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CASE REPORT

Serious generalized pustular psoriasis with evolution to plaque psoriasis: approach with spesolimab

Psoríase pustulosa generalizada grave com evolução para psoríase em placas: abordagem com spesolimab

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Abstract

Generalized pustular psoriasis (GPP) is characterized by an acute and severe variant of psoriasis, often accompanied by systemic symptoms, with the eruption of multiple sterile pustules over an area of erythema, associated or not with the form of plaque psoriasis. Epidemiological data on disease are limited, but a global prevalence is estimated at around 1-7 cases per million people, affecting mainly females, with a higher incidence in the fourth and fifth decades of life. Exacerbations are marked by varying degrees of inflammation and systemic symptoms and have an unpredictable evolution. Hyperactivity of the interleukin-36 (IL-36) inflammatory pathway was discovered as the main pathway responsible for causing the disease. Recently, the active substance spesolimab has shown excellent results in the treatment of GPP, with a mechanism of blocking IL-36 receptor activation, leading to the suppression of pro-inflammatory and profibrotic pathways in inflammatory skin and intestinal diseases.

Keywords: Psoriasis. Pustular psoriasis. Generalized pustular psoriasis. Plaque psoriasis. Spesolimab. Anti interleukin-36.

Resumo

A psoríase pustulosa generalizada (PPG) caracteriza-se por uma variante aguda e grave da psoríase, muitas vezes acompanhada de sintomas sistêmicos, com erupção de múltiplas pústulas estéreis sobre área de eritema, associada ou não à forma de psoríase placas. Os dados epidemiológicos sobre a doença são limitados, mas estima-se uma prevalência global em torno de 1-7 casos por milhão de pessoas, acometendo principalmente o sexo feminino, com maior incidência na quarta e quinta décadas de vida. As exacerbações são marcadas por graus variáveis de inflamação e sintomas sistêmicos e apresentam evolução imprevisível. A hiperatividade da via inflamatória da interleucina 36 (IL-36) foi descoberta como a principal via responsável por causar a doença. Recentemente, a substância ativa spesolimab tem mostrado ótimos resultados ao tratamento de psoríase pustulosa generalizada (PPG), com mecanismo de bloqueio da ativação de IL-36R, levando à supressão das vias pró-inflamatórias e pró-fibróticas em doenças inflamatórias cutâneas e intestinais.

Palavras-chave: Psoríase. Psoríase pustulosa. Psoríase pustulosa generalizada. Psoríase em placas. Spesolimab. Anti interleucina 36.

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Introduction

Generalized pustular psoriasis (GPP) is characterized by an acute and severe variant of psoriasis, often accompanied by systemic symptoms, with the eruption of multiple sterile pustules over an area of erythema, associated or not with the form of plaque psoriasis[1,2].

Epidemiological data on GPP are limited; it is estimated that the global prevalence is around 1-7 cases/million people, with a predominance of female patients[3]. The peak incidence appears to occur around the fourth and fifth decades of life, but cases have been described in all age groups[4].

The evolution of PPG exacerbations is unpredictable. In addition to the cutaneous symptoms described, exacerbations are marked by varying degrees of inflammation and systemic symptoms such as fever, fatigue, and myalgia, in addition to changes in laboratory tests – high C-reactive protein (CRP), neutrophilia, hypocalcemia, and hypoalbuminemia. Other organs are often affected and cholestasis, renal failure, or even circulatory shock can be part of the clinical picture of the disease, with a consequent increase in the risk of death[1-6].

GPP is considered a distinct entity from plaque psoriasis, with different clinical, genetic, and pathological characteristics[1,2,5].

Case report

A 42-year-old female Caucasian patient with a previous diagnosis of subcorneal pustulosis for 10 years under satisfactory control with dapsone 100 mg/day, developed in the previous 40 days clustered pustules in the inguinal region and lower limbs bilaterally. The medication was changed by a private dermatologist for methotrexate, with no clinical response within 2 weeks. She progressed with daily fever, severe arthralgia, loss of appetite, and headache, with progression of the lesions on the abdomen, back, and upper limbs, with no response to the introduction of amoxicillin with potassium clavulanate and prednisone 60 mg/day.

On admission to the dermatology ward, she presented with pustules disseminated throughout the integument over areas of erythema and confluence of pustular lesions forming lakes of pus, geographic tongue (Fig. 1), fever (maximum temperature of 38.9°C), and severe arthralgia, predominantly in the knees. There were no reports in the history of recent infections, use of other medications, or vaccinations. Histopathological examination demonstrated psoriasiform dermatitis with intraspinous, subcorneal, and intracorneal pustules (Fig. 2), supporting the diagnosis of

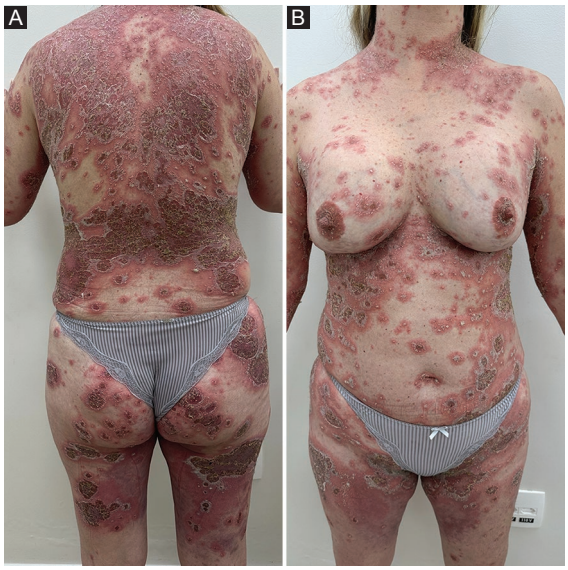

Figure 1. A and B: generalized pustular psoriasis in the acute phase: multiple pustules on an erythematous area.

GPP. Laboratory tests showed hemoglobin of 12.4 g/dL, leukocytosis (20,910 cells/μL, with 87.5% of neutrophils), CRP (34 mg/dL), erythrocyte sedimentation rate (105 mm), hypoalbuminemia (3.2 g/dL), in addition to urinary nitrite. In this case, cyclosporine 300 mg/day (5 mg/kg/day) was started as rescue therapy, corticosteroid therapy was suspended, and antimicrobial therapy was escalated to ceftriaxone with clindamycin to cover a possible cutaneous and urinary septic focus. During the hospital stay, there was a drop in hemoglobin to 7.8 g/dL and albumin to 1.8 g/dL, without the need for targeted treatment. The patient presented an excellent response to cyclosporine, with fever, arthralgia, and pustular pain resolving within 6 days (Fig. 3). After 1 month, she developed acute renal failure, with cyclosporine being reduced and secukinumab introduced (induction dose, 5 doses of 300 mg each with a 1-week interval between them). The gradual reduction of cyclosporine led to the return of the pustular condition, even after the 5 doses of secukinumab. At that time, ANVISA approved the drug spesolimab for the treatment of GPP. Anti-IL-17 therapy was then suspended, and a 900mg dose of the new biologic was administered, resulting in complete resolution of the pustules within 4 days. However, after 12 days, there was a recurrence of pustules in small quantities, along with erythematous plaques. Another dose of Spesolimab 900 mg was administered, with an interval of 16 days from the first dose. Two days after the second dose, there was complete remission of the pustules, with only erythematous and scaly plaques

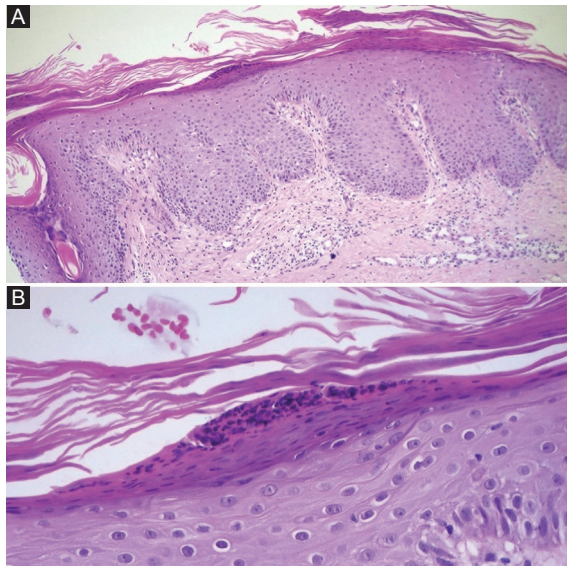

Figure 2. A: skin fragment showing psoriasiform dermatitis (H&E, ×100). **B:** fragment of skin showing intracorneal pustule, parakeratosis, and agranulosis (H&E, ×400).

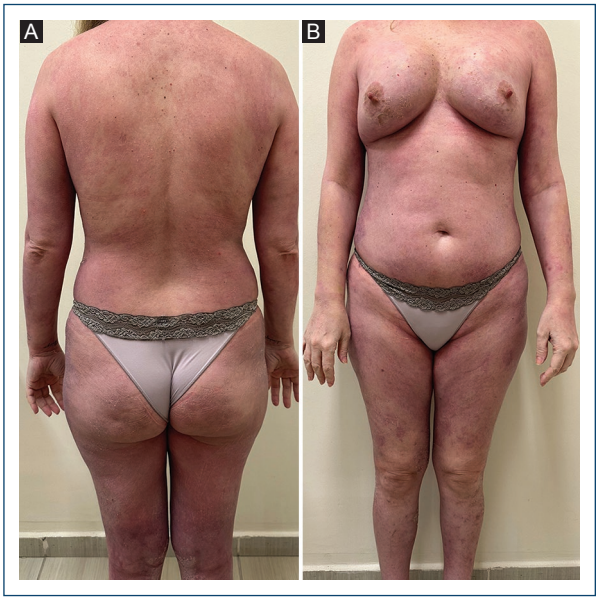

Figure 3. A and **B:** resolution of skin lesions 6 days after introduction of 5 mg/kg/day of cyclosporine.

scattered across the body (Fig. 4), confirmed by a new histopathological examination that diagnosed plaque psoriasis. Secukinumab was reintroduced at a maintenance dose of 300 mg/month, achieving complete control of the psoriatic plaques 1 week after resuming the medication. The patient used secukinumab for 7 months without

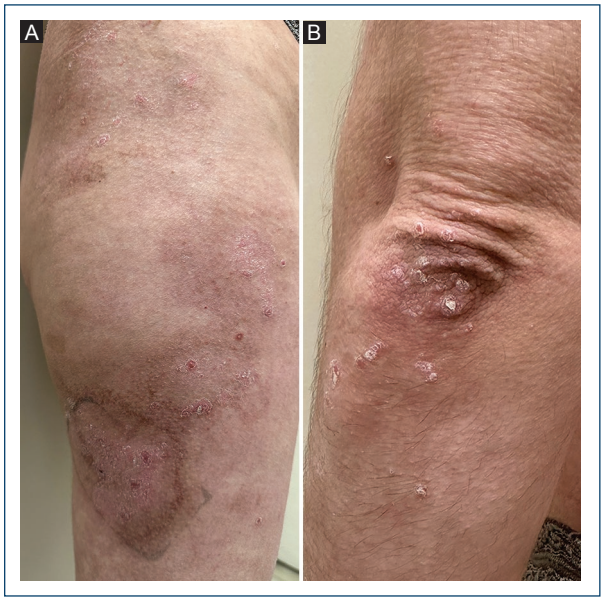

Figure 4. A and **B:** papules and small erythematous – scaly plaques 12 days after the use of spesolimab.

presenting any lesions. Currently, the patient remains under monthly follow-up with the assisting team, but at the patient's request, secukinumab was discontinued, and she has been without any medication and lesions for 5 months.

Discussion

Recently, hyperactivity of the interleukin-36 (IL-36) inflammatory pathway was discovered as the main pathway responsible for causing the GPP[2]. Different mutations in the IL36RN gene, which encodes the IL-36 receptor antagonist (IL-36Ra), have been described and confirm this pathway as the main one involved in the pathogenesis of GPP[5]. Spesolimab is a humanized IgG1 monoclonal antibody that binds to the human IL-36 receptor (IL-36R) and blocks (IL36R) signaling, inhibiting its binding to IL-36α, IL-36β, and IL-36γ. Thus, Spesolimab blocks the activation of IL-36R, leading to the suppression of pro-inflammatory and profibrotic pathways in inflammatory skin and intestinal diseases. In patients with GPP, blocking IL-36R signaling is a novel targeted therapeutic approach with excellent results[7,8], as in the present case.

Conclusion

Since generalized pustular psoriasis (GPP) has an inflammatory cascade distinct from plaque psoriasis,

marked by hyperactivity of the interleukin 36 (IL-36) inflammatory pathway, it is crucial to use targeted and effective therapies that block the IL-36 pathway. In this context, spesolimab has shown excellent results in controlling GPP flare-ups, through the mechanism of blocking IL-36R activation, leading to the suppression of pro-inflammatory and pro-fibrotic pathways in inflammatory skin and intestinal diseases. Given this and the case presented, this substance brings a new targeted therapeutic approach with satisfactory results, providing rapid relief of symptoms and a significant improvement in the quality of life of patients, representing another promising advance in immunology in dermatology.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript or for the creation of images, graphics, tables, or their corresponding captions.

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