Herpes Simplex Virus-Associated Recurrent Erythema Multiforme: The Implication of MHC Class Molecules on Susceptibility

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Erythema multiforme is an acute mucocutaneous hypersensitivity reaction caused by a variety of etiologies. Here we report a case of herpes simplex virus-associated recurrent erythema multiforme. This 21-year-old male presented with recurrent oral ulcers for more than 10 years. During the last two years, multiple erythematous to violaceous papules and plaques with a central vesicle over all four limbs had developed 10 to 14 days after the occurrence of oral ulcers. The patient’s blood test was HSV 1 IgG positive and HLA typing revealed that he was DQB1 0402, DQB 1527 positive. The patient was successfully treated with valaciclovir 500mg daily, and by periodic prednisolone 20 mg per day for seven days during attacks of erythema multiforme. (Dermatol Sinica 26: 165-170, 2008)

Key words: Erythema multiforme, Herpes simplex virus

INTRODUCTION

Erythema multiforme (EM) was first described by Hebra in 1860. It is an acute mucocutaneous disorder and is characterized by a polymorphous eruption composed of symmetrically distributed macules, papules, bullae and other typical target lesions with a central vesicle or bulla. EM has been reported to be triggered by numerous agents, especially herpes simplex virus (HSV), but can also be caused by other herpesviruses, such as varicella-zoster virus, cytomegalovirus and Epstein-Barr virus. Furthermore, many other viruses including adenoviruses, enteroviruses, such as coxsackie virus B5 and echoviruses, hepatitis viruses A, B and C, influenza, paravaccinia, parvovirus B19, poliomyelitis, vaccinia and variola have been implicated in the disease. Nonetheless, it has been estimated that 15% to 63% of cases of EM are secondary to infection with HSV.1 Herpes simplex virus-associated erythema multiforme (HSV-EM) is usually regarded as a self-limiting disorder. Here we report a case of recurrent HSV-EM that had lasted for more than ten years and the disease was eventually controlled successfully by treatment with daily valacyclovir and periodic prednisolone.

CASE REPORT

This 21-year-old male patient suffered
from recurrent oral ulcers since he was an elementary school student. The oral ulcers were triggered by stress or the common cold and were very painful (Fig. 1A, 1B). The oral ulcer that started from macules and progressed to ulceration. The intraoral lesions were most pronounced in the anterior parts of the mouth. Besides, the lips became swollen, bleeding and crusted. Over the last two years, multiple erythematous to violaceous papules and plaques with central vesicles had developed over the distal parts of all four limbs (Fig. 1C, 1D, 1E, 1F). These target-like skin lesions were always preceded by the presence of oral ulcers. The period between the appearance of oral ulcers and the occurrence of the skin lesions has usually been between 10 and 14 days. Neither the genital nor the conjunctival mucosa was involved. When he first visited our Dermatology outpatient clinic, there had been eleven attacks of oral ulcers and skin lesions over the lately six months. Under the impression of recurrent erythema multiforme, skin biopsies of the lip and forearm were performed. The pathology revealed dyskeratotic cells in the epidermis, perivascular mononuclear cells infiltration in the upper dermis and edematous or cleft formation over the epidermal-dermal junction. Direct immunofluorescence examination revealed fibrinogen deposition in the basement membrane zone, but without IgG, IgA or IgM deposition. There was no evidence of any other autoimmune bullous disease such as pemphigus vulgaris or bullous pemphigoid. Laboratory blood tests revealed that the patient was HSV 1 IgG was positive, but tests for other viral or bacterial antibodies including HSV 2 IgG, HSV 2 IgM, anti-HCV Ab, *Mycoplasma pneumonia* Ab and ASLO were negative. An autoimmune disease survey was also negative and included testing for ANA (<1:40), anti RNP (-), anti-Sm (-), anti SS-A (-), anti SS-B (-), anti-CENPB (-), anti Scl-70 (-) and anti Jo-1 (-). In order to test for a genetic predisposition to HSV infection, HLA typing was carried out and the patient was found to be HLA B15, HLA B35, HLA A33, HLA DR53 and HLA DQB1 0301 positive. Besides, he was also found to be DQB1 0402, DQB 1527 positive, but was negative for A1, A24, B4006, B8, DR3 and DQB1.

The therapeutic strategy used for this patient involved valaciclovir 500mg daily to reduce the viral load and prednisolone 20mg daily for seven days to prevent the erythema multiforme, which is a type IV hypersensitivity reaction triggered by the HSV. Under this regimen, his oral ulcers and skin lesions improved rapidly. The treatment with valaciclovir 500mg/day was to prevent the formation of oral ulcers and thus EM and this treat-
ment was initially carried out for 5 months; during this period the patient had just only one event. However, after taking the oral valaciclovir for 5 months, he discontinued the drug for 7 months. During this period, he experienced several attacks of oral ulcers and EM. Since that time, he has reinstated the treatment and over the lately 5 months he has had only one attack, which followed an infection with the common cold (Fig. 2). During this common cold, he also had oral ulcer which was followed by target-like macules, plaques over four limbs.

DISCUSSION

We review in this report the clinical characteristics of, the pathogenesis of, the genetic predisposition to and therapeutic strategy for HSV-EM as our patient had experienced a devastating clinical course and had not received proper diagnosis and treatment for more than ten years from his local medical doctors. Patients suffering from HSV-EM are younger at the disease’s onset compared to other causes of EM and more often male. The frequency of the attacks varies from twice a year to 24 times per year and in a small proportion of cases is continuous.\(^2\)\(^-\)\(^4\) Although remission occurs in 20% of patients, the condition continued for more than 10 years in 33% of cases.\(^5\) Mouth lesions are the most common mucosal manifestations of recurrent EM (69%)\(^6\) and are typically found on the non-keratinised mucosae, the anterior parts of the mouth.\(^7\) The lesions progress from diffuse and widespread macules to blisters and ulceration. Lips become swollen, cracked, bleeding and crusted.

It has been proposed that there may be a genetic predisposition to HSV-EM associated with HLA B15, HLA B35, HLA A33, HLA DR53 and HLA DQB1 0301 genotypes.\(^8\) Patients with extensive mucosal involvement seem to be have the rare HLA DQB1 0402 and those with mild mucosal involvement are associated the HLA DQB1 0302.\(^9\) HLA A1, B8 and DR3 are associated with autoimmune disease and reflect an increased host response to tissue self antigens.\(^3\)\(^-\)\(^7\) Our patient was positive for HLA DQB1 0402 and for HLA

![Fig. 2](image)

Clinical course and treatment dosages.
DQB 1527, which is compatible with HSV-EM and the extensive mucosal involvement. The absence of HLA A1, B8 and DR3 in our patients may be indicative of a poor host response to antigens, which in the case of recurrent EM is the HSV. Thus, the antigen can not be cleared quickly from the host and we suspect that this may be the underlying cause of the recurrent clinical course in this patient.

HSV–DNA has been detected in between 36% and 81% of patients with the HSV-EM using polymerase chain reaction amplification.11 The efficiency of HSV antigen presentation depends on the transporter associated with antigen processing (TAP), that translocates peptides generated by proteosomal protein degradation into the endoplasmic reticulum for loading onto MHC class I molecules. To escape immune surveillance, HSV compromises the host’s cytotoxic T lymphocyte response via ICP47, an 88-amino-acid that blocks TAP function.12 Virus peptide-loaded MHCII heterodimers stimulate generation of CD4+ T cell and antibody production. Binding of glycoprotein B of herpes simplex virus to MHCII heterodimers inhibits peptide loading and prevents presentation of viral peptides.13 The patient with certain HLA typing genes such as HLA B15, HLA B35, HLA A33, HLA DR53 and HLA DQB1 0301 can not eradicate the HSV out of the human body efficiently.

There are no specific treatments available for EM but supportive care is important.7 EM seems to respond to either topical corticosteroids or systemic corticosteroids although it is controversial. Valaciclovir is an antiviral agent, which when activated by viral thymidine kinase in HSV-infected cells, inhibits virus replication.14 The role of valaciclovir in the suppression of recurrent HSV infection is well documented. Isolated reports have shown that continuous valaciclovir is effective for recurrent EM, confirming the efficacy. In our case, oral valaciclovir treatment was initiated early to prevent the subsequent development of EM. When, however, the valaciclovir treatment is inadequate, EM eventually still occurs. According to the previous paper, we suggest the valaciclovir treatment for recurrent EM should has last for more than 6 months.15 This finding suggests that there is a relationship between the amount of activated HSV and the extent of the subsequent EM.

REFERENCES
與單純性皰疹相關的反覆多型性紅斑：
主要組織適應性之複合物分子對於其敏感性的含意

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多型性紅斑是一種急性侵犯到皮膚及黏膜的疾病，它可由許多種原因所造成。在此我們
報告一單純性皰疹病毒導致反覆性多型性紅斑的病例。這是一位21歲的男性病人為反覆性口
腔潰瘍所苦已經十年。在最近的這兩年期間，在口腔潰瘍發生之後的10至14天,在四肢產生
許多紅色及紫羅蘭色，中間有一水泡的丘疹及斑塊。病人的血液呈HSV 1 IgG陽性，及HLA
DQB1 0402、HLA DQB 1527也是陽性。我們成功的為病人用全身性抗病毒藥物valaciclovir 每
天 500mg治療，降低病人體內的病毒量，並且在多型性紅斑發作時用類固醇prednisolone每天
20mg來治療。（中華皮誌: 26: 165-170, 2008）