

The importance of patch tests in the differential diagnosis of adverse drug reactions *

A importância das provas epicutâneas de contacto no diagnóstico diferencial de reações a medicamentos

Ana Rita Travassos¹

Joana Antunes¹

Luís Soares Almeida³

David Pacheco¹

Raquel Silva²

Paulo Filipe³

Abstract: Exudative erythema multiforme is an acute self-limited skin disease often associated with infections (usually viral), and also with systemic diseases and drugs. We report the case of a 39-year-old woman diagnosed with systemic lupus erythematosus, who presented at the emergency clinic with exudative erythema multiforme which started 10 days after taking amoxicillin and clavulanic acid for tonsillitis together (almost simultaneously) with the pneumococcal vaccine. Rowell's syndrome was also considered to be a possibility. Skin patch tests were carried with the standard battery of patches (GPEDC) and the active ingredients of the suspected drugs (Chemotechnique[®]), with readings at D2 and D3. The tests were positive for amoxicillin 10% pet (++) , ampicillin 10% pet (+ +) and penicillin G potassium 10% pet (+). We accepted the diagnosis of erythema multiforme due to amoxicillin, confirmed by patch testing.

Keywords: Amoxicillin; Erythema multiforme; Lupus erythematosus, Systemic; Patch tests

Resumo: O eritema exsudativo multiforme é uma erupção aguda, autolimitada, frequentemente associada a infecções (geralmente virais), doenças sistêmicas e fármacos. Apresenta-se o caso de uma mulher de 39 anos, com o diagnóstico de lúpus eritematoso sistêmico, que recorreu à Urgência com quadro de eritema exsudativo multiforme, com início 10 dias após tomar amoxicilina e ácido clavulânico por amigdalite e, quase simultaneamente, receber a vacina antipneumocócica. Colocou-se também a hipótese de síndrome de Rowell. Efetuaram-se testes epicutâneos de contacto com bateria básica (portuguesa) e princípios ativos dos fármacos suspeitos (Chemotechnique[®]). Encontrou-se hipersensibilidade à amoxicilina 10% vas (++) , à ampicilina 10% vas (++) e à penicilina G potássica 10% vas (+), atribuindo-se à amoxicilina a causa mais provável do eritema exsudativo multiforme.

Palavras-chave: Amoxicilina; Eritema multiforme; Lúpus eritematoso sistêmico; Testes do emplastro

INTRODUCTION

Exudative erythema multiforme (EEM) is an acute self-limited muco-cutaneous syndrome usually associated with acute infections, including herpes simplex virus (HSV) and *Mycoplasma pneumoniae* and less frequently with systemic diseases (inflammatory bowel disease, systemic lupus erythematosus (SLE) / Rowell's syndrome or Behcet's disease) and drugs [non-steroid anti-inflammatory drugs (NSAIDs), sulfonamides, anticonvulsants, allopurinol].^{1,2,3} The incidence of EEM associated with amoxicillin is quite rare in the literature.³

CASE REPORT

We describe the case of a white 39-year-old woman with a known history of SLE for nine years who presented at the emergency clinic with erythematous papules. The papules were violet and concentric, with a pale central ring (target or iris lesion) distributed symmetrically and predominating on the extremities, clinically suggestive of EEM (Figure 1). The patient denied fever, arthralgia or other systemic symptoms.

The patient had been regularly medicated with

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¹ MD, Dermato-venereology intern at the University Dermatology Clinic, Santa Maria Hospital (HSM), Lisbon, Portugal.

² MD, Dermatologist, University Dermatology Clinic, Santa Maria Hospital (HSM), Lisbon, Portugal.

³ PhD, University Dermatology Clinic, Santa Maria Hospital (HSM), Lisbon, Portugal.

Meticorten[®] (prednisone 5mg/day) and Plaquenil[®] (hydroxychloroquine) for SLE and, 10 days before the episode that led to the emergency, had been started on antibiotics (amoxicillin and clavulanic acid) for tonsillitis, at the same time as receiving the pneumococcal vaccine Pneumo 23[®].

Diagnostic hypotheses were as follows: EEM associated with (i) prior viral infection, (ii) amoxicillin and clavulanic acid or pneumococcal vaccine or (iii) SLE (Rowell's syndrome).

The patient's history suggested a possible temporal relationship between amoxicillin/ clavulanic acid and pneumococcal vaccine. This required clarification. The patient was admitted to the Dermatology Service and treated with prednisolone (30mg/day) with rapid clinical improvement.

Histological examination of skin biopsies revealed interstitial neutrophilic dermatosis, with a positive but weak *lupus band test (LBT)* result. Analysis revealed: the presence of antibodies (Ab), anti-Epstein-Barr virus (EBV), positive IgG and IgM, positive antinuclear antibody (ANA) (up to 1/640), homogeneous nuclear pattern, anti-double-stranded DNA (ds-DNA-Ab) and positive anti-Ro antibodies.

After reducing the dose of prednisolone to 5mg/day (dose previously established to control the SLE), the patient was referred for contact patch tests. These were performed 8 weeks later with the standard battery (GPEDC) and the suspect active drug ingredients in vaseline (Chemotechnique[®]). Readings taken at 48 and 72 hours revealed hypersensitivity to amoxicillin 10% vas (++) , ampicillin 10% vas (+ +) and penicillin G potassium 10% vas (+) (Figure 2).

DISCUSSION

EEM, the *Stevens-Johnson Syndrome (SJS)* and toxic epidermal necrolysis (TEN) were considered from a *classical nosographic perspective* to be related dermatoses, given that they possessed common reactive and etiological characteristics (infections, drugs and systemic diseases)^{4,5}. Agreement exists at present on the concept of separating the EEM spectrum from the SJS/TEN spectrum.¹

Despite the infections (especially HSV) being considered as the main cause of EEM, as opposed to SJS and TEN, whose etiology is largely due to drugs, their association with drug reactions is described in the literature (in particular: sulfonamides, phenytoin, NSAIDs and allopurinol).^{1,4,3,5}

Allergic reactions to drugs are traditionally classified according to Coombs and Gell as the following: immediate hypersensitivity reactions (Type I), cytotoxic reactions (Type II), immune-mediated (Type III) reactions and delayed hypersensitivity reactions (Type IV-mediated by T cells).^{6,7} According to the latest knowledge about the function of T cells, Type IV reactions were subclassified as IVa-IVd, with the reactions associated with type IVc: maculopapular, bullous and neutrophilic skin reactions (with a prevalence of SJS and TEN), in which the role of cytotoxic T cells predominates through *cytotoxicity mediated by CD8+ T cells*, with the destruction of keratinocytes.⁷

In some cases, both agents (drugs and infection) can be identified as potentially precipitating EEM.³ Viral infections have been associated with increased risk of allergic reactions and, although the exact mechanism is not yet fully known, a breakdown



FIGURE 1: Erythematous papules in a violet-colored ring with pale iris, symmetrically distributed



FIGURE 2: Reading done 72 hours after patch tests for amoxicillin and ampicillin

of tolerance or an enhanced immune reaction to drugs after a viral infection have been suggested. Two mechanisms have been proposed: (i) *antigenic expression changes* occurring in the drug or its metabolites, probably associated with changes in the expression of enzymes that metabolize the respective drugs, or (ii) changes in the regulation of immune response.³

With regard to the diagnosis of Rowell's syndrome in this particular case, the currently-accepted criteria as defined by Zeitoun *et al.* are not fulfilled, despite the existence of a strong etiological link to the ingestion of drugs (amoxicillin).^{8,9,10} RS is defined by the presence of three major criteria: (i) recognition of SLE, discoid lupus or sub-acute lupus; (ii) erythema multiforme lesions, with or without mucosal involvement; and (iii) positive ANA in speckled pattern and at least one minor criteria: (i) perniosis; (ii) anti-Ro or anti-La positive antibodies; and (iii) a positive rheumatoid factor (RF).^{8,9,10}

We believe that the most likely cause for the EEM was amoxicillin. The epicutaneous contact tests proved hypersensitivity to ampicillin was 10% (+ +) and amoxicillin 10% was (+ +) and (less intensely) to penicillin G potassium was 10% (+). For these reasons we recommended ruling out treatment with any antibiotic in this group of drugs.

It is worth noting the presence of some possible EEM triggers: viral infection (EBV), drugs (amoxicillin) and systemic disease (SLE). Note also the importance of using contact patch tests for the clinical imputation of amoxicillin and the clinical characterization of cross-reactions, both of which provided the patient with a more accurate list of medicines to be avoided. □

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MAILING ADDRESS / ENDEREÇO PARA CORRESPONDÊNCIA:

Ana Rita Travassos
 Clínica Universitária de Dermatologia - Hospital
 de Santa Maria
 Avenida Professor Egas Moniz
 1649 028 Lisboa, Portugal
 Tel./Fax: 00351-9-6234-1475 00351-2-1795-4447
 E-mail: ritatravassos@gmail.com

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