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 biopse 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 amoxicilllin 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.

Key words: Erythema multiforme. Epstein Barr virus. Amoxicillin. Intradermal test. Patch test. Cell mediated hypersensitivity.

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Maculopapular and urticarial rashes are nonimmediate manifestations common during aminopenicillin (AP) treatment, moreover the incidence of rashes following intake of the ampicillin during an acute episode of infectious mononucleosis rises in adults 28.8–69 %, with up to 100 % incidence reported in children[1], but severe cutaneous reactions as erythema multiforme or Stevens-Johnson syndrome are exceedingly rare. The reasons for this unusual high risk has not been elucidated, however, it is well known that viral infections enhace the risk of drug allergic reactions[2].

CASE REPORT

A seven year old girl, previously in good health had a clinical picture of fever, pharyngitis and lymphoadenopathy, 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 mononucleosic syndrome (she showed activated lymphocytes in periferal blood) and amoxicillin–clavulanic acid was withdrawn, but her clinical condition deteri-

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 generalized 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 areas.

Laboratory investigation revealed normal complete blood count, urinalysis, liver and renal function test, electrolytes, coagulation study, serum immunoglobulin, 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 biopse of a lesion on the arm revealed lymphocyte accumulation at the dermal epidermal interface, with vacuolar degeneration of the basal layer, scattered necrotic keratinocytes, spongiosis, and extravasated erythrocytes and eosinophils, features consistent with the diagnosis of erythema multiforme. The patient started treatment with oral steroid for 12 days. Skin lesions healed with transitory hyperpigmentation.

Skin tests

Two months later, prick and intradermal test (IT) were carried out using penicilloyl-poly-L-lisyne (PPL) and minor determinant mixture (MDM) (both from Allergopharma, Reinbek, Germany) at concentrations of 5×10^{-5} and 2×10^{-2} 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 immediate readings were negative for all the reagents, but the 24 hours reading showed erythematous, indurated wheals larger than 10mm, reaching the maximum size at 48 hours for aminopenicillins (amoxicillin and ampicillin).

Patch tests (PT) were administered with PPL, MDM, AX, AM, cefazolin and cefotaxime with a concentration of 5 % in petrolatum, following the recommendations of Brockow et al[3]. 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 aminopenicillins.

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

DISCUSSION

Erythema multiforme (EM), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are mucocutaneous diseases associated with significant morbidity and mortality, being relatively uncommon disorders in children[4].

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 being sulphonamides, hydantoins, nonsteroidal antiinflamatory drugs and allopurinol the most common implicated agents[5]. Studies examining the incidence in patients receiving amoxicillin therapy in particular, find that it is rare[6].

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 reactions[2]. Although the exact mechanism for this eruptions is not known, breakdown of tolerance or enhancement of the immune reaction to drugs following viral infection could involve two mechanism: a change in the antigenic expression of the drug or its metabolites probably due to changes in the expression of drug-metabolizing enzymes[7] or an alteration of immune regulation system[8]. So in this case, as proposed previously in the literature, is biologically plausible that the interaction between Epstein Barr virus and amoxicillin could precipitate the skin reaction.

Levine[9] 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 reactions to drugs such as maculopapular exanthems, urticaria and/or angioedema, TEN, erythrodermia, erythema multiforme and generalized eczema[3]. Both IT and PT seem valuable instruments for the diagnosis of NIR to AP.

Renn et al[10] 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 an 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[11,12].

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[13], in this case skin tests performed again one year later, went on positives.

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