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A case of acute generalized exanthematous pustulosis due to amoxicillin-clavulanate with multiple positivity to beta-lactam patch testing

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Key words

AGEP, patch testing, beta-lactam, delayed hypersensitivity reaction, amoxicillin-clavulanate

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Summary

We present a case of acute generalized exanthematous pustolosis (AGEP) induced by amoxicillin-clavulanate. Clinical diagnosis was confirmed by symptoms presentation and histological features (Euroscar score point compatible with definite diagnosis). Patch testing performer six months later confirmed sensitization to the culprit drug and showed positivity also to other beta-lactam antibiotics (penicillin G and cephalexin). We believe that a T cell delayed response to betalactams common ring could be involved.

Introduction

Acute generalized exanthematous pustolosis (AGEP) is a rare cutaneous reaction characterized by sudden onset of non fullicular sterile pustules rash on edematous erythema. Most often AGEP is drug- induced (90% of cases) (1), even if viral (2-4), bacterial (5-7) heavy metals (mercury) (8), spider bites (9), chemotherapy (10), radiation and PUVA (11,12) etiology have been described. Antibiotic drugs in particular are the most frequent cause, especially aminopenicillins (13,14,15), but also quinolones (16). We present a case of AGEP induced by amoxicillin/clavulanate with multiple positivity to betalactam patch testing.

Case report

A 32-years old man was treated by his family doctor with amoxicillin-clavulanate 1 g twice a day and betametasone 1 mg/day for pharyngitis. On day two he developed face, neck and trunk erythema, rapidly spreading to the body surface. He was admitted on day four to Dermatology department with fever of 38.3° C, edematous erythema and non fullicular pustules on his neck, trunk and proximal limbs (figure 1). His blood test showed leucocytosis (14390/mm3) with neutrophilia (13600/mm3), normal eosinophil count (400/mm3) and elevated C-reactive protein (1.75 mg/dl). Liver and renal function tests were normal. Bacterial cultures from lesions and blood were negative. Skin biopsy showed subcorneal pustules with some epithelial cells, consisting with AGEP. He was treated with methyl-prednisolone 60 mg/day and from day 7 pustules start cleaning following desquamation; a complete resolution was achieved on day 14. Six months later he was evaluated in our Allergy Outpatient Clinic. He denied previous personal history of atopy, adverse drug reaction and skin disease. He referred having taken amoxicillin-clavulanate several times before the AGEP episode, last assumption 5 months before the re-

Figure 1 - Pustular lesions affecting the trunk; two purpuric macules are also present.

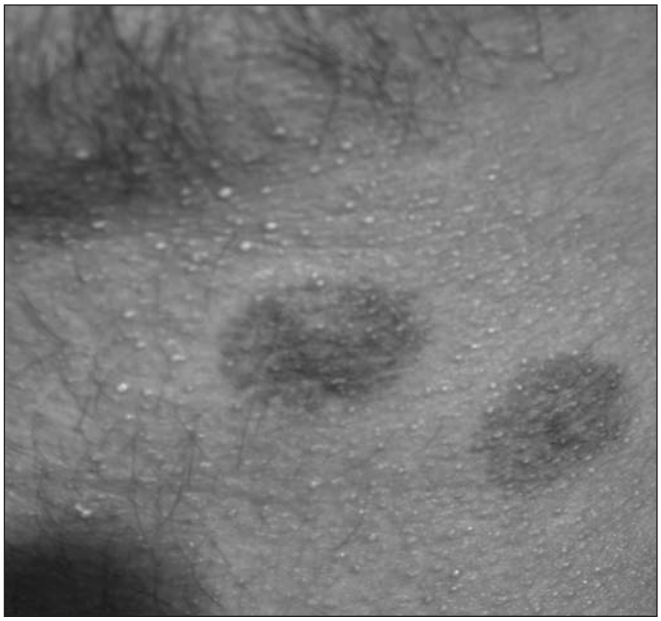
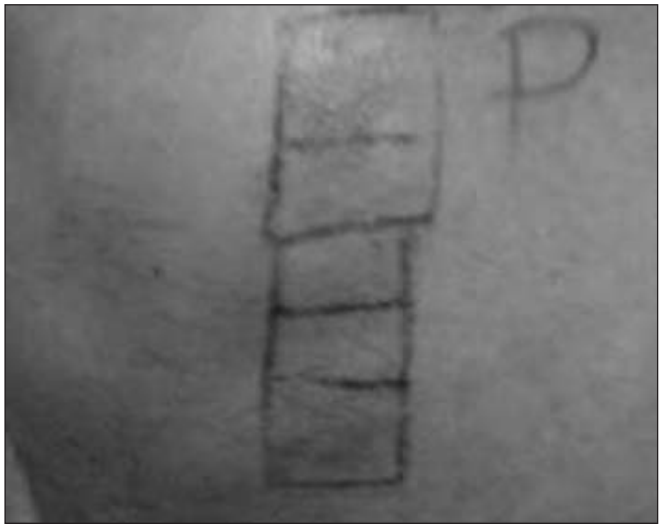


Figure 2 - Patch testing of penicillin G, cephalexin, cephazolin, cefuroxime and amoxicillin at a concentration of 5% in petrolatum showing a positive result with pustular lesion to penicillin G and amoxicillin (first and last one respectively), a milder reaction to cephalexin (second patch).



action. Patch tests with a panel of betalactam antibiotics (penicillin G, amoxicillin, cephazolin, cefuroxime, cephalexin at a concentration of 5% in petrolatum) were performed resulting positive results for penicillin G, amoxicillin and cephalexin (figure 2). The patient was told to avoid betalactam antibiotics.

Comments

AGEP is a rare drug-induced disease: from the inclusion rate in the EuroSCAR study the incidence rate was estimated to be in the range of 1 to 5 cases per million per year (17). AGEP diagnosis is based on clinical aspect, disease course and histological features of skin biopsy; the EuroSCAR study group developed an AGEP score system in which the achievement of 8-12 points represents a definite diagnosis (17); the case score was 9 (Table 1). Typically AGEP has a benign course and complications are rare (18, 19). Systemic involvement in AGEP is not frequent and generally consisted of slight renal function reduction and mild hepatic enzymes elevation (20). Differential diagnosis of AGEP is mainly pustular psoriasis, but our patient had no previous history of psoriasis.
Kokaji et al. suggested that a bacterial infection could be a condition leading to the cloning of drug-specific Tcells (21), but on the other hand the EuroSCAR case-control study showed that infections played no prominent role in causing AGEP (1). Although AGEP pathophysiology is not completely understood a IV- type allergic reaction has been proposed; T cells production of IL-8 and CXCR8 activate and recruit neutrophils which leads to sterile pustular eruption (22). According to Pichler's new sub-classification of de-

Table 1 - EuroSCAR AGEP score system in our patient. The achievement of 8-12 points represents a definite diagnosis.

Pustules Typical	2
Erythema Typical	2
Distribution/pattern	2
Postpustular desquamation yes	1
Mucosal involvement no	0
Acute onset (<10 d) yes	0
Resolution < 15 days yes	0
Fever >38.75° C no	-1
Polymorphonuclear neutrophils >7000/mm3 yes	1
Exocytosis of PMN yes	2
Total score	9

layed IV- type hypersensitivity reactions (a-d), AGEP can be considered a type IV d reaction (23).

In clinical practice patch testing to drugs in AGEP is used in differential diagnosis in ambiguous cases with a good sensitivity (50% rising to 80% for some antibiotics) (24). Generally patch testing with the specific drug is a safe procedure even if some cases of reactions not limited to the application site have been reported (12). Little is known about cross-reactivity in betalactam-induced AGEP; a case of recurrent episodes of AGEP due to different betalactam antibiotics (piperacillin, ceftazidime and meropenem) has been described (25), but patch testing was not performed. In our patient we found a multiple positivity to penicillin, aminopenicillin and cephalosporin and patch test mimic the morphological characteristics of the original pustular lesion. These findings suggest a T cell delayed response to betalactam common ring.

In conclusion, we present a case of AGEP induced by amoxicillin/clavulanate in which patch tests were helpful to identify multiple positivity to betalactams and to provide specific indications of avoidance.

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