EBV-induced erythema multiforme: a case report

To the Editor,

Erythema multiforme (EM) is a type of dermatosis that occurs as a hypersensitivity reaction in response to medications or infections. Erythema multiforme is mostly associated with the herpes simplex virus (HSV) or mycoplasma infections,[1] but it is rare that EM is associated with the Epstein Barr Virus (EBV).

We report on an 11-year-old male patient admitted to our hospital with redness, swelling, burning sensation, an itchy rash on hands and feet, and a rash on the body that had begun four days previously. The patient suffered fever, sore throat and nose running a day before these complaints manifested. The skin rash began on the sole of the right foot, which was noticed upon a sensation of something stuck on the right sole, and then spread to the left sole and the hands. At the outset, the skin rash was pinhead sized, then increased in size, and swelling in the hands and feet occurred. The first physician consulted wrote a prescription for cefuroxime, cetirizine and feniramine. However, the patient's complaints were not resolved after one day of using this medication, and so he was referred to our hospital.

In our physical examination of the patient, a maculopapuler rash that included desquamation regions which paled under pressure, was observed on both palms, soles, arms and legs. His body temperature was 37 °C. Other system examinations revealed no abnormal findings (Figures 1 and 2). Face, body and mucosal involvement was not noted.

Laboratory examination revealed leukocyte count: 9900 /mm^3, haemoglobin: 14.1 gr/dl, platelet count: 214000 /mm^3, erythrocyte sedimentation rate: 22 mm/hour, urea: 32 mg/dl, creatinine: 0.8 mg/dl, serum sodium: 134 MEq/L, potassium: 4.5 MEq/L, AST: 31 IU/L, ALT: 22 IU/L.

The patient was also tested for the Rickettsia IgG, HSV type I IgM, HSV type II IgM, EBV VCA IgM, CMV IgM, the Parvovirus IgM, and Mycoplasma pneumoniae IgM antibodies in order to rule out rickettsiosis and other infectious skin eruptions because of the symmetrical maculopapular rash involving the hands and feet. Doxycycline treatment was subsequently initiated with a clinical presumptive diagnosis of rickettsiosis. On the second day following the patient's admission to hospital, typical target lesions appeared, the largest of which was 2 cm in diameter, on both thighs and the proximal area of the forearms (Figure 3). EBV VCA IgM and Rickettsia IgG were positive at a titer of 1/10 and 1/64 respectively. In the repeated tests performed one week and one month later, there was no increase in the Rickettsia IgG titres. Doxycycline treatment was halted on day seven, and EBV infection was thought to be responsible for EM in our patient. Other viral markers and examinations for mycoplasma were found to be negative. On the fifth day of admission, the patient was discharged from the hospital as the rash had a tendency to pale. The rash disappeared on the 14th day from the beginning and the patient was cured without sequela.

One month later, in order to rule out a possible adverse drug reaction due to cefuroxime use reported in the patient's history, a patch test (10 mg/ml) was done, which

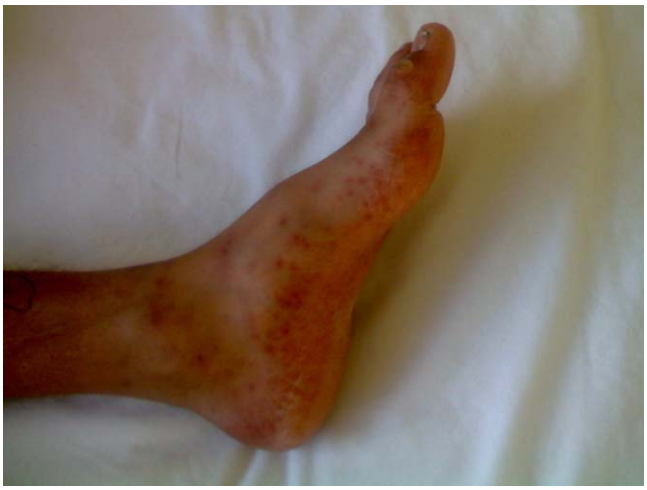

Figure 1 A dispersed red-purple colored maculopapular rash that pales under pressure was shown around ankle and medial side of the foot.

came out negative. Then a prick test and an intradermal test were applied using cefuroxime. Since these tests also turned out negative, an oral provocation test using cefuroxime was performed, which turned out negative too.

Erythema multiforme is acute, usually self-limited and at times life threatening dermatosis which may present with multiforme lesions. They include multiple, symmetric, persistent macules, papules, vesicles, and bullae. What has become pathognomonic for erythema multiforme is the so-called iris or targetoid lesions, representing plaques of central duskiness in expanding erythematous macules and papules. Areas commonly involved are extensor surfaces: the palms, the soles, and sites of trauma.[1] The appearance of the rash in our patient shortly after pricking caused us to think that trauma played a facilitating role in this case.

In EM, aetiology mostly consists of herpes simplex and mycoplasma. Medications and some vaccines also participate in the aetiology, but in half of the cases an underlying cause cannot be found.[2] EBV VCA IgM, tested in our patient was found to be positive. Erythema multiforme occurring during EBV infection is dramatically rare.[2,3,4,5,6]

Although it is not certain, the pathophysiological mechanism for the EBV-related EM is thought to be immunocomplex mediated.[4] Hughes et al. demonstrated perivascular IgM and C3 deposition in direct immunofluorescent examination.[2] In addition, Carrera et al. investigated the presence of specific gene sequence of EBV and Herpes simplex by PCR in a tissue biopsy of a case with acute cholestatic hepatitis and EM; however the result was negative.[5] On the other hand, Chen et al. detected an EBV specific gene sequence in two 32 EM cases by PCR.[6] Due to a lack of the facilities for investigating EBV in tissue with PCR, since we diagnosed EM clinically, and also for ethical issues, we did not perform a tissue biopsy in our patient.

It is well known that during viral infections, drug-related allergic reactions increase.[7] Rashes related to aminopenicillins during infectious mononucleosis are often seen; however, serious cutaneous lesions such as EM and Stevens Johnson Syndrome (SJS) are rare.[8] Our patient was evaluated for cephalosporin-related drug reaction due to previous

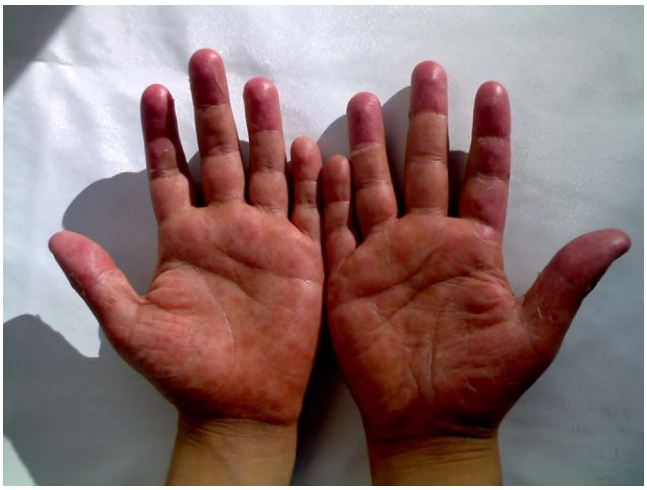

Figure 2 Red-purple colored erythematous maculopapular lesions that show desquamation in patches were seen on bilateral palmar regions.

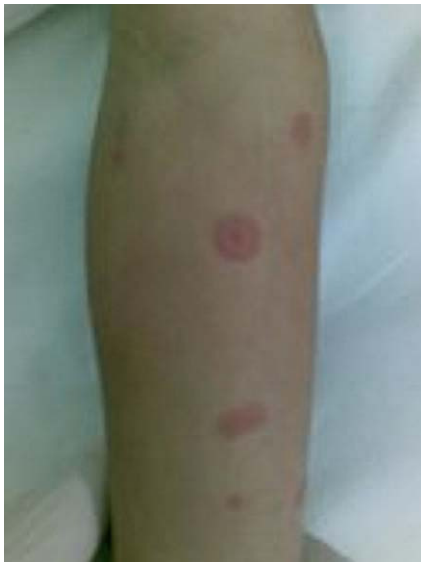

Figure 3 Dispersed target lesions were shown on the proximal part of the fore arm.

cefuroxime use, but skin tests and oral provocation test results came out negative. Delgado et al. reported a case of EM due to aminopenicillin use during EBV infection.[8] Contrary to our patient, they found a positive patch test and a delayed reading of an intradermal test performed for an evaluation of drug sensitivity. They claimed that cell-mediated hypersensitivity was responsible for the development of drug-related EM. In research conducted by Jappe, who evaluated 41 patients with drug eruptions following the intake of amino-penicillins, 20% of patients had a florid infectious mononucleosis at the time of the drug eruption.[9] In our case, in terms of explaining aetiology, EBV infection was determined and an evaluation was made due to a cefuroxime drug allergy in light of existing knowledge about virus-drug interaction, and the result was determined to be negative.

80% of erythema multiforme is classified as minor, is usually postinfectious, and affects primarily the skin and no more than one mucosal surface.[1] It is thought that there is a relationship between the severity of the disease and factors that exist in aetiology. While viral infections usually cause erythema multiforme minor and major, medications cause SJS which progresses with a more serious clinical course.[10] Our patient was diagnosed as erythema multiforme minor, because there was no mucosal involvement. The drug allergy tests of the case were negative and the viral infection related EM was mostly encountered in minor form. Consequently, our patient was diagnosed as EBV related EM.

The prognosis is quite good in EM minor, and it can be cured without sequela in 2-4 weeks by eliminating the triggering cause or by treatment of the underlying infection. Progression to SJS does not occur in these cases. Our patient was closely monitored for six weeks with only the first five days in hospital, and it was observed that his lesions healed completely.

As a result, even though HSV is the most observed of the viral infections in EM aetiology, EBV might be a rare but a causative factor.

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