Artigo de Revisão

Erupções Pustulosas em Crianças como Manifestações de Doenças Auto-Inflamatórias

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RESUMO – Atualmente, na prática clínica, quando se observa uma criança com uma erupção pustulosa e inflamação sistémica, é mandatório pensar numa doença auto-inflamatória, após excluir uma causa infecciosa. Apesar de rara, a doença auto-inflamatória deve ser reconhecida o mais precocemente possível, diagnosticada corretamente (incluindo estudo genético), e tratada com terapia dirigida, se disponível.
PALAVRAS-CHAVE – Criança; Dermatopatias Vesiculobolhosas/etiologia; Doenças da Pele/etiologia; Doenças Hereditárias Autoinflamatórias/complicações.

Pustular Eruptions in Children as Manifestations of Autoinflammatory Diseases

ABSTRACT – *Nowadays, in clinical practice, when attending a child with a pustular eruption and systemic inflammation, it is mandatory to think of an autoinflammatory disease, once infectious causes have been ruled out. Although rare, autoinflammatory disease must be recognized as early as possible, accurately diagnosed (including gene testing), and treated with targeted therapy if available.*
KEYWORDS – *Child; Hereditary Autoinflammatory Diseases/complications; Skin Diseases/etiology; Skin Diseases, Vesiculobullous/etiology.*

INTRODUCTION

The monogenic autoinflammatory diseases (AIDs) are a group of disorders of dysregulation of innate immune system, characterized by recurrent or continuous inflammation (usually manifested by elevated acute phase reactants), in the absence of the typical features of autoimmunity, such as autoantibodies or antigen-specific T lymphocytes.[1] Since the first characterization of the genes underlying familial Mediterranean fever (FMF) in 1997, over 30 diseases have been included to the list of AIDs due to improvement in genetic sequencing and immunologic research.[2-4]

AIDs share an early onset, recurrent fevers, and a variable multisystemic involvement.[2-8] The dermatologist assumes here a privileged role in the early diagnosis of an AID, since the skin is one of the major organs involved with urticaria, erysipela-like erythema, erythema nodosum-like lesions, pustular eruptions, acne and pyoderma gangrenosum.[5-8]

The purpose of this article is to review the monogenic AIDs that can present a pustular eruption in infants and children, emphasizing their clinical manifestations. The classification of AIDs we use is based on clinical grounds, as it seems to be more useful for the clinician.[5-10] (Table 1)

1. Deficiency of interleukin-1 receptor antagonist (DIRA)

Deficiency of interleukin-1 receptor antagonist (DIRA) is an autosomal recessive AID, first described in 2009[11] and with 19 patients reported to date,[12] caused by loss-of

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Tabela 1 - Summary of the characteristics of monogenic autoinflammatory diseases that present with pustular eruptions.

		SKIN MANIFESTATIONS	OTHER MANIFESTATIONS
With inflammatory bone disease	Deficiency of IL-1 receptor antagonist (DIRA)	Early onset pustulosis	Osteomyelitis Periostitis Elevated APR
	Majeed syndrome	Pustules Sweet syndrome Psoriasis	Osteomyelitis Anemia Fever
With pyogenic arthritis	Pyogenic arthritis, pyoderma gangrenosum and acne syndrome (PAPA)	Severe acne nodulo-cystic Pyoderma gangrenosum	Sterile pyogenic arthritis
With inflammatory bowel disease	Early-onset IBD	Folliculitis	Enterocolitis Perianal disease
Without other organ involvement	CARD14-mediated pustular psoriasis (CAMPS)	Generalized pustular psoriasis	
	Deficiency of IL-36 receptor antagonist (DITRA)	Generalized pustular psoriasis	Fever Elevated APR
	Pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND)	Severe acne Sterile skin abscesses Pyoderma gangrenosum Hidradenitis suppurativa Vasculitis	Fever Elevated APR
With immunodeficiency	PLCγ2-associated antibody deficiency and immune dysregulation (PLAID)	Cold induced urticaria Acral lesions Granulomas	Sinopulmonary infections Hypogammaglobulinemia Vitiligo and autoimmune thyroiditis ANA positive
	Autoinflammation and PLCγ2-associated antibody deficiency and immune dysregulation (APLAID)	Vesiculopustular lesions Recurrent erythematous plaques	Mild immunodeficiency

APR: acute phase reactants; PLCγ2: Phospholipase Cγ2.

function mutations in the IL-1 receptor antagonist gene (*IL1RN*). The absence of the IL-1-receptor antagonist results in an uninhibited production of the proinflammatory cytokine IL-1. The two major organs affected in this potentially life-threatening condition are the skin and bone.[5-7,11]

Patients with DIRA present, in the first months of life, with a pustular skin eruption (localized or generalized) over erythematous plaques, simulating a severe pustular psoriasis. Then skin can evolve to a diffuse ichthyosiform desquamation. Pathergy and nail changes, such as onychomadesis, pitting and anonychia, are also observed. Stomatitis or oral ulcerations are present in some patients. Histological findings of the affected skin show extensive neutrophilic infiltration of the epidermis and dermis, subcorneal pustules, acanthosis and hyperkeratosis.[2,4-8,10-15]

Additionally, patients in the first months of life develop aseptic multifocal osteomyelitis and periostitis. Skeletal alterations on radiography include widening of the anterior rib ends and clavicles, periosteal elevation along multiple long bones, multifocal osteolytic lesions, heterotopic ossifications, and cervical vertebral fusion secondary to collapsing vertebral osteolytic lesions.[2,4-8,11-15]

Fever is often low-grade or can be absent in DIRA, however a persistent elevation of inflammatory markers (leukocytosis with neutrophilia, erythrosedimentation rate, C-reactive protein) is observed. Less frequent manifestations include interstitial lung disease, respiratory distress, hemophagocytosis, hepatosplenomegaly, hypotonia, venous thrombosis and central nervous system vasculitis. Preterm labour was described in almost all patients.[4,6-8,11-15]

The conjugation of these severe cutaneous and skeletal alterations, associated with a persistent elevation of the inflammatory markers, with negative cultures, should alert for DIRA. The detection of mutations in *IL1RN* is mandatory for a definitive diagnosis.[6,9,13]

If not timely recognized or treated, DIRA can escalate to life-threatening systemic inflammation and death, with a mortality rate over 30% in early infancy.[6,11-15] Concerning to treatment, daily injection of the recombinant IL-1 receptor antagonist (anakinra) is described to be lifesaving in these patients, leading to a rapid resolution of skin lesions and systemic inflammation. Long-term therapy with canakinumab can replace anakinra with much fewer injections needed.[4,6,7,10-15]

2. Majeed syndrome

Majeed syndrome is an exceedingly rare autosomal recessive AID, mostly identified in Middle Eastern families, caused by loss-of-function mutations in *lipin* 2 gene, which encodes *LPIN2*, a phosphatidate phosphatase important in lipid metabolism.[4,9,16]

Cutaneous alterations in Majeed syndrome are not always present, although patients can have a neonatal-onset recurrent pustular dermatitis, Sweet syndrome-like lesions and psoriasis.[4-9,16-19]

Typical manifestations are chronic recurrent multifocal osteomyelitis (affecting clavicles, sternum and long bones) that starts early (3 weeks to 2 years of life) and congenital dyserythropoietic anemia. Other features include fever, hepatomegaly, a retarded growth and joint contractures.[2,5,7,9,16-19]

This syndrome shares with DIRA the relevant osseous involvement and the excellent therapeutic response to anakinra.[5,7,16-19]

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

The PAPA syndrome is an autosomal dominant AID described in 1997, caused at least in a few cases by gain-of-function mutations in the gene encoding CD2-binding protein 1, also known as proline-serine-threonine-phosphatase-interacting protein 1 (PSTPIP1). This results in abnormal inflammasome and innate immune cell activation and over-production of IL-1ß.[2,5-9,20]

Cutaneous manifestations include severe scarring nodulocystic acne that can begin in childhood or puberty and tends to persist into adulthood. The inflammatory character of acne predominates, but retentional elements can also be present. Pathergy is frequent and may be induced early in life upon vaccination or minimal trauma. The other key features of this syndrome are pyoderma gangrenosum and childhood-onset flares of painful sterile monoarthritis, which can be deformating. By puberty, the joint symptoms tend to decrease and skin symptoms become more prominent.[5-9,20,21]

Fever is rarely observed in PAPA patients. Laboratory findings are non-specific and may include leukocytosis and increased erythrosedimentation rate and C-reactive protein during flares.[6,20]

Treatment of PAPA syndrome is challenging and depends on the dominant clinical manifestation. It can include corticosteroids, thalidomide, cyclosporine, dapsone, tacrolimus and intravenous immunoglobulin (IVIG) used with variable individual responses. Anakinra was also used with variable results, but monoclonal anti-TNF antibodies (infliximab, etanercept and adalimumab) were considered more effective to treat skin alterations.[4,6,7,9,10,20-24]

Several other syndromes that conjugate acne and pyoderma have been reported in the literature, like PASH (pyoderma, acne and hidradenitis suppurativa), PAPASH (pyoderma, acne, pyogenic arthritis, and hidradenitis suppurativa), PASS (pyoderma, acne, and seronegative spondyloarthritis), PsAPASH (psoriatic arthritis, pyoderma, acne, and hidradenitis suppurativa), and PAC (pyoderma, acne, and ulcerative colitis). So far, *PSTPIP1* mutations have been implicated in PASH, PAPASH and PAC syndrome.[25-27]

4. Early-onset inflammatory bowel disease (IBD)

Early-onset inflammatory bowel disease (IBD) is caused by loss-of-function mutations in interleukin-10 and interleukin-10 receptors. These patients have refractory enterocolitis and perianal disease manifesting in the first year of life. The most frequent extraintestinal symptom is folliculitis followed

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by oral aphthous lesions, arthritis, and hearing impairment. Other manifestations include fever, arthritis, and recurrent infections.[4,28,29]

This is a very severe disease, and hematopoietic stem cell transplantation was successful in the majority patients.[4,28,29]

5. Deficiency of IL-36 receptor antagonist (DITRA)

Deficiency of IL-36 receptor antagonist (DITRA) is a rare disease caused by homozygous or compound heterozygous mutations in the gene encoding the IL-36 receptor antagonist (*IL-36RN*), causing its deficiency and an exaggerated proinflammatory response in the nuclear factor-ƙB pathway, thus differing from IL-1receptor antagonist deficiency in patients with DIRA.[5,6,7,30-32]

DITRA was first described in 2011 when Marrakchi *et al* identified recessively inherited mutations in nine Tunisian families with generalized pustular psoriasis (GPP). It was also later reported in sporadic GPP (both children and adults) without psoriasis vulgaris (PV). *IL36RN* mutations were also described in patients with acrodermatitis continua of Hallopeau, severe acute generalized exanthematous pustulosis and impetigo herpetiformis, as a genetic predisposing or causative factor.[6,30-32]

DITRA is clinically suspected when, early in childhood, a recurrent and sudden-onset diffuse, erythematous skin eruption, with pustules, similar to a severe GPP appears (Fig. 1). Subsequent diffuse desquamation can be observed. Along with cutaneous findings, systemic symptoms are observed such as high-grade fever, asthenia, and elevation of inflammatory markers. Other clinical features are geographic tongue, nail dystrophy, arthritis and cholangitis.[2,4,5,7,30,34]

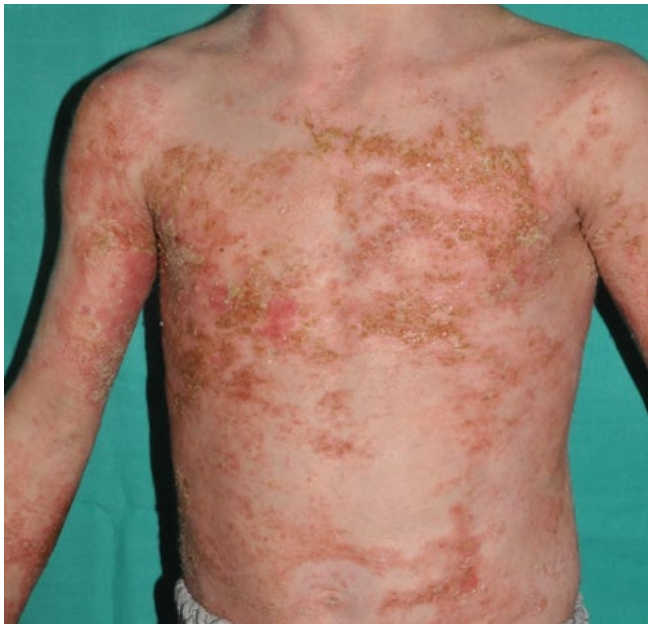

Figure 1 - Patient with a diffuse, erythematous and pustular skin eruption, compatible with DITRA.

Histopathological studies have shown intraepidermal spongiform pustules, acanthosis and parakeratosis in the stratum corneum, and infiltration of the skin by CD8 and CD3 T cells and macrophages.[30]

Although the disease usually occurs in childhood (between 1 week and 11 years of age in Marrakchi families), its occurrence in adults has also been described. The frequency of flares was variable and they were associated with viral or bacterial infections, withdrawal of retinoid therapy, menstruation, and pregnancy. The disease may be life threatening and death due to septicemia has been reported in 5 cases.[30]

Comparing to DIRA, DITRA patients can have higher fever and asthenia, but systemic involvement is less aggressive.[5]

The majority of cases of GPP without PV are caused by recessive *IL36RN* mutations, so Hussain *et al* recommended that patients with GPP with an early-onset, systemic inflammation and absence of PV, should be screened for *IL36RN* mutations.[35,36]

Optimal treatment is not yet entirely clear and similar treatments in patients with identical mutations result in different outcomes. Beyond the conventional anti-psoriatic systemic treatment, there are case reports of variable response to IL-1 blockade (anakinra), infliximab, etanercept, adalimumab, ustekinumab, and more recently, secukinumab, identifying IL-17 as a potential therapeutic target that warrants further investigation.[4,6,7,30-34,37-39]

6. CARD14-mediated pustular psoriasis (CAMPS)

Caspase recruitment domain family member 14 (*CARD14*) is considered a key regulator of skin immune homeostasis, being an activator of the nuclear factor-ƙB within the epidermis.[6,9,40-42]

In 2012, gain-of-function mutations in *CARD14* were identified as the cause of familial PV and familial pityriasis rubra pilaris (PRP). Later, other inflammatory skin disorders associated with *CARD14* mutations/variants were added like GPP with PV, palmoplantar pustular psoriasis and psoriatic arthritis.[6,28,40-43]

The term *CARD14*-associated papulosquamous eruption (CAPE) was recently introduced to describe the patients with *CARD14* mutations that present characteristics of both psoriasis and PRP.41

CAMPS can present as a childhood-onset severe pustular psoriasis. Fever and other systemic manifestations are generally not present but can occur during skin superinfections.[4,6,40] A rare gain-of-function variant (p.Glu138Ala) was reported in a sporadic patient with severe early-onset GPP.[40] Recently, another gain-of-function variant (p.Asp176His) has been reported, being a predisposing factor for GPP with preceding or concurrent PV, underlying 20% of GPP cases with PV in Japan.[44]

In 2014, *AP1S3* mutations were found in 15 European patients with various forms of pustular psoriasis, including GPP.[45,46] However, the majority of patients with GPP do not

carry mutations in any of the three genes - *IL36RN*, *CARD14*, or *AP1S3* -, probably indicating a condition with a complex mode of inheritance with more genes/genetic factors to be unveiled.[46]

The treatment includes the same options for moderate--to-severe psoriasis, and there is one report of successful response to ustekinumab.[10,41,47]

7. Pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND)

Pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND) is a newly described AID by Masters *et al* in 2016, resulting from mutations in the *MEFV* gene encoding pyrin. It differs from FMF by its autosomal dominant inheritance, fever lasting weeks as opposed to days in FMF, and absence of amyloidosis and serositis.[5,48,49]

From a clinical point of view, PAAND is characterized by recurrent, childhood-onset episodes of neutrophilic dermatosis, with severe acne, sterile skin abscesses, pyoderma gangrenosum, hidradenitis suppurativa, and neutrophilic small-vessel vasculitis. These episodes coexist with elevated acute-phase proteins, fever, and arthralgia/myalgia.[48,49]

PAAND shares some features with sterile pyogenic disorders such as PAPA, PASH, and PAPASH syndromes.[48,49]

One patient was successfully treated with anakinra, after previously showing an inadequate response to corticosteroids and methotrexate, and other was treated with adalimumab.[49,50]

8. Phospholipase Cγ2-associated antibody deficiency and immune dysregulation (PLAID) / autoinflammation and PLCγ2-associated antibody deficiency and immune dysregulation (APLAID)

PLAID and APLAID are two allelic conditions that present with autoinflammatory phenotypes associated to an immunodeficiency, caused by autosomal dominant gain-of-function mutations in phospholipase Cγ2 (PLAID – gene deletion of an inhibitory region and APLAID – missense hypermorphic mutations), an enzyme that plays a key role in the regulation of immune responses.[2,51-53]

Cutaneous manifestations can be quite variable. PLAID phenotypes have cold-induced urticaria within the first year of life, neonatal-onset ulcerative cutaneous lesions in cold--sensitive regions of the body (spontaneous ulceration of the nasal tip, finger and toes), granulomatous skin lesions and atopy. APLAID leads to an early-onset papulo-pustular eruption in infancy, that evolved to recurrent erythematous plaques and vesiculopustular lesions that may worsen with heat and sun exposure (Fig. 2). Cutaneous histiocytic granulomas with accumulation of neutrophils in the upper dermis have been identified in APLAID.[2,5,51-53]

In both conditions patients also presented fever, sinopulmonary infections and common variable immunodeficiency. Distinctive findings of PLAID are autoimmune manifestations such as autoimmune thyroiditis and vitiligo with positive anti-nuclear antibodies.[2,5,51-53]

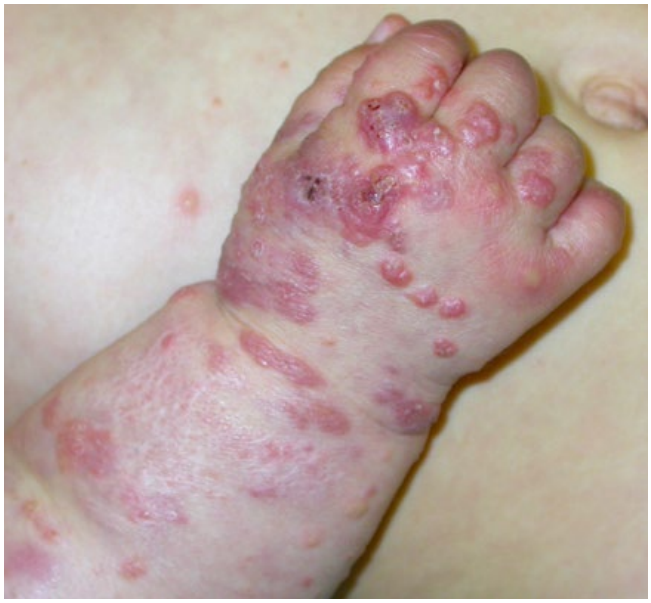

Figure 2 - Patient with a papulopustular eruption compatible with APLAID.

Patients with a history of cold urticaria, granulomatous skin disease or a history of acral lesions in the early neonatal period should be tested for PLCG2 mutations.[52]

APLAID patients were partially responsive to anakinra and to high-dose corticosteroids.[51-53]

CONCLUSION

The diagnosis of an AID should combine phenotypic features and gene testing. The dermatologist has here the opportunity to be the first to suspect an AID, when patients present cutaneous lesions associated with fever and multisystemic inflammation, mainly in the first year of life.

Early identification of these entities is critical, as it will guide the approach and the adequate treatment, in order to minimize organ damage resulting from uncontrolled systemic inflammation. An example is DIRA where therapy with anakinra can be lifesaving.[2,5,9]

Since there are no diagnostic criteria (with the exception of FMF), the genetic testing is recommended, although not always feasible, and must be interpreted cautiously, requiring a precise correlation between all the specialties involved.[2,9]

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