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ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS (AGEP). CASE REPORT

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SUMMARY

Acute Generalized Exanthematous Pustulosis (AGEP) is a drug-induced dermatosis characterized by an acute episode of sterile pustules over erythematous-edematous skin. It is accompanied by an episode of fever, which regresses a few days after discontinuation of the drug that caused the condition or as a result of corticosteroid treatment. The main triggering drugs are antibiotics, mainly beta-lactam ones. Other medications, such as antifungal agents, non steroid anti-inflammatory drugs, analgesics, antiarrhythmic, anticonvulsant and antidepressant drugs, may also be responsible. Histologically, it is characterized by the existence of vasculitis, associated with non-follicular subcorneal pustules. A case of a Caucasian female outpatient unit of Dermatology with AGEP, who presented with generalized pustulosis lesions after the use of cephalosporin for urinary infection is related. The diagnosis was confirmed by the clinical and pathological correlations, the resolution of the dermatosis after discontinuation of the drug and use of systemic corticosteroid treatment, and the recurrence of the disorder after the introduction of a similar drug. The importance of the recognition of this drug-induced dermatosis is given by its main differential clinical and histological diagnoses: generalized pustular psoriasis and subcorneal pustulosis.

KEYWORDS: Antibiotics; Drug-induced dermatosis; Pustular psoriasis.

INTRODUCTION

Acute generalized exanthematous pustulosis (AGEP) is an uncommon disorder characterized by an acute episode and sudden onset of erythematous and edematous eruptions of hundreds of sterile pustules. It is accompanied by fever and is manifested in patients without a previous history of psoriasis. It has a rapid course and resolves within a few days, sometimes in response to corticosteroid treatment[6,7,17,32]. MACMILLAN, in 1973, was probably the first author to describe a case. He called it Drug-Induced Generalized Pustular Rash[25].

In 1980, in France, BEYLOT *et al.* introduced the term Acute Generalized Exanthematous Pustulosis to describe the cases previously reported by BAKER & RYAN[4] in 1968 and set the following criteria for the diagnosis of AGEP[7,17].

- Clinical criterion: acute rash in individuals with no previous history of psoriasis, occurring after an infection or use of drugs, with spontaneous cure.
- Histological criterion: existence of vasculitis associated with non-follicular subcorneal pustulus.

In 1991, ROUJEAU *et al*., in a retrospective study of 63 cases of AGEP collected from nine different french health settings, characterized the illness as having a drug etiology, thus distinguishing it from pustulous psoriasis[28].

The first Brazilian case was described in 1996 by CAMPBELL & FURTADO, who reported the history of a female patient who developed AGEP after treatment with ampicillin[10].

The etiopathogenesis is still obscure. Viral causes have been reported, as exemplified by HARO-GABALDON *et al.* in 1996, who reported a case of AGEP in a patient with positive serum diagnosis for cytomegalovirus. The origin has also been traced to pharmaceutical drugs, related to the treatment of infectious processes. Nevertheless, data suggest that a viral etiology is responsible for no more than 25% of the cases. In some studies, serum conversions for enterovirus were observed, in particular for Coxsackie A9 and Echovirus 11 and 30 and positive serum diagnoses for hepatitis B and Epstein Barr virus are also reported[17,28]. Pharmaceutical drugs are the origin of some 87% of the cases, among which the most important are antibiotics, especially beta-lactam and macrolides. The chronological relationship with the administration of the drug has its own characteristics. The cases due to antibiotic use usually occur within a short span of time - less than 24 hours - after the administration of the medication. This can be accounted for by the fact that people have been sensitized by the widespread use of penicillin. Other prescription drugs may take an average of 18 days to bring the patient to the clinical picture described[28].

Hidroxychloroquine and norfloxacin are described as drugs that can lead to lesions located on photoexposed areas, and hidroxychloroquine

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has been described as an isolated agent[1,2] or one associated with PUVA[9]. Mercury (BOLZINGER *et al.*, 1993) and ultraviolet radiation have also been held responsible for triggering AGEP. In 5% of the cases, the cause was proven[1,2,4,7,8,9,11,12,13,14,15,18,20,21,22,23,24,26,27,28,31,33].

The etiopathogenesis may be explained by the occasional existence of leukocytoclastic vasculitis, which evokes an Arthus-like hypersensitivity mechanism[30]. This could account for the surrounding immune complexes introduced by the infection or drug.

Nevertheless, ROUJEAU *et al*. (1991) reported that AGEP is often present in subjects with a psoriatic history (11 out of 63 cases), but this fact is argued by other authors[28]. BAKER & RYAN[4] in a study that comprised 104 cases of pustulous psoriasis, discussed five cases that they believed had a transitory psoriasiform reaction, occasionally a toxidermal one. They were not convinced of the psoriatic etiology and described it as a psoriasiform reaction under the influence of infection and drugs, without a genetic predisposition. However, they reminded their readers that corticosteroids, acetylsalicylic acid and promethazine are all drugs that can induce pustulous psoriasis[6,10,28].

In 1980, BEYLOT *et al.* mentioned that, in some cases, AGEP may manifest as initial psoriasis, which is disregarded if there is no recurrence of the psoriasiform lesion within the two years following the clinical presentation[7].

In the present paper, the authors report one case of AGEP caused by an antibiotic (cephalosporin) and demonstrate the importance of differential diagnosis.

CLINICAL REPORT

A thirty-one year-old Caucasian female patient, with a urogenital anomaly since birth, suffered episodes of pyelonephritis and repetitive intra-abdominal abscesses. She had no previous history of psoriasis. Forty-eight hours after starting treatment with ceftriaxone, erythematous lesions appeared on her abdominal area and extend to the limbs. These lesions were covered by innumerous spread pustules and accompanied by a febrile peak. The pustulous lesions ruptured, leaving ulcerative and desquamating areas that recovered the whole tegument (Fig. 1 and 2).

Laboratory tests showed hypocalcemia (6.5 mg/dL); leukocytosis with neutrophilia (160%), and increased levels of urea (81 mg/dL) and creatinine (1.5 mg/dL). Bacterial and fungal cultures of the pustulous lesions were negatives.

Histopathological exam of a skin biopsy with hematoxylin-eosin stain showed the presence of subcorneal spongiform pustules, keratinocyte necrosis, and a perivascular acute inflammatory infiltrate rich in neutrophils and eosinophils, with focal areas of leukocytoclastic vasculitis (Fig. 3 and 4). After the diagnosis of AGEP, ceftriaxone was discontinued and a 60 mg/day of prednisone was introduced, resulting in remission of lesions on the 7th day of treatment. Prednisone was gradually discontinued within 15 days because the patient still needed a broad spectrum antibiotic to treat the urological disease, cefpime hydrochloride was introduced. There was then a recurrence of the condition, with disseminated erythematous lesions covered by innumerous pustules and, this time, associated with purpuric lesions on the upper and lower limbs from 3rd day of treatment. The suspension of the antibiotic was followed by resolution of the condition and disappearance of the lesions, using only topical corticoid and hydration. In the second episode, the patient presented with improvement of the clinical picture six days after interruption of drug use. Her laboratory parameters of urea and creatinine were still slightly altered due to the urogenital condition, but serum calcium (8.0 mg) and leukocytosis (10,000) were normal. There was no recurrence of the disorder during 11 months of follow-up.

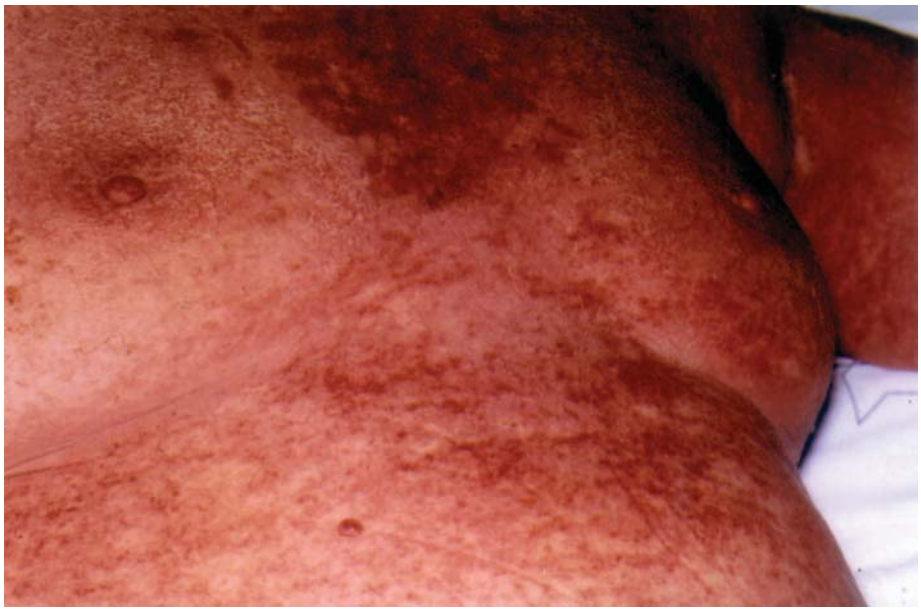

Fig. 1 - Erythematous lesions with sterile pustules in the abdominal area.

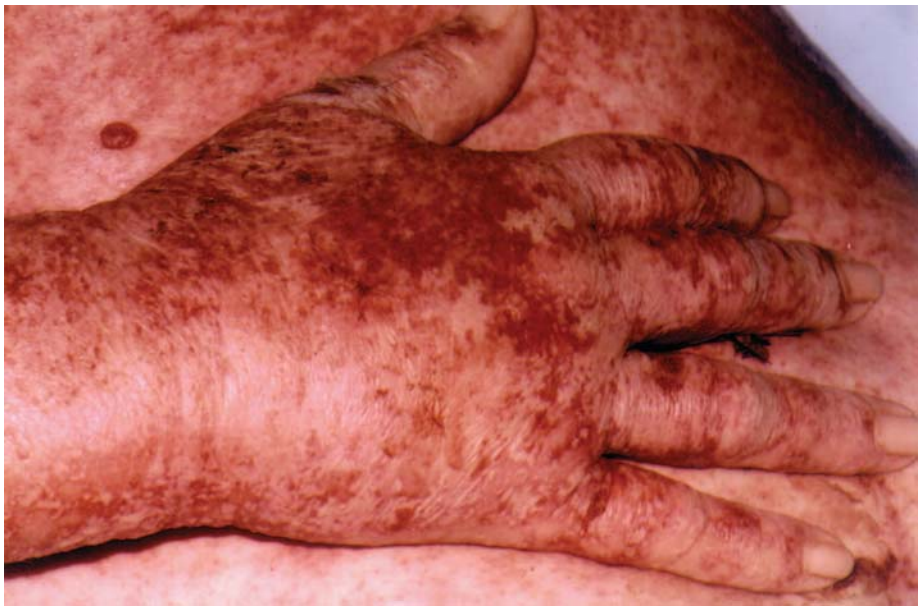

Fig. 2 - Purpuric lesions and sterile pustules in the hand.

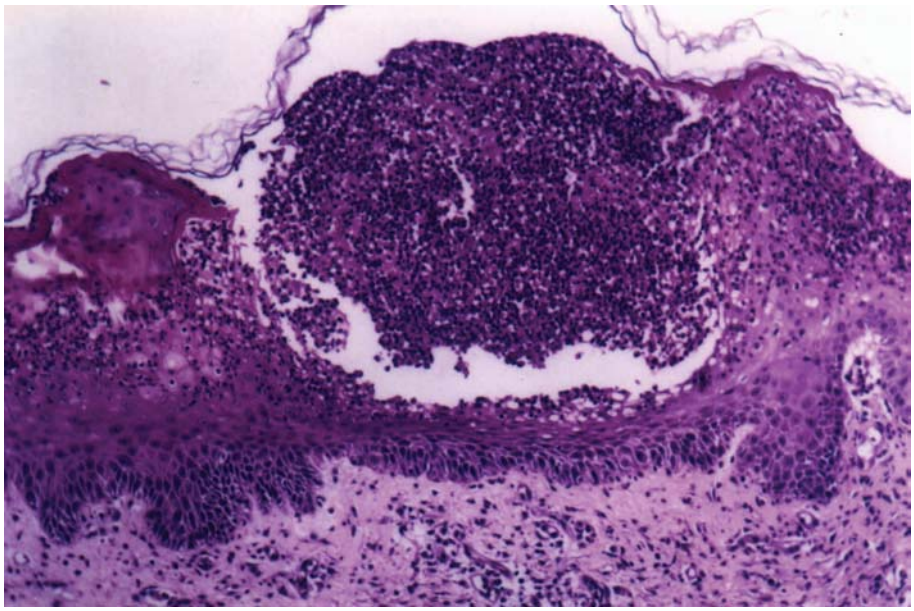

Fig. 3 - Epidermis with spongiform pustule. Mixed inflammatory infiltrate and edema in the upper dermis. (63X HE).

DISCUSSION

Diagnosis of drug-induced cutaneous eruption demands circumstantial evidence and the exclusion of other diagnostic possibilities. Although there are clinical and histological similarities between AGEP and generalized psoriasis, the criteria proposed by BEYLOT *et al.* in 1980 enables distinction between the two entities and differentiation from other pustulous dermal conditions (Snnedon-Wilkinson Disease; Toxic Epidermal Necrosis; Pustular Miliaria; Contact pustular dermatitis and Pustular infected disease of the skin)[7,25,28,29]. In order to establish the diagnosis between the two entities, four criteria have been proposed[7] :

- history of reaction to the drug
- recent administration of the drug
- duration of pustules
- fever

AGEP is defined by rapid onset following the introduction of the

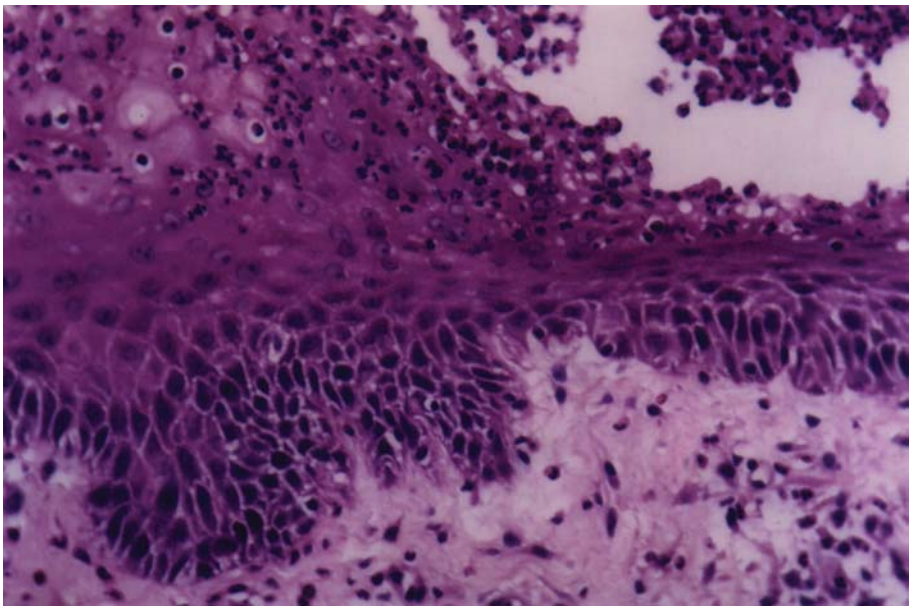

Fig. 4 - Spongiform pustule bottom in the epidermis and edema and neutrophils in papillary dermis. (160X HE).

drug (less than 24 hours) and marked predominance of antibiotics as triggering agents (80% of the cases). Clinically, it is characterized by polymorphism of eruption, single episode, quick course of action, absence of arthritis and frequent administration of drugs[3,10,28]. However, in pustulous psoriasis, the eruption is monomorphic, last longer and recurs. Arthritis is associated in 32% of the cases, and drugs are rarely implicated in the etiology. The involution of the condition is slower, taken between 10 and 14 days (Table I)[3].

Clinically, lesions begin on the face and, within a few hours, they spread to the trunk and limbs, or begin to arise in intertriginous areas. After that there is annular desquamation for a few days, possibly accompanied by polymorphic lesions, especially purpuric lesions on the legs and feet. The mucous membranes are affected in 25% of the cases. Sometimes the pustules converge, giving the false aspect of positive Nikolsky's sign, and leading to misinterpretation of toxic epidermal necrosis or staphylococcal scalded skin syndrome (SSSS)[6,7,10,17,32].

Table 1
Comparison of clinical, laboratory and histopathology aspects of AGEP and GPP

Characteristics	AGEP	GPP
Age	Adults	Adults
Cause	Drugs; viral infection	Respiratory tract infection
Clinical characteristics	Numerous confluent, generalized, diffuse on erythematous skin	Confluent pustules on erythematous skin
Fever	High	Prolonged
Leukocytosis	Yes	Yes
Course	Self-limited	Recurrent
Histology	Spongy, subcorneal pustules, leukocytoclastic vasculitis, eosinophils	Spongy, subcorneal pustules, psoriasiform acanthosis

AGEP = Acute Generalized Exanthematous Pustulosis; GPP = Generalized Pustular Psoriasis.

In the present case, the clinical condition started with erythematous lesions on the abdominal region, unlike what has been described in the literature, with an onset of pustules that spread over 24-hour period of time. The clinical picture included fever, and there were no mucous lesions or arthritis, thus coinciding with the description of AGEP in the international literature. There was regression of the condition after discontinuation of medication and introduction of corticosteroid treatment. Nevertheless, we observed a clinical recurrence manifested by polymorphic lesions in the form of purpuric lesions on upper and lower limbs after the introduction of a similar drug, cefpime hydrochloride.

Reactions of hypersensitivity to cephalosporins are among the most common drug adverse effects, and there is no evidence that one cephalosporin has a higher or lower likelihood of causing sensitization. The observed reactions seem to be identical to those caused by penicillin; this could be related to the beta-lactam structure shared by two groups. Both generations of cephalosporins have the same beta-lactam structure. Owing to the similar structures of penicillin and cephalosporin, patients allergic to one of these drug classes may manifest cross-reactivity when taking a drug from the other class. There are no skin patch tests capable of safely predicting whether a patient is allergic or not to the various groups of cephalosporins[16]. In lab tests we may observe leukocytosis with neutrophilia and eosinophilia. Hypocalcemia may also be found, mainly in the cases accompanied by hypoalbuminemia. Transitory renal failure may occur. In some cases there is a momentary increase in aminotransferasis. The culture of pustules is negative[28,32]. In the present case, leukocytosis with neutrophilia, hypocalcemia and sterile culture of pustules were

observed. The histopathological condition presented in this case was compatible with the diagnosis of AGEP, including the presence of spongy pustules and necrosis of keratinocytes. The occurrence of eosinophil-rich subcorneal or intraepidermal pustules, the perivascular infiltrate with eosinophils and leukocytoclastic vasculitis with fibrinoid deposit is consistent with AGEP. Histologically, the differential diagnosis from pustulous psoriasis is made by the presence in the latter of hyperplasia of the epidermis and papilloacanthosis[3,28]. In the present case, clinical and histological characteristics, chronological relation with administration of cephalosporin and, above all, the quick resolution of the condition following the interruption of medication, met the criteria for diagnosis of AGEP.

CONCLUSION

The authors reported a case of AGP following the administration of cephalosporin, concluded that differential diagnosis among pustulous affections is important and essential before introduce the treatment to the patient.

RESUMO

Pustulose exantemática aguda generalizada (AGEP)

A pustulose exantemática aguda generalizada (AGEP) é uma dermatose induzida por droga, caracterizada por episódio agudo de aparecimento de pústulas estéreis sobre base eritemato-edematosa, acompanhado de febre. Este quadro regride espontâneamente após a suspensão da droga ou em resultado do tratamento com corticóide sistêmico. As principais drogas envolvidas são agentes antifúngicos, antiinflamatórios não hormonais, analgésicos, antiarrítmicos e anticonvulsivantes. Histologicamente caracteriza-se por vasculite associada a pústulas subcórneas não foliculares. Relatamos caso de paciente branca, feminina, que se apresentou com lesões pustulosas generalizadas após o uso de cefalosporina. O diagnóstico foi confirmado pelos achados clínicos e histológicos; pela resolução do quadro após a suspensão da droga e pela introdução de corticóide sistêmico, e pela recorrência após a introdução de droga similar. A importância do reconhecimento deste tipo de dermatose induzida por droga reside na necessidade importante de seu diagnóstico diferencial, clínico e histológico, com a psoríase pustulosa generalizada e a pustulose subcórnea, particularmente no que tange às opções terapêuticas que se apresentam para o tratamento das mesmas.

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