptor family, pyrin domain containing 3). More than 175 different mutations in *NLRP3*, mainly concentrated in exon 3, have been associated with the three CAPS phenotypes and reported in the registry of hereditary autoinflammatory disorder mutations, Infefers (<http://fmf.igh.cnrs.fr/ISSAID/infefers/>) (23, 24). *NLRP3* encodes the protein, cryopyrin, which is responsible for the uncontrolled overproduction of IL-1 β via the inflammasome (23).

Cutaneous features: urticarial presentation

The urticarial rash affects almost all patients with CAPS and shows similar aspects in all three CAPS phenotypes (25, 26). Individual lesions are rose or red

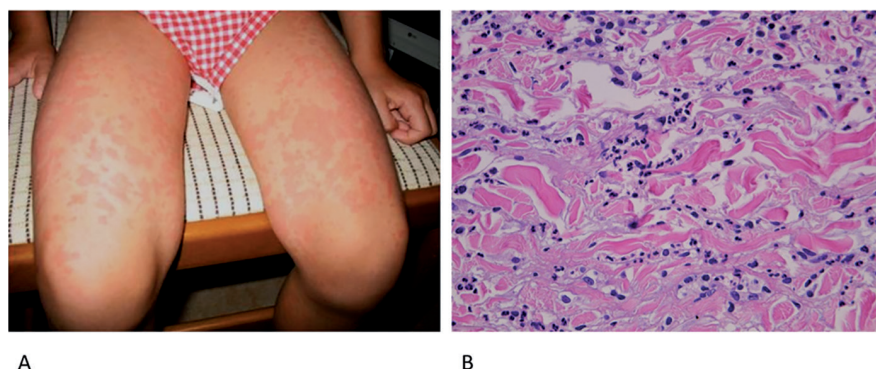


Fig. 1. Cryopyrin-associated periodic syndromes (CAPS).

(A) Urticarial rash characterised by erythematous and confluent wheals on the thighs of an adolescent with Muckle-Wells syndrome. Notably, lesions have a symmetrical distribution. (B) Histopathological aspects: dense neutrophilic perivascular and interstitial inflammatory infiltrate. Courtesy of Dr Angelo Cassisa.

macules or slightly elevated papules or plaques that predominantly involve the trunk and less frequently the lower and upper limbs. The lesions may sometimes display an annular configuration and a peripheral halo of vasoconstriction can rarely be seen. Individual lesions usually heal within 24 to 48 hours without scarring or residual hyperpigmentation; more solid and persistent lesions, that mimic the wheals in urticarial vasculitis, can also develop (Fig. 1A). The lesions often have a symmetrical distribution and, similarly to urticarial vasculitis, they are associated with pain or burning sensation rather than itching; pruritus, if present, is only slight. The skin eruption generally occurs as recurrent crops but may also follow a chronic course in some patients. It is notable that in FCAS, the urticarial eruption is triggered by cold exposure and accompanied by fever spikes, headache, and fatigue as well as arthralgia and conjunctivitis (25).

Histopathological aspects

The histological pattern of the CAPS urticarial lesions consists of a dense neutrophilic perivascular and interstitial inflammatory infiltrate (25-27). Leukocytoclasia is frequently observed but fibrinoid necrosis of dermal small vessel wall is always absent, which is an important clue to differentiate the histology of CAPS from that of urticarial vasculitis. Dermal oedema, which is the typical finding of chronic spontaneous urticaria histology, is also absent. Lipsker and colleagues coined

the term “neutrophilic urticarial dermatosis” (Fig. 1B) to define the clinicopathological features which characterise the skin involvement in CAPS but are also seen in association with lupus erythematosus and adult-onset Still’s disease (25, 26). Finally, non-specific histological aspects occur in CAPS patients presenting with only flat wheals or erythema (9).

Differential diagnosis

Urticarial vasculitis and common urticaria are the main differential diagnoses of CAPS urticarial lesions. Urticarial vasculitis is a small vessel vasculitis with predominant skin involvement manifesting as wheals that persist for more than 24 hours (9, 28). In urticarial vasculitis, the wheals resolve leaving an ecchymotic-hyperpigmented patch; other cutaneous manifestations, including livedo reticularis, purpura, bullae, and necrotic-ulcerative lesions, may also be present. Skin biopsy is crucial for a differential diagnosis since the urticarial vasculitis histology shows a pattern typical of leukocytoclastic vasculitis. Common urticaria is a frequent disease that is subdivided into acute and chronic forms. Chronic spontaneous urticaria cases resistant to conventional antihistamine treatment may be difficult to differentiate from CAPS cases. However, unlike chronic spontaneous urticaria patients, CAPS patients generally do not suffer from intense itching, lack wheals with surrounding flare and their urticarial lesions tend to be symmetrically distributed. Histol-



Fig. 2. Deficiency of IL-36 receptor antagonist (DITRA).

(A) Widespread eruption consisting of erythematous, polycyclic lesions covered by pustules. (B) Detail of the pustular lesions. (C) Histology showing parakeratotic hyperkeratosis and acanthosis associated with intraepidermal spongiform pustules. Courtesy of Dr Raffaele Gianotti.

ogy, as previously mentioned, as well as the presence of systemic symptoms and signs in CAPS are important clues for a differential diagnosis (9).

Deficiency of IL-1 receptor antagonist (DIRA) and deficiency of IL-36 receptor antagonist (DITRA)

In 2009, DIRA was described both clinically and genetically as an autosomal recessive autoinflammatory disorder (10) in which a homozygous mutation led to a loss of function in IL1RN, the gene encoding the IL-1RA (29). Mutation provokes a lack of contrasting IL-1 signalling, resulting in an uncontrolled systemic inflammation. Heterozygous carriers are asymptomatic (29). Patients present in the neonatal period with systemic inflammation, manifested by elevations of acute phase reactants, as well as bone and skin inflammation. One third of children are born small for their gestational age, with evidence of an intrauterine onset. Infants can also develop a life-threatening systemic inflammatory response syndrome due to uncontrolled escalating inflammation. In 2011, a mutation in the IL-36 receptor antagonist gene (IL-36RN) was identified in nine Tunisian families (11). The mutation had an autosomal recessive behaviour which lead to a clinical phenotype suggesting generalised pustular psoriasis. The gene IL-36RN is located on chromosome 2 and encodes the IL-36RA, which binds the IL-36R causing a negative feedback in IL-36 signalling (11). IL-36 belongs to the IL-1 family cytokine and by binding the IL-36 receptor enables the transduc-

tion via nuclear factor kappa B (NFkB) and mitogen activated protein (MAP) kinases (29). Deficiency of IL-36RA leads to an exaggerated inflammatory response, analogous to that resulting from IL-1RA deficiency in patients with DIRA, and further implicates the relevance of these pathways in pustular disease pathogenesis (11). Mutations in IL-36RN have been reported to account for 46% to 82% of cases of generalised pustular psoriasis without associated plaque psoriasis (30, 31), suggesting there is an overlap between DITRA and the generalised variant of pustular psoriasis.

Cutaneous features: pustular presentation

Both DIRA and DITRA manifest as clearly defined, raised bumps on the skin that are filled with pus (pustules) (10, 11). Skin pathergy may be elucidated by mechanical injury on the skin and leads to the development of the pustular lesions. Severity of cutaneous presentation ranges from rare pustules to a disseminated pustulosis resembling the generalised variant of pustular psoriasis (Figs. 2A and 2B). Psoriatic nail changes, such as pitting and onychomadesis, may also be present. Ichthyosis may also enrich the cutaneous findings (10, 11). Interestingly, DIRA pustular eruption can anticipate systemic complications such as respiratory insufficiency and thrombotic events. However, mortality secondary to multi-organ failure has rarely been reported. Bone changes are typical clinical findings of DIRA and include epiphyseal

ballooning of long bones, anterior rib-end widening, periosteal elevation of long bones, and multifocal osteolytic lesions. Central nervous system involvement manifesting as vasculitis may rarely be seen (10). DITRA is clinically suspected when, early in childhood, a patient displays recurrent and severe generalised pustular psoriasis that is enriched by systemic symptoms such as fever, asthenia, and laboratory markers including neutrophilia and elevated inflammatory markers (11). Although the disease usually occurs in childhood, its occurrence in some adults has also been described. Mortality is a possible complication due to the large disruption of the skin barrier and consequent septicaemia (10, 11). Interestingly, DITRA patients do not experience other subtypes of psoriasis consolidating the view that the causative mutation provokes a specific clinical phenotype.

Histopathological aspects

Histology shows intraepidermal spongiform pustules with clusters of neutrophils consolidated in microabscesses (Fig. 2C). Parakeratosis, acanthosis with elongation of rete ridges and dermal neutrophilic infiltration are also seen (10, 11).

Differential diagnosis

DIRA and DITRA must be differentiated from variants of pustular psoriasis which occur outside the setting of autoinflammation, including generalised pustular psoriasis, palmoplantar pustulosis, and acrodermatitis continua of Hallopeau. Bone and central nervous

system involvements, as seen in DIRA, are relevant clinical clues for differential diagnosis. The other differential diagnosis is acute generalised exanthematous pustulosis which, however, has a predilection for the major flexures and is triggered in the vast majority of cases by medications, particularly antibiotics, antimycotics, and anticonvulsants (32). The identification and withdrawal of the offending drug are both helpful for differential diagnosis and the essential first therapeutic step.

Syndromic pyoderma gangrenosum (PG)

Neutrophilic dermatoses are a heterogeneous group of conditions characterised clinically by polymorphic skin lesions, including pustules, bullae, abscesses, papules, nodules, and ulcers, and histologically by a neutrophil-rich inflammatory infiltrate (13, 33, 34). The possible involvement of almost any organ system gave rise a number of years ago to the term “neutrophilic disease” (14). The prototype of neutrophilic dermatoses is PG, which, in its classic presentation, manifests as single or multiple skin ulcers with undermined, raised erythematous to violaceous borders (Fig. 3A); it may also present with pustular, bullous, and vegetating plaque-type lesions (18, 33, 34). PG may be isolated or associated with systemic conditions, including inflammatory bowel diseases, rheumatological disorders, lymphoproliferative forms or other haemopathies. It is noteworthy that PG may also manifest as syndromic PG, occurring in the context of autoinflammatory forms such as PAPA (35), PASH (PG, acne, and suppurative hidradenitis, also known as hidradenitis suppurativa [HS]) (36–38), or other more recently described syndromes such as pyogenic arthritis, acne, PG, and suppurative hidradenitis (PAPASH) (39). While PAPA is a classic monogenic autoinflammatory syndrome due to mutations in a single gene regulating innate immunity, namely *PSTPIP1* (proline-serine-threonine phosphatase-interacting protein 1) (35, 39), there is increasing evidence that mutations in different genes involved in autoinflammation are associated with PASH as well as with isolated PG and

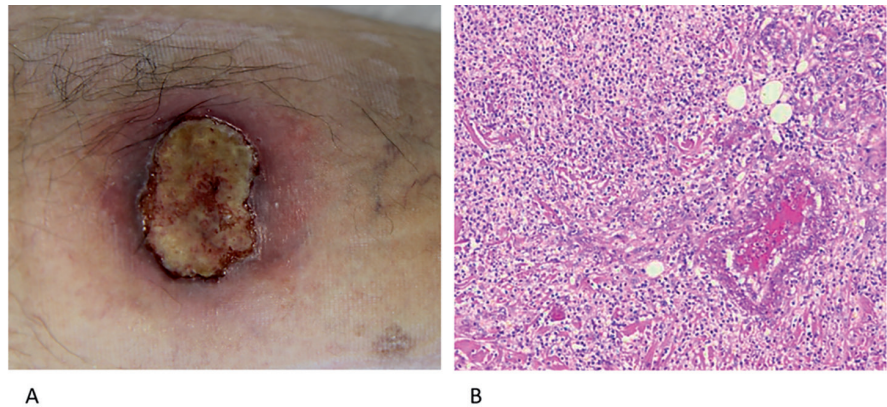


Fig. 3. Pyoderma gangrenosum. (A) Typical ulcer of pyoderma gangrenosum. (B) Histology showing a dense dermal-hypodermal inflammatory infiltrate consisting of lymphocytes, histiocytes and neutrophils. Courtesy of Dr Raffaele Gianotti.

neutrophilic dermatoses in general (37, 39, 40), with all these forms thus representing polygenic AIDs.

Pyogenic arthritis, pyoderma

gangrenosum and acne (PAPA syndrome) PAPA syndrome is a rare autosomal dominant disease first described by Lindor *et al.* in 1997 (41). Clinically, it is characterised by sterile inflammation of the skin and joints (42). PAPA syndrome is due to different mutations on chromosome 15q involving the *PSTPIP1* gene (43, 44). The originally identified mutations, namely A230T and E250A, as well as others more recently found, interfere with the ability of *PSTPIP1* to phosphorylate proinflammatory pyrin domains eventually leading to an altered assembly and activation of the inflammasome and consequent release of IL-1 β (44–46). The overexpression of IL-1 β induces an uncontrolled production of several proinflammatory cytokines and chemokines, which are responsible for the recruitment and activation of mature neutrophils, leading to a neutrophil-mediated inflammatory scenario (15, 46–48).

Cutaneous features:

polymorphic presentation

PG may occur early in life with possible preceding events that act as triggering factors; these may include vaccination or minimal trauma, according to the so-called pathergy phenomenon. However, PG tends more frequently to develop around puberty and to be accompanied by acne, often in its more

severe nodulocystic presentation; both conditions may persist into adulthood (42, 44, 45, 48). PG generally presents with its typical skin ulcer displaying undermined, elevated erythematous-violaceous borders and usually involves the legs, however, pustular, bullous or vegetating lesions can coexist or replace the classic ulcer. Painful, recurrent aseptic monoarticular arthritis with a neutrophil-rich infiltrate generally occurs in childhood and may also be the first manifestation of the disease, possibly leading to joint erosion and destruction (48). It is noteworthy that in young adults articular symptoms tend to decrease while cutaneous manifestations become more prominent. In a recent clinical trial, PASH was described and proposed to be an autoinflammatory syndrome (Figs. 4A, 4B, and 4C) (37, 40). Presence of HS and absence of aseptic arthritis distinguish PASH syndrome from PAPA syndrome; however, the combination of sterile arthritis with symptoms of PASH has been reported and christened PAPASH (39). HS is a chronic inflammatory disease involving the terminal portion of the hair follicle, clinically characterised by nodules, often ulcerating, abscesses and fistulas, evolving into retracting or hypertrophic scars in apocrine gland-bearing sites (49), such as the axillary, inguinal, and anogenital regions.

Histological aspects of pyoderma gangrenosum

Histopathological features of PG, albeit non-specific, are helpful in excluding

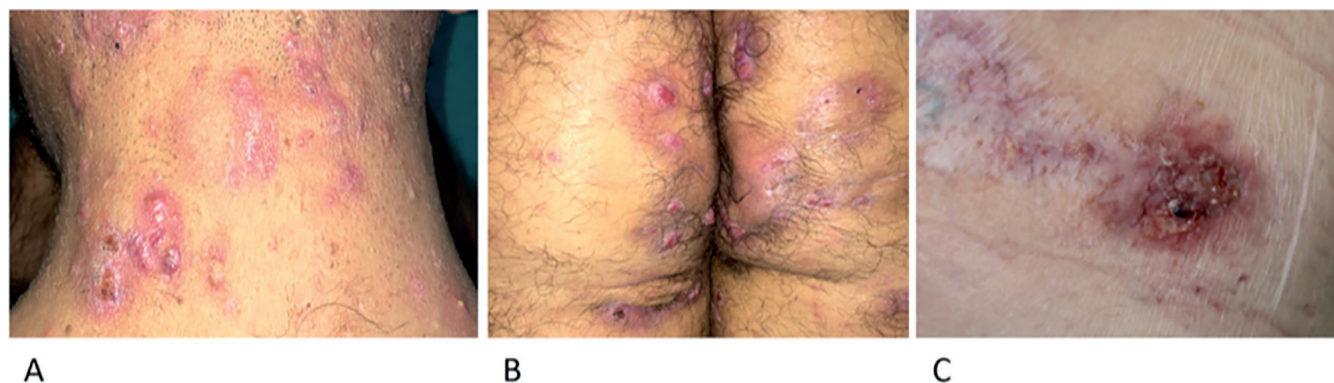


Fig. 4. Pyoderma gangrenosum, acne and hidradenitis suppurativa (PASH).

(A) Inflammatory acne presenting with papules, nodules, and pustules on the nape. (B) Hidradenitis suppurativa: erythematous ulcerated nodules, abscesses and fistulas with hypertrophic scarring on the buttocks and intergluteal fold. (C) Ulcerative pyoderma gangrenosum associated with cribriform scarring on the back.

other causes of ulceration. The time and site of the biopsy must be carefully selected. It is recommended to take an elliptic specimen that includes the border and the floor of the ulcer. The typical histology of ulcerative PG shows epidermal ulceration and a dermal-hypodermal inflammatory infiltrate mainly consisting of neutrophils; leukocytoclasia may also be seen but fibrinoid necrosis of vessel wall is always absent (13, 34, 50). In late phases of the disease, lymphocytes, histiocytes, and macrophages predominate in the infiltrate, with possible presence of plasma cells and giant cells, the latter forming sometimes granulomas (Fig. 3B). Special histochemical stains and microbiological cultures are negative; this finding is of paramount diagnostic relevance.

Differential diagnosis of pyoderma gangrenosum

For the diagnosis of ulcerative PG, other causes of ulceration must be ruled out. Microbiological analysis must always be performed to exclude more common bacterial infections or rare fungal infections such as blastomycosis, a deep and severe mycosis with ulcerative presentation. Colour Doppler ultrasonography and/or other more specific instrumental examinations may exclude vascular causes of ulceration. An important differential diagnosis is cutaneous small vessel vasculitis, the most common form of vasculitis in dermatology; however, the latter may be ruled out if coexisting cutaneous manifestations,

particularly palpable purpura and livedo reticularis, and the typical histology showing a leukocytoclastic vasculitis pattern are lacking (51). A rare PG-like presentation of granulomatosis with polyangiitis (Wegener's granulomatosis) has also to be considered; however, anti-neutrophil cytoplasmic antibodies (ANCA) negativity and the absence of granulomatous aspects on histology allows the exclusion of this diagnosis (52). Neoplastic causes of ulceration, namely basal cell carcinoma, squamous cell carcinoma or lymphoma, may be ruled out on the basis of the histology. Finally, factitial ulcers may be excluded by means of a psychiatric evaluation.

Pathophysiology of autoinflammation in pyoderma gangrenosum and its syndromes

A recent comprehensive immunological investigation, which used skin samples of lesions occurring on patients with PG and on patients with PASH, identified a constant inflammatory profile showing overexpression of IL-1 β , tumour necrosis factor (TNF)- α , IL-8, and the chemokines C-X-C motif ligand (CXCL)1/2/3 and CXCL16 (40). Overexpression of IL-1 β in PG suggests that autoinflammation occurs through the activation of the inflammasome similarly to the PG-associated syndromes, such as the monogenic autoinflammatory syndrome PAPA (44). Dysfunction or altered activation of the inflammasome depends on genetic alterations, and in particular gene mutations as occurs in the autoinflammatory syndromes,

and can trigger the autoinflammatory cascade leading to the development of PG (53). IL-17 is another key cytokine which is involved in the regulation of the innate immunity. IL-17 also plays an important role in autoinflammation via the recruitment and activation of neutrophils, which stimulates the production of cytokines and chemokines that amplify the accumulation of neutrophils into the skin and the inflammatory network (53). IL-1 β , IL-17, and TNF- α are also overexpressed in lesional skin of other neutrophilic dermatoses, including HS that is a leading player in the PASH syndrome (17, 54-59). These cytokines also increase the production of matrix metalloproteinases, which are important effectors in inducing tissue damage in PG (17). Recently, various mutations have been reported in genes encoding signalling molecules, which are involved in triggering the innate immunity (60). In particular, gain-of-function mutations in the NLRP3 gene have been identified as an aetiological factor of CAPS. In the monogenic syndrome presenting with PG, PAPA, mutations involving the PSTPIP1 gene lead to decreased inhibition of the inflammasome and consequent activation of caspase-1; this proteolytic enzyme cleaves pro-IL-1 β into its biologically active isoform, IL-1 β , with exaggerated production of this cytokine that drives the autoinflammation associated with the PAPA triad of symptoms (61). A recent comprehensive analysis of the main genes involved in autoinflammation demonstrated that both isolated PG

and PASH are associated with a number of mutations in classic autoinflammatory genes, including Mediterranean fever, NLRP3, NLRP12, NOD2, lipin 2 (LPIN2), and PSTPIP1 (40). On the basis of these findings, PG and PASH may be regarded as different phenotypes of a spectrum of autoinflammatory polygenic conditions. Moreover, the physiopathological model of autoinflammation acting in PG and its syndromic form PASH is likely to be the same involved in PAPA.

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