Erythema multiforme to amoxicillin with concurrent infection by Epstein-Barr virus

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ABSTRACT

Background: The incidence of rashes following the intake of aminopenicillins during an acute episode of infectious mononucleosis is high, but severe cutaneous reactions as erythema multiforme or Stevens-Johnson syndrome are rare manifestations in childhood.

Material and methods: We report the case of a 7 year old girl that developed a generalized purpuric rash with target shaped areas, 9 days after starting treatment with amoxicillin-clavulanic acid. Laboratory investigation revealed a significant increase of Epstein Barr virus (EBV) specific IgM antibody. After skin biopsy she was diagnosed as erythema multiforme syndrome.

Prick, intradermal and patch tests were performed with penicilloylpolylysine, minor determinant mixture, benzylpenicillin, ampicillin, amoxicillin, cefazoline and cefotaxime, the 24 hours reading was positive for aminopenicillins. Patch tests were also positive only for aminopenicillins, other betalactams were negative.

Conclusions: The interaction between an infectious agent (EBV) and amoxicillin could precipitate the severe skin reaction. Patch test and delayed intradermal reading with amoxicillin were an useful tool for the diagnosis of the etiological agent in this reaction. The negative response to other beta-lactams, suggests that the aminobenzyl group of the side chain of amoxicillin plays a predominant role in this reaction.


CASE REPORT

A seven year old girl, previously in good health had a clinical picture of fever, pharyngitis and lymphadenopathy, that was treated with some doses of paracetamol and amoxicillin – clavulanic acid. Nine days after starting such antibiotic she developed a maculopapular rash. She was diagnosed as mononucleosis syndrome (she showed activated lymphocytes in periferal blood) and amoxicillin-clavulanic acid was withdrawn, but her clinical condition dete-
orated, so she was admitted to the Department of Pediatrics. She had received amoxicillin-clavulanic previously with good tolerance.

Physical examination of the patient on admission revealed slight fever, oral enanthema and general-ized macular rash on face, neck, chin and trunk that spread later to extremities, with tendency to coalescence and being purpuric in chin and neck; target-shaped lesions were also observed in some ar-eas.

Laboratory investigation revealed normal com-plete blood count, urinalysis, liver and renal function test; electrolytes, coagulation study, serum immuno-globulin, erythrocyte sedimentation rate was 32 mm the first hour. Her antibodies against herpes virus (HSV) did not increased, but she showed an increase of EBV specific immunoglobulin M antibody.

Skin biopsy of a lesion on the arm revealed lymphocyte accumulation at the dermal epidermal inter-face, with vacuolar degeneration of the basal layer, scattered necrotic keratinocytes, spongiosis, and extravasated erythrocytes and eosinophils, features consistent with the diagnosis of erythema multi-forme. The patient started treatment with oral steroid for 12 days. Skin lesions healed with transitory hyp-perpigmentation.

Skin tests

Two months later, prick and intradermal test (IT) were carried out using penicilloïd-poly-L-lysine (PPL) and minor determinant mixture (MDM) (both from Al-ligopharma, Reinebek, Germany) at concentrations of $5 \times 10^2$ and $2 \times 10^3$ mM respectively, initially diluted 1:100 in 0.9 % NaCl and as immediate reading was negative, testing were carried out with the undiluted solution, benzylpenicillin (BP) diluted in 0.9 % NaCl and administered at concentrations of 100 IU/ml and 10.000 IU/ml, amoxicillin (AX) (Beecham, Toledo, Spain) and ampicillin (AM) (Antibiotic SA, León, Spain) both at concentrations of 2 and 20 mg/ml, cefazolin (Normon, Spain) and cefotaxime (Aventis pharma S.A) both at 2 and 20 mg/ml also were carried out, the im-me-diate readings were negative for all the reagents, but the 24 hours reading showed erythematous, in-durated wheals larger than 10mm, reaching the maxi-mum size at 48 hours for amoxicillin-penicillin (amoxicillin and ampicillin).

Patch tests (PT) were administered with PPL, MDM, AX, AM, cefazolin and cefotaxime with a con-cen-tration of 5 % in petrolatum, following the rec-ommendations of Brockow et al⁷. Only amoxicillin and ampicillin produced positive reactions (2 +) with erythema, infiltration, papules and vesicles.

No specific IgE to amoxicillin and to ampicillin was detected by CAP immunoassay (Pharmacia, Upsala, Sweden).

One year later, the patient was retested with the same allergen battery, showing a persistent positive response to amoxicillin-penicillin.

After the episode previously related, the patient took paracetamol with good tolerance.

DISCUSSION

Erythema multiforme (EM), Stevens-Johnson syn-drome (SJS) and toxic epidermal necrolysis (TEN) are mucocutaneous diseases associated with significant mor-bidity and mortality, being relatively uncommon disorders in children⁸.

The causative factors of these disorders that have been identified include infectious agents and drugs. Herpes simplex and mycoplasma pneumoniae are the most common infectious agents and have been casually associated with EM and SJS. All three of the disorders have been linked to drugs, with TEN being exclusively attributed to this factor. More than 100 drugs have been associated with these diseases be-ing sulphonamides, hydantoins, nonsteroidal antiin-flammatory drugs and allopurinol the most common implicated agents⁹. Studies examining the incidence in patients receiving amoxicillin therapy in particular, find that it is rare⁹.

In some cases, both factors: drugs and infectious agents have been identified as possible precipitants to the disease. It is well known that viral infections enhance the risk of drug allergic reactions⁹. Although the exact mechanism for this eptions is not known, breakdowm of tolerance or enhancement of the im-mune reaction to drugs following viral infection could involve two mechanisms: a change in the antigenic ex-pression of the drug or its metabolites probably due to changes in the expression of drug-metabolizing enzymes ¹ or an alteration of immune regulation sys-tem.² So in this case, as proposed previously in the literature, is biologically plausible that the interaction between Epstein Barr virus and amoxicillin could pre-cipitate the skin reaction.

Levine⁴ reported delayed positive IT, consisting of erythema and variable induration in patients with skin rashes after penicillin intake, since then a number of studies have reported that PT can also be used as a diagnostic procedure for studying nonimmediate re-actions to drugs such as maculopapular exanthems, urticaria and/or angioedema, TEN, erythrodemia, erythema multiforme and generalized eczema². Both IT and PT seem valuable instruments for the diagno-sis of NIR to AP.

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Renn et al. also suggest that allergy testing may be helpful in patients with aminopenicillin-induced skin rashes in infectious mononucleosis and would enable to identify sensitized patient and to avoid severe exanthemas, especially in young adults and children.

In our patient, both patch test and delayed intradermal reading with aminopenicillins were an useful tool for the diagnosis of the aetiological agent in this unusual reaction to amoxicillin with concurrent Epstein Barn infection, moreover the positivity of such tests suggests a cell mediated hypersensitivity. The negative response to BP and cephalosporins indicates that amino-benzyl group plays a predominant role and the side-chain determinants would be the responsible of the reaction as suggested by other authors with larger series of patients.

Perhaps some reactions after treatment with aminopenicillins during an episode of mononucleosis represent true sensitizations to aminopenicillins and not a transient phenomenon as proposed by other authors, in this case skin tests performed again one year later, went on positives.

REFERENCES


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