Boletín Médico del
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CLINICAL CASE

Acute generalized exanthematous pustulosis

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Abstract

Background: *Acute generalized exanthematous pustulosis is a rare disease. Although it is usually related to drug intake, it is occasionally associated with infections, especially in the pediatric age. It is characterized by the sudden onset of sterile non-follicular pustules on an erythematous fundus, fever, and leukocytosis, with frequent and prompt spontaneous resolution. It mainly affects adults and is uncommon in childhood. Complications have been reported in approximately 20% of cases.* **Case report:** *We report the case of a 10-year-old female patient with a 5-day history of fever and dermatosis characterized by countless non-follicular pustules, predominantly on the trunk, inguinal folds, and proximal thighs but not involving palms, soles, and mucous membranes. The patient reported an incident of upper respiratory tract infection that occurred 7 days earlier. Histopathological examination confirmed the diagnosis of acute generalized exanthematous pustulosis. Spontaneous resolution occurred within 2 weeks.* **Conclusions:** *This disease is one of the severe cutaneous adverse reactions that usually have a self-limited and benign course within a few weeks. We propose that a previous respiratory infection triggered the acute generalized exanthematous pustulosis in this pediatric case. Knowledge of this pathology by the medical professionals, in general, and the pediatricians, in particular, will prevent an aggressive and inappropriate approach and management.*

Keywords: *Acute generalized exanthematous pustulosis. Severe cutaneous adverse reactions. Drugs. Infections. T cells. Children*

Pustulosis exantemática generalizada aguda

Resumen

Introducción: *La pustulosis exantemática generalizada aguda es una enfermedad rara. Aunque usualmente se relaciona con el consumo de drogas, ocasionalmente se asocia con infecciones, sobre todo en edad pediátrica. Se caracteriza por el inicio súbito de pústulas no foliculares estériles sobre un fondo eritematoso, fiebre y leucocitosis, con frecuente y pronta resolución espontánea. Afecta principalmente a los adultos, y no es frecuente en la niñez. Se han reportado complicaciones en cerca del 20% de casos.* **Caso clínico:** *Se presenta el caso de una paciente de 10 años con fiebre e historia de dermatosis de 5 días de evolución caracterizada por incontables pústulas no foliculares de predominio en tronco, pliegues inguinales y parte proximal de muslos, respetando palmas, plantas y mucosas. Refirió antecedente de infección respiratoria alta 7 días antes. El examen histopatológico confirmó el diagnóstico de pustulosis exantemática generalizada aguda. Presentó resolución espontánea en el transcurso de 2 semanas.* **Conclusiones:** *Esta enfermedad es una de las reacciones adversas cutáneas severas, que tiene un curso usualmente autolimitado y benigno en pocas semanas. Proponemos que la pustulosis*

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Date of reception: 18-06-2021
Date of acceptance: 18-08-2021
DOI: 10.24875/BMHIM.21000125

Available online: 31-08-2022
Bol Med Hosp Infant Mex. 2022;79(4):268-273
www.bmhim.com

exantemática generalizada aguda en este caso pediátrico fue desencadenada por la infección respiratoria previa. El conocimiento de esta patología por parte del gremio médico, en general, y del pediatra, en particular, evitará un abordaje y manejo agresivo e inapropiado.

Palabras clave: *Pustulosis exantemática generalizada aguda. Reacciones adversas cutáneas severas. Drogas. Infecciones. Células T. Niños.*

Introduction

Acute generalized exanthematous pustulosis (AGEP) is a severe cutaneous adverse reaction. AGEP is characterized by the sudden development of numerous millimetric, sterile, disseminated, non-follicular pustules on an erythematous-edematous base and is usually associated with fever and leukocytosis[1]. Drugs cause approximately 90% of cases; the remainder is caused by viral and bacterial infections and contact with mercury and spider bites[2]. Its worldwide incidence is 1 to 5 cases per million individuals per year. It is more frequent in adult women and rare in children[2-4].

In 1968, Baker and Ryan published on five patients with no history of psoriasis who presented with pustular eruptions of sudden onset, rapid remission, and no recurrence. They named the pathology exanthematous pustular psoriasis, suspecting that drugs or infections were the triggers. In 1980, Beylot et al.[5] introduced the term acute generalized exanthematous pustulosis. In 1991, Roujeau et al. initially described diagnostic criteria using the European Study of Severe Cutaneous Adverse Reactions (EuroSCAR)[6]:

1. Acute pustular rash
2. Fever > 38 ºC
3. Neutrophilia with or without eosinophilia
4. Subcorneal or intraepidermal pustule on skin biopsy
5. Spontaneous resolution in less than 15 days[3]

In 2001, based on these criteria, Sidoroff et al. included a more detailed, rigorous, and specific scoring system, validated by the EuroSCAR study group[5,6].

This study aims to encourage physicians, in general, and pediatricians and first contact physicians, in particular, to learn more about this rare disease in children. Although AGEP is a severe cutaneous adverse reaction, it is usually benign and uncomplicated. Therefore, a thorough understanding of this disease will prevent aggressive and inappropriate management.

Clinical case

We present the case of a 10-year-old female scholar with pruritic dermatosis associated with a fever of five days' evolution. The patient reported that a week before the onset of the symptoms, she had had a transient, febrile upper respiratory tract infection resolved with symptomatic management. On examination, the patient was in good general condition, with a temperature of 39 ºC, 31.5 kg of weight, and 134.5 cm of height. The patient complained of pruritus and a burning sensation in the lesions distributed on the trunk, inguinal region, and proximal thighs (Figure 1A). The lesions consisted of numerous 1-3 mm small non-follicular pustules, some confluent, on an erythematous base (Figure 1B), with no involvement of the palms, soles, and mucous membranes. A skin biopsy was performed, and symptomatic management with oral hydroxyzine and an emollient cream was indicated. Two days later (at 7 days of evolution), pustules were no longer observed, but erythema and pruritus with residual desquamation persisted (Figure 1C). Laboratory studies reported the following results: culture for pustule bacteria, negative; immunoglobulin (Ig)G and IgM for herpes simplex type 1 and Tzanck's test, negative; hemoglobin (Hb), 13.6 g/dL; hematocrit (HCT), 40.8%; platelets, 370,000/µL; leukocytes, 6,420/µL; neutrophils, 2,620/µL; lymphocytes, 2,630/µL; eosinophils, 460/µL; glucose, cholesterol, triglycerides, transaminases, uric acid, blood urea nitrogen (BUN), and creatinine levels were normal. Biopsy confirmed the diagnosis of AGEP (Figure 2). According to the EuroSCAR scale for AGEP, the following diagnostic scores are used for the diagnosis: 1-4, possible; 5-7, probable; 8-12, definitive. As the patient obtained a score of 11, the diagnosis of AGEP was definitive.

Discussion

AGEP mainly affects adults and is infrequent in children. The estimated global incidence of this condition is 1 to 5 cases per million individuals per year. In contrast, it is approximately 1 case per million children per year[7]. Pediatric publications on AGEP are mainly case reports and a case series with few patients[7-9]. In a systematic review, RegiSCAR reported 49 pediatric cases up to 2014[10]. AGEP is usually observed around the sixth decade of life, with a slight predominance in females. Its

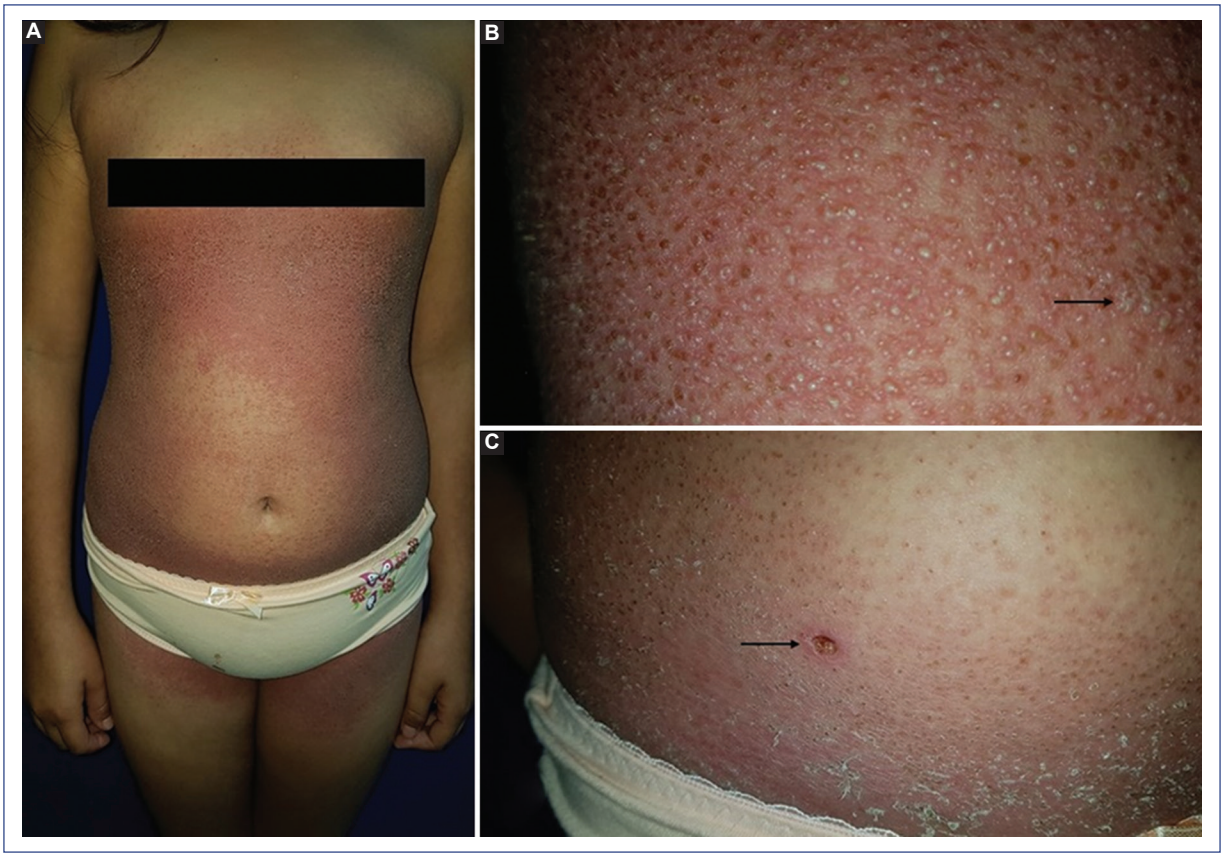

Figure 1. A: acute generalized exanthematous pustulosis. Dermatosis on trunk, inguinal region, and thighs. **B:** hundreds of non-follicular pustules on an erythematous base are observed in the lumbar region, some confluent (arrow). **C:** two days later, erythema persists, but pustules are no longer observed. Post-pustular desquamation is also observed. The arrow indicates the biopsy site.

main risk factors are drug intake, the mean age of 50, and other comorbidities such as diabetes mellitus, psoriasis, and a history of drug hypersensitivity. Seventeen percent of individuals with AGEP have a previous history of psoriasis[11,12].

Drug intake causes more than 90% of the reported cases of AGEP, most frequently antibiotics, mainly beta-lactams and macrolides[3]. Other drugs involved include aminoglycosides, sulfonamides, quinolones, antifungals, antimalarials, acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), antihypertensives, calcium channel blockers, and antiepileptics[11,13,14]. The remaining 10% of the cases of AGEP have been associated with viral (enterovirus, adenovirus, parvovirus B19, cytomegalovirus, hepatitis B, Epstein Barr, among others), bacterial (*Chlamydia pneumoniae*, *Escherichia coli*, *Mycoplasma pneumoniae*, among others), and mycotic (pustulosis caused by fungi) infections, spider bites, mercury poisoning[15,16], parasites, and food allergens, as well as radiotherapy, chemotherapy, and pregnancy[11,13,14]. It has been suggested that viral infections could be the most frequent trigger in the pediatric population[2]. The latency between drug exposure and the onset of AGEP varies from a few hours to 1 to 2 weeks, classically ranging from 48 to 72 hours; in the case of antimicrobials, it is usually less than 24 hours[1,16].

Research studies on the pathophysiology have suggested that AGEP is a T-cell-mediated disease. Following drug exposure, specific CD4+ and CD8+ T cells are activated, proliferate, and migrate to the dermis and epidermis. CD8+ T cells induce apoptosis of keratinocytes within the epidermis by forming subcorneal and intraepidermal vesicles using perforin/B-granzyme and Fas ligand mechanisms. CD4+, CD8+ T cells, and natural killer (NK) cells have also been shown to express granulysin in different reactions to drugs or AGEP, suggesting that this substance may also play a role in pathogenesis. During the initial phase, vesicles formed from keratinocyte apoptosis contain mainly

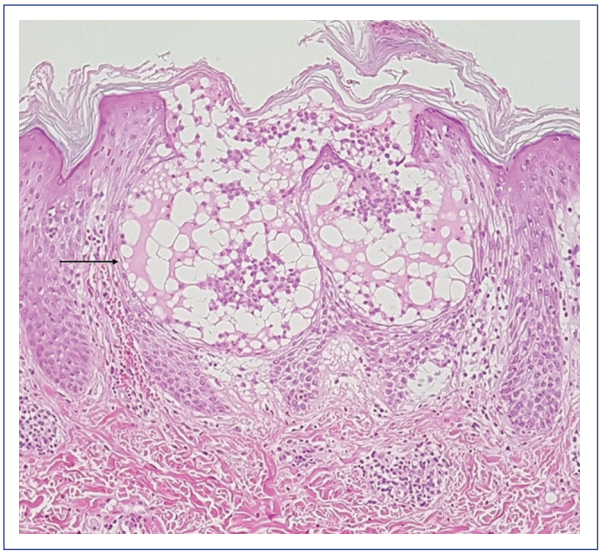

Figure 2. Acute generalized exanthematous pustulosis. Subcorneal blister in the stratum of Malpighi containing fibrin, few neutrophils, and eosinophils (arrow). Spongiosis and lymphocyte exocytosis are observed. Papillary and upper reticular dermis with mild lymphocytic inflammatory infiltrates and few eosinophils with perivascular distribution and intravascular neutrophils. Dilated capillaries with mild wall edema, some congestive with focal erythrocyte extravasation (hematoxylin-eosin stain, 10x).

drug-specific CD4+ T cells and keratinocytes, which release large amounts of a potent neutrophil cytokine (CXCL8). CXCL8 transforms vesicles into sterile pustules by neutrophil chemotaxis[1,17]. Analysis of drug-specific CD4+ T cells from AGEP patients shows a predominant Th1 profile with increased production of interferon-gamma (IFN-γ) and granulocyte/macrophage colony-stimulating factor (GM-SCF), which increases neutrophil survival by enhancing sterile pustule formation.

IFN-γ and GM-SCF can induce the release of CXCL8 by keratinocytes, promoting neutrophil accumulation. Furthermore, CD4+ T cells of some AGEP patients have a Th2 profile with elevated production of IL-4 (interleukin 4) and IL-5 (a potent stimulator of eosinophil growth and proliferation), which explains the eosinophilia found in up to 30% of AGEP cases[1]. A higher level of IL-17 expression by neutrophils, mast cells, and macrophages and a lower level by T cells has been described in patients with AGEP, suggesting that innate cells may be involved in pathogenesis[17]. *IL36RN* gene mutations and increased CXCL8-mediated neutrophilic chemotaxis have been found in some patients with AGEP, suggesting their involvement in its pathogenesis[7]. The genetic predisposition for the development of AGEP is unknown; however, there might be a correlation between mutations of *IL-36RN*, which encodes the interleukin-36 receptor antagonist (IL-36Ra), and the development of generalized pustular eruptions after drug consumption. This suggests that patients with such a mutation are predisposed to develop AGEP [1,17]. In addition, IL-36 Ra deficiency in some patients with AGEP appears to play a role in the increased expression of several proinflammatory cytokines and chemokines, such as IL-1, IL-6, IL-12, IL-23, IL-17, tumor necrosis factor-alpha (TNF-α) and CXCL8/IL-8, which enhances the recruitment and activation of neutrophils[1].

In cases of AGEP of infectious etiology, there is no precise pathophysiological mechanism. However, it is hypothesized that infectious antigens could cross-react with drug antigens, act as haptens, or synergistically with some drugs, triggering the same immunologic reaction as in classical drug-induced AGEP[16]. Regarding the underlying pathogenesis, it has been proposed that drug-like infections lead to T-cell activation[7].

AGEP manifests clinically as a cutaneous eruption of acute onset and is characterized by the appearance of numerous sterile, non-follicular pustules < 5 mm in diameter on an erythematous and edematous base. The dermatosis predominates on the trunk, upper extremities, and intertriginous regions, mainly the neck, axillae, and inguinal areas. However, it may be disseminated without affecting the face, palms, and soles, as in the present case. Occasionally, pustules may coalesce and lead to superficial collarette-shaped desquamation at the sites of the previous lesions[18]. The reaction is limited to less than 15 days after discontinuation of the causative agent or remission of the infection. It may be accompanied by fever, leukocytosis, neutrophilia, and sometimes eosinophilia, depending on the case. Systemic involvement with hepatic, renal, or pulmonary involvement has been described in 17% of patients[17]. Other symptoms include pruritus or burning sensation and mucosa involvement in up to 20% of cases, generally in severe forms and usually restricted to the oral mucosa or rarely to the conjunctivae[1,16]. Edema of the scrotum, hands, face, purpura, petechiae, vesicles, blisters and target lesions have been reported in 50% of patients[11,17]. In addition, severe atypical presentations of AGEP have occasionally been described. These extreme forms have been considered the overlap between AGEP and toxic epidermal necrolysis (TEN) or drug reaction with eosinophilia and systemic symptoms (DRESS). They may present with a clinical course similar to these conditions but with the histopathology of AGEP[6,16,17].

The diagnosis of AGEP is based on clinical and histological criteria validated by the EuroSCAR study group[3]. A more precise evaluation based on morphology, course, and histopathological findings was proposed by Sidoroff et al. and validated by the EuroSCAR group. According to the score obtained, the case can be classified as possible (1 to 4 points), probable (5 to 7 points), or definitive (8 to 12 points)[5,6,19]. According to this scale, the reported case was diagnosed as definitive for AGEP, scoring 11 points.

Histopathology confirmed the clinical diagnosis. Usually, subcorneal or intraepidermal spongiform pustules, edema of the papillary dermis, perivascular infiltrates of neutrophils, and some eosinophils are observed (Figure 2). In addition, focal keratinocyte necrosis and leukocytoclastic vasculitis are occasionally detected[17,20].

Patch tests are helpful when it is necessary to identify the drug involved[4]. A multicenter study showed that 58% of AGEP patients showed positive patch tests[4,10]; another study found positivity in 80%[19]. A negative test does not rule out the involvement of a particular drug. Dermoscopy with polarized light can be helpful: in the early stages, small, milky macules and papules, round globules, and sparsely scattered crusts on a pinkish/reddish background are observed[21].

The differential diagnosis of AGEP should be made primarily with generalized pustular psoriasis of the von Zumbusch type. However, it is sometimes difficult to differentiate, as both may present with a similar clinical picture and unclear histopathology. In the latter, however, there is usually a previous history of psoriasis, fever, and a rash that persists longer, has a more generalized distribution with a tendency to recur, and can be fatal if not adequately treated[11,17]. The history, clinical picture, and histopathological findings can easily exclude other pustular eruptions of bacterial or fungal origin and neutrophilic dermatoses[17]. Differential diagnoses with drug-induced skin disorders such as DRESS syndrome, Stevens-Johnson syndrome, and NET should be considered in severe cases[3]. The most critical factor for differential diagnosis is the faster resolution time observed in AGEP[17].

Although AGEP is benign and self-limited in most cases, it can present renal, hepatic, pulmonary, and bone marrow complications[17]. These complications are infrequent and occur mainly in the elderly, patients with comorbidities, or those with mucous membrane involvement[1,11]. Visceral involvement occurs in < 20% of cases, and amoxicillin is the most commonly implicated drug[16]. In these cases, it can cause death due to multiorgan dysfunction and disseminated intravascular coagulation, although mortality occurs in < 5% of cases[1].

Cases have been reported of patients with AGEP presenting with systemic involvement: hepatomegaly, anemia, acute respiratory failure, hypotension, acute renal failure, cholestasis, and spinal cord involvement, as well as elevated liver function test values (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and gamma-glutamyl transferase), and increased urea and creatinine[20]. In addition, high absolute neutrophil count and C-reactive protein levels were associated with systemic organ involvement[1].

There are no evidence-based treatment guidelines for the management of AGEP[16]. However, since its resolution is usually spontaneous, treatment is supportive, so topical corticosteroids, moisturizers, emollients, antipyretics, and oral antihistamines are frequently adequate[15]. The most critical measure is the suspension of the causative drug (or the remission of the infectious condition). With this, the cutaneous and even systemic involvement resolution occurs in < 15 days[16], as in this case. In the pustular phase, moist dressings with antiseptic solutions and topical steroids can be used, while in the desquamative (post-pustular) phase, emollients could optimize the barrier function[16,17]. Antibiotics are counter-indicated unless there is superinfection of the lesions[1,13]. Medium and high potency topical corticosteroids are used for symptomatic relief of pruritus and inflammation[22]. Systemic corticosteroids are not usually necessary. Some authors consider them effective in cases of extensive cutaneous involvement (prednisone 0.5-1 mg/kg/day)[3,13], although two cases of oral corticosteroid-induced AGEP have been reported[17]. The usefulness of cyclosporine and etanercept in patients resistant to corticosteroid treatment has also been described[18]. In cases of AGEP mimicking NET, intravenous immunoglobulin has been used[16]. Reintroducing the implicated drug should be avoided because of the risk of recurrence, usually with a more rapid onset[13].

The prognosis of this disease is generally favorable, even if there is systemic involvement[13]. The condition resolves spontaneously approximately 10-15 days after discontinuation of the causative drug. Initially, pustules and fever disappear, followed by the collarette-shaped desquamation[6]. The same evolution is observed in cases of AGEP with infectious etiology, which is more frequent in children, as in the case described.

In conclusion, AGEP is a rare disease in pediatric patients. However, this condition should be considered a possible diagnosis in the presence of a sudden onset picture with numerous non-follicular pustules on an erythematous base and associated with fever. Pharmacological etiology is predominant,

although AGEP is often associated with infections in children. The EuroSCAR scale facilitates the confirmation of the diagnosis. In most cases, treatment is supportive with an excellent prognosis. Knowledge of this pathology will improve the diagnostic and therapeutic approach to avoid aggressive and inappropriate management.

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 has this document.

Conflicts of interest

The authors declare no conflicts of interest.

Funding

No funding.

Acknowledgments

We thank Dr. Benilda Martel, Specialist in Dermatology, for her spontaneous and timely collaboration in performing the skin biopsy of the case described.

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