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# Use of Valacyclovir Prophylaxis in Herpes Virus-Associated Recurrent Erythema Multiforme Cases

## Herpes Virüs İlişkili Tekrarlayan Eritema Multiforme Olgularımızda Valasiklovir Profilaksisi Kullanımı

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## ABSTRACT

Erythema multiforme (EM) is an immune-mediated condition characterized by symmetric erythematous rash with typical target lesions. Drugs, infections, immunologic conditions and food additives are among etiologic causes; but Herpes simplex virus infection is the most commonly seen reason.

We report three cases of recurrent EM associated with herpes labialis infection. They all presented with typical target lesions appearing nearly one week after the herpes labialis lesion had begun. Each patient had similar EM episodes with different frequencies. All three patients were initially treated orally with valacyclovir, then prophylactic valacyclovir with a daily dose of 500 mg for six month period.

Autoreactive T cells triggered by Herpes virus infection, are suggested to play an important role in Herpes-associated EM (HAEM) pathogenesis. The first line management of recurrent HAEM is antiviral treatments and they are generally safe and well tolerated in pediatric and general populations. Early administration of oral acyclovir or valacyclovir are recommended to reduce the severity and duration of the EM rash. Prophylactic antiviral treatment using for 6 months may be effective in controlling recurrent epizodes of HAEM. HSV infection and HAEM may recur; but prophylactic treatment may reduce the frequency and severity of epizodes.

**Key Words:** Children, Erythema Multiforme, Herpes Simplex Virüs

## ÖZ

Eritema multiforme (EM) tipik hedef lezyonlarıyla simetrik eritematöz döküntü ile karakterize, immün aracılı bir durumdur. İlaçlar, enfeksiyonlar, immünolojik durumlar ve gıda katkı maddeleri etiyolojik nedenler arasındadır, ancak Herpes simplex virus enfeksiyonu en yaygın olanıdır.

Herpes labialis enfeksiyonu ilişkili üç rekürren EM olgusu sunuyoruz. Hepsi herpes labialis döküntüsünden yaklaşık bir hafta sonra ortaya çıkan tipik hedef lezyonlarla başvurdu. Her hastanın farklı sıklıkta tekrarlayan benzer atakları vardı. Her üç hastaya da önce oral valasiklovir tedavisi, ardından günlük 500 mg dozda 6 ay profilaktik valasiklovir tedavisi uygulandı.

Herpes virüs enfeksiyonu ile tetiklenen otoreaktif T hücrelerinin, Herpes ilişkili EM (HAEM) patogenezinde önemli bir rol oynadığı ileri sürülmüştür. Tekrarlayan HAEM'in birinci basamak tedavisinde, antiviral tedaviler genellikle güvenlidir ve pediyatrik ve genel popülasyonlarda iyi tolere edilir. EM döküntüsünün şiddetini ve süresini azaltmak için oral asiklovir ya da valasiklovir tedavisinin erken uygulanması önerilir. Altı ay süreyle verilen profilaktik oral asiklovir veya valasiklovir, tekrarlayan HAEM ataklarını kontrol etmede etkili olabilir. HSV enfeksiyonu ve HAEM tekrarlayabilir ancak profilaktik tedavi bu epizotların sıklığını ve şiddetini azaltabilir.

**Anahtar Kelimeler:** Çocuk, Eritema Multiforme, Herpes Simplex Virüs

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## INTRODUCTION

Erythema multiforme (EM) is an immune-mediated condition characterized by symmetric erythematous rash with target lesions, often accompanied by erosions or bullae involving the oral and other mucus membranes (1,2). Drugs, infections, immunologic conditions and food additives are among the etiologic causes (Table I). But Herpes simplex virus (HSV) type1 and to a lesser proportion HSV type 2 infection has been identified in up to 70% of the EM cases. Periodic reactivations of HSV induce frequent reactivations of EM which is named herpes associated EM (HAEM). The annual incidence of EM is estimated to be less than 1%, which is highest in males and in the 2nd decade of life. Children comprise of 20% of all the cases (2).

Erythema multiforme minor refers without or with only mild mucosal involvement and systemic symptoms. EM major is the term used to describe EM with severe mucosal involvement and may be associated with systemic symptoms, such as fever and arthralgias. Although it was previously thought that EM was on the same pathologic spectrum with Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN); now it was accepted that these are separate entities (3,4).

In this report, we aimed to emphasize that among other predisposing factors, HSV also may cause recurring EM and recurrences can be prevented with prophylactic antiviral treatment.

**Table I: Predisposing factors of erythema multiforme.**

| |
|---|
| Infectious agents |
| Herpes simplex virus type 1/2 |
| Epstein-Barr virus |
| Cytomegalovirus |
| Hepatitis C virus |
| Influenza virus |
| Mycoplasma pneumoniae |
| Vulvovaginal candidiasis |
| Drugs |
| Erythromycin |
| Nitrofurantoin |
| Penicillins |
| Sulfonamides |
| Tetracyclines |
| Antiepileptics |
| Barbiturates |
| Nonsteroidal |
| anti-inflammatory drugs |
| Phenothiazines |
| Statins |
| Sulfonamides |
| Tumor necrosis factor-α inhibitors |
| Other conditions |
| Vaccines |
| Inflammatory bowel disease |
| Malignancy (leukemia, lymphoma) |
| Menstruation |
| Food additives/chemicals |

## CASE REPORTS

We report three cases of recurrent HAEM. All three patients presented with typical target lesions appearing nearly one week after the herpes labialis rash had begun. Symmetric eruptions were presented especially on the extremities, more intensely on their hands and feet including palms and soles.

First patient was 17 years old female patient. She had recurrent attacks every 2-3 months in the last 9 years.

Second patient was 12 years old male patient. He had EM lesions more frequently on his face and hands (Figure 1 and Figure 2). He had about five similar attacks per year in the last six years.

Third patient was 12 years old male patient. He had mucosal involvement including the eye and mouth preventing him from feeding (Figure 3). He had two similar episodes that had recurred in an interval of 1.5 months.

These episodes were not related to drugs and other triggering factors. In either patients there was no considerable feature in the patient and family history of the patients. Herpes infections were supported with typical lip rash and detection of positive serology for HSV type1. There was no history for other viral, bacterial and fungal infections, acute or chronic drug usage and the other diseases, thus the diagnosis was confirmed as HAEM. Due to the recurrences of HSV infection we evaluated the patients with immunological screening tests (complete blood count, differential serum Immunglobulins (Ig), Ig G subclasses, lymphocyte subpopulations, Nitroblue tetrazolium test, CH50, complement C3, C4, lymphocyte blastic transformation) to investigate congenital immunodeficiency disease or primary immunodeficiencies that may be the cause of susceptiblity to

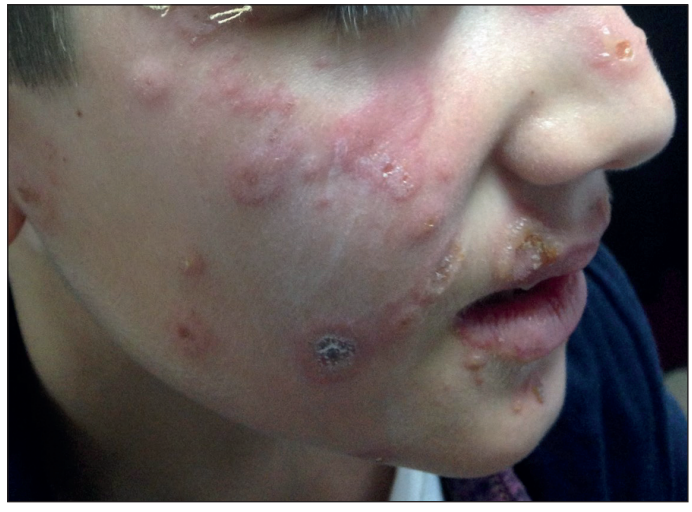

**Figure 1:** Fasial lesions of the second case.

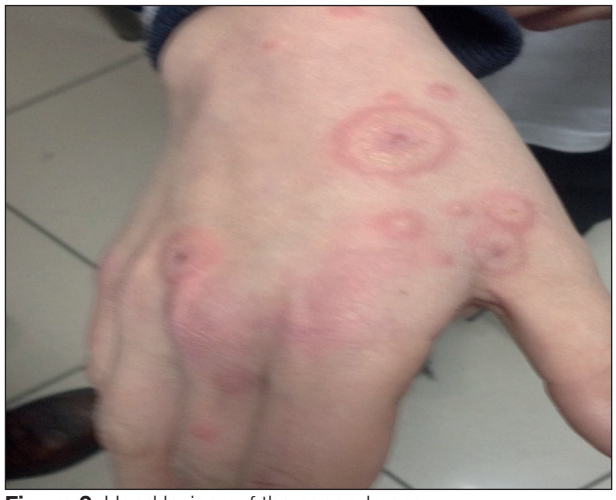

**Figure 2:** Hand lesions of the second case.

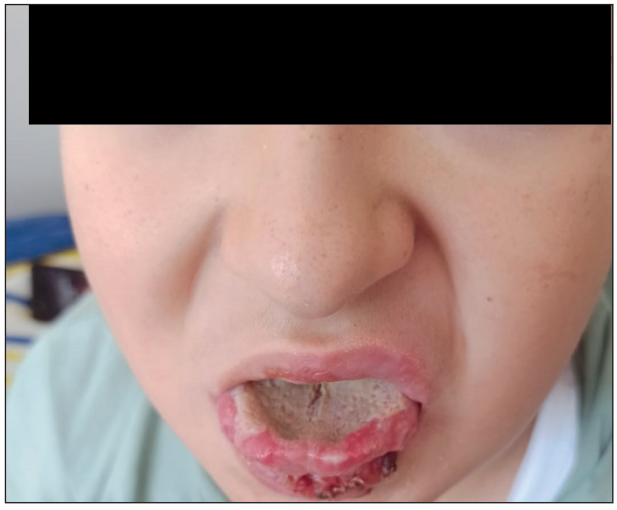

**Figure 3:** Oral mucosal lesions of the third case.

viral infections. Our third patient had low Ig G, 744 mg/dl (normal range for age 835-2094 mg/dl) and Ig A 57 mg/dl (range 67-433 ) and his other tests were within normal limits. There was no abnormality in the screening tests of the other two patients.

All patients were initially treated orally with a prolonged course of the antiviral drug valacyclovir. Dosage was 500 mg twice per day for four weeks. Orally methylprednisolone was given in dose of 40 mg/day for five days and reduced and stopped in the following 5 days in third patient with mucosal involvement. We used topical corticosteroids for mouth and skin lesions. Skin lesions healed with skin hyperpigmentation in about 4 weeks in our patients.

Prophylactic valacyclovir treatment with a daily dose of 500 mg were begun to all patients. In all of our patients valacyclovir prophylaxis discontinued after 6 months of drug usege. During this period renal functions were monitored with intermittent blood tests. No oral or skin lesions developed during prophylactic treatment. After prophylaxis treatment; in the first patient mild rashes recurred only on the hands 2-3 times per a year, in the six year follow-up period. There was no recurrence in the one year follow-up of the second patient. Only one recurrence was observed two months after the ending of prophylactic treatment in the one year follow-up of our third case. He had only mild rashes on the hands and feet without developing mucosal lesions.

## DISCUSSION

A target lesion is a round skin lesion with three concentric colour zones: A darker centre with a blister or necrosis, a ring around this that is paler pink and raised due to edema and a brightered region outer ring. Target lesions typically occur in EM. They can arise on any body site and mucous membranes. An iris lesion represent an early target lesion and has two parts; a central dark or blackish zone and a red outer zone. Target lesions appear within the first 3 days of an episode of erythema multiforme and once one lesion has appeared, it stays in the same location for 7 days or more until the skin heals. Atypical target lesions show just two zones. In EM, these lesions are raised papular in SJS and TEN, they are flat as erythematous or purpuric macules. Targetoid lesions can be caused by several skin conditions such as melanocystic naevus, urticaria, fixed drug eruptions, subacute cutaneous lupus erythematosus, immunobulluous disorders like pemphigoid and some forms of vasculitis which include Kawasaki disease and acute haemorrhagic edema of ancy. As targetoid lesions are descriptive rather than diagnostic, a careful medical history and full skin examination are necessary to make the correct diagnosis (3,5). Considering the time course of development, drug history, total number and type of skin lesions and if necessary a skin biopsy can help to distinguish these disorders.

Erythema multiforme is a rare condition which is characterized by target lesions. Eruptions appear within 72 hours and remain for an average of 7 days in a typical episode. Lesions generally resolve without sequelae in approximately two weeks, but in darker pigmented individuals , pigmentary alterations at the site of lesions can be long-standing. Mucous membran involvement is usually presented as erythematous macules on the lip and buccal mucosa, followed by epithelial necrosis, bullae and ulcerations (4).

Among the various etiologic factors of EM, infection with HSV is the most commonly seen. Periodic reactivations of HSV, induce recurrences of erythema multiforme which is named HAEM (6). Eruptions of HAEM often develop 10-14 days after a HSV infection. Recurrences are seen in approximately 20-25% of HAEM cases and patients may experience 2-24 episodes a year, an average of 6 attacks annually, with each episode may last nearly 2 weeks (2). Most patients experience a single self-limited episode of EM (4). HSV DNA has been detected in 60% of patients clinically diagnosed with recurrent HAEM and in 50% of patients with recurrent idiopathic EM using polymerase chain reaction (PCR) of skin biopsy specimens.

(7). Detection of interferon-gama (IFN-γ) in HAEM lesions can also be used as evidence of viral antigens (6). Detecting specific IgM and IgG antibodies to identify HSV-1 and HSV-2 may confirm a suspected history of HSV infection, although it is not necessary for diagnosis (8). We did not consider biopsy because our patients had clinical signs of herpes labialis before typical rashes and had serologically detected HSV-1 positivity.

The presence of the human leukocyte antigens A33, B62, B35, DQW3 and DR53 is associated with an increased risk of HAEM, particularly in the recurrent form (4).

When compared to general population, male predominance rate was higher in pediatric population and had lesser attacks per year. Hospitalization was more common in children. The severity of skin lesions was similar between the children and the general population. But there is a higher incidence of mucosal involvement in children (6,9). Consistent with the literature, two of our cases were male and one of them had mucosal involvement (6).

New data have been presented showing that autoreactive T cells triggered by virus infection play an important role in HAEM pathogenesis. Disease begins with viral DNA fragmentation and the transport of DNA fragments by mononuclear cells (Langerhans cells) to distant skin areas. The HSV genes in DNA fragments (specifically DNA polymerase) deposited on the skin, are expressed by langerhans cells to HSV spesific CD4 Th1 cells . IFN-γ is produced by these Th1 cells and initiates an inflammatory cascade involving the increased sequestration of leukocytes, monocytes, natural killer cells and autoreactive T cells in the skin lesions (10).

Immune system must be evaluated in all HAEM cases. Monogenic defects of innate immunity components have been described in children which affect antiviral responses. TLR3, IRF3, TBK1, TRIF, TRAF3 and UNC93B1 deficiency (associated HSV encephalitis), TLR3, IRF7, IRF9 deficiency (associated severe infuenza) are some of the mutations previously identified (11,12). Bucciol and colleagues detected a pathogenic variant at TLR3 in a patient with HAEM. This mutation is thought to affect the antiviral response by reducing the production of type 1 interferon (5,11). One patient was diagnosed with Ig G1 subclass deficiency in another study (13). We also detected borderline hypogamaglobulinemia in the third patient. He had mucosal involvement in both EM recurrences.

Management of EM depends on the underlying etiology and the disease severity. If HSV is the etiologic cause, expert opinion recommends early administration of oral acyclovir treatment to reduce the severity and duration of the EM eruption (5). However, there is no evidence that antiviral therapy improves the time to lesion resolution (1,6).

The first line management of recurrent EM are antiviral treatments and they are generally safe and well tolerated in pediatric and general populations (6,13). It has been recommended that based on pathophysiologic reasoning that therapy may be continuous or intermittent. But only continuous therapy has been studied (3,14). A single placebo-controlled trial of 20 patients was reported that there was a significant reduction in recurrences with 400 mg of acyclovir treatment which was administered twice daily over a six-month period (15).

In cases that were unresponsive to acyclovir therapy, treatment with valacyclovir and famciclovir which have better bioavailability, reported to cause remission in both children and adults. Acyclovir (400 mg twice per day), valacyclovir ( 500 mg twice per day), or famciclovir (250 mg twice per day) are options that can be used. But there are limited studies to determine the recommended duration of treatment (3,5). We applied low dose valacyclovir prophylaxis of 500 mg daily to our patients continuously.

Mucosal EM may be very painful. Treatment options are topical corticosteroid gel and oral antiseptic or anesthetic solutions. Topical emollients, systemic antihistamines, and nonsteroidal antiinflammatory drugs can be used symptomatically. Severe cases of mucocutaneous EM may cause decreased oral intake, which may lead to hospitalization (1,4). Ocular involvement should be evaluated by an ophthalmologist immediately because visual sequelae may be permanent.

Prednisone was found to be effective in the treatment of recurrent EM, but no controlled studies have supported this treatment (3,6). In cases unresponsive to antiviral therapy, immunosuppressive treatments (dapson, azathioprine, mycophenolate mofetil), antimalarials, corticosteroids and IVIG therapy can be applied. There is little evidence to support these treatments (1,5). A small study indicated thalidomide as a treatment for reducing the duration of EM episodes, but further research is necessary (15). Heinze and colleagues' series of 26 patients, remission rate with immunosuppresive treatment was found lower in children compared to the general population (6).

In conclusion, use of antiviral drugs in HAEM treatment was seen to be effective if it was started in the first few days when semptoms had begun. Prophylactic oral acyclovir or valacyclovir that are given for 6 months, may be effective in controlling recurrent episodes of HAEM. Despite treatment HSV infection, HAEM may recur; but treatment may reduce the frequency and severity of episodes as we also seen in our patients.

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