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Diltiazem-Induced Acute Generalized Exanthematous Pustulosis: a Case Report and Review of the Literature

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To the Editor:

The term acute generalized exanthematous pustulosis (AGEP), coined by Beylot in 1980, refers to a rare form of cutaneous hypersensitivity characterized by multiple, small, sterile, nonfollicular pustules, appearing in groups on an area of erythematous skin.¹ Although AGEP has sometimes been attributed to enterovirus infection or exposure to mercury, in 90% of cases it constitutes a drug-induced skin reaction.¹ The antimicrobials, mainly the aminopenicillins, macrolides, and terbinafine figure among the most frequently implicated agents, although cases of AGEP have been reported associated with a long list of drugs including allopurinol, cyclooxygenase-2 inhibitors, omeprazole, and antiepileptic drugs.^{2,3} We present a case of AGEP that occurred in the context of the administration of diltiazem.

The patient was an 84-year-old woman with a history of long-standing systemic hypertension and atrial fibrillation. She was admitted to our hospital for decompensation of her heart failure. She denied any history of psoriasis. Her usual treatment included furosemide, verapamil, omeprazole, and acenocoumarol. At the time of admission, verapamil was changed to diltiazem (60 mg/d), but there were no other changes to her treatment. After 11 days in the hospital, she developed an erythematous rash on the trunk and abdomen and in the groin; numerous, nonfollicular, slightly confluent, pustular lesions then rapidly appeared on the rash (Figure 1). There was associated fever and general malaise, but no involvement of mucosal surfaces. The important finding in the blood tests was the presence of leukocytosis (20 400 cells/ μ L, with 87% neutrophils). Microbiological study was negative. Skin histology revealed multiple subcorneal pustules in different phases, formed of neutrophils, associated with a perivascular and periadnexal lymphocytic infiltrate (Figure 2). With the suspected diagnosis of diltiazem-related AGEP, treatment with that drug was interrupted. The fever resolved within

48 hours and the rash disappeared rapidly after a few days, associated with minimal desquamation.

From a clinical point of view, AGEP is characterized by the sudden onset of a pustular rash, predominantly affecting the trunk and skin folds, arising on an edematous area of diffuse erythema.² The rash is usually associated with systemic manifestations (fever, leukocytosis, and renal failure), although life-threatening disease is very rare. Mucosal involvement is rare and is limited to the oral



Figure 1. Edematous, erythematous rash with multiple, small, partially confluent pustules: A, on the trunk and upper limbs, and B, on the lower limbs.

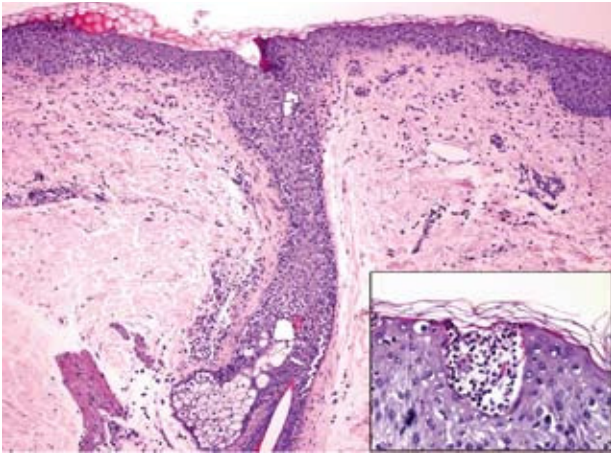


Figure 2. Skin biopsy showing multiple subcorneal pustules with focal areas of spongiosis and a moderate periadnexal lymphocytic infiltrate (hematoxylin-eosin, $\times 40$; inset, $\times 100$).

cavity.¹ In 1991, Roujeau⁴ proposed a series of clinical and histological criteria to establish the diagnosis; these criteria include an acute onset of the rash and complete resolution

in less than 15 days. The differential diagnosis includes generalized pustular psoriasis of von Zumbusch, and other severe forms of toxic skin disorders, such as exudative erythema multiforme major.^{1,2,4} Histologically, AGEP presents subcorneal spongiform pustules and collections of neutrophils, with papillary edema and focal necrosis of keratinocytes.^{2,4} The absence of eccrine involvement and of vacuolar changes at the dermoepidermal junction, common in exudative erythema multiforme major, is suggestive of AGEP. The differential diagnosis with generalized pustular psoriasis is more difficult, although the longer duration of the rash and the absence of a recent history of taking medication would suggest generalized pustular psoriasis.⁴ Although the etiology of AGEP is unknown, the in vitro demonstration of a specific lymphoproliferative response to drugs and the frequent positivity of skin patch tests in these patients would suggest a T-cell-mediated disorder, and the possibility of a common etiologic mechanism with psoriasis has been proposed.^{1,5}

Up to 5% of patients who receive treatment with diltiazem present some type of dose-dependent adverse reaction (headache, edema, atrioventricular blocks).³

Table. Review of the 13 Cases of Acute Generalized Exanthematous Pustulosis Triggered by Diltiazem Reported in the Literature

Patient	Author, Year (reference)	Age, y/ Sex	Dose of Diltiazem	Days Until Onset	Days Until Resolution	Comments
1	Lambert et al, ⁸ 1988	77/F	60 mg/8 h	10	5	Accidental re-exposure after 5 mo
2	Janier et al, ³ 1993	83/F	NG	4	7	
3		80/F	NG	15	10	
4	Sánchez et al, ¹⁰ 1994	67/M	NG	16	5	
5	Wakelin and James, ¹ 1995	58/F	90 mg/12 h	10	7	Treatment with methotrexate was required. SPT positive
6	Blodgett et al, ⁴ 1997	65/F	NG	14	7	
7	Vicente-Calleja et al, ⁷ 1997	71/F	100 mg/12 h	21	Very few	SPT positive 2 mo after resolution
8	Knowles et al, ⁶ 1998	48/M	120 mg/24 h	10	12	Treatment with corticosteroids was required
9	Jan et al, ⁹ 1998	82/F	200 mg	24 h	NG	Previous episodes of pustular rash after diltiazem. SPT positive
10	Arroyo et al, ¹¹ 2002	47/F	NG	NG	NG	
11	Girardi et al, ⁵ 2005	72/F	NG	NG	NG	Correlation between SPT and the in vitro lymphoproliferative response
12	Gesierich et al, ² 2006	60/F	NG	14	Very few	SPT positive 3 mo after resolution
13	Present case, 2008	84/F	60 mg/12 h	11	5	

Abbreviations; F, female; M, male; NG: not given; SPT: skin patch test.

Skin toxicity can present with a wide spectrum of manifestations: pruritus, urticaria, a maculopapular or, more rarely, petechial rash, photosensitivity, exudative erythema multiforme major, toxic epidermal necrolysis, and vasculitis.^{1,6} Exposure to diltiazem is a rare but well-documented cause of AGEP.¹⁻¹¹ The Table summarizes the clinical features and course of the 13 cases reported up to now in the literature in English and Spanish, including the present case (search in PubMed using the key words: “diltiazem” or “calcium-channel blocker” and “pustulosis” or “AGEP”). The review of these cases shows a marked female predominance (male to female ratio, 2 to 11). The delay in the onset of symptoms varies between 24 hours⁹ and 3 weeks⁷ after starting treatment with diltiazem (mean [SD], 11.4 [5.5] days). After withdrawal of treatment, complete resolution of the rash occurs in 7.3 (2.4) days. Those cases in which the accidental rechallenge was documented provide the most conclusive evidence in favor of the implication of diltiazem as a trigger of the condition.^{8,9} The use of patch tests constitutes a valid option for confirming this association, as positive results have been found in all cases in which those tests were performed.^{1,2,7,9} In conclusion, the calcium channel blockers and, in particular, diltiazem, must be considered to be potential triggers of AGEP. Positive skin patch testing will confirm the diagnosis in cases of atypical clinical presentation.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Chronic Painless Dactylitis as the Initial Finding in Disseminated Lung Adenocarcinoma

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To the Editor:

Cutaneous metastases secondary to primary visceral tumor are uncommon events, occurring in 0.7% to 9% of cases.^{1,2} They usually appear in patients previously diagnosed with a primary tumor. We present the case of

a patient who developed chronic painless dactylitis that was histologically compatible with a previously unknown underlying metastatic lung adenocarcinoma.

The patient was a 56-year-old woman, a nonsmoker with hypertension, who was admitted for evaluation