

Kobkan Thongprasom

## Liječenje trudnice od *erythema multiforme* povezanog s herpesom (HAEM): prikaz slučaja

### *Treatment of a Pregnant Patient with Herpes Associated Erythema Multiforme (HAEM): A case report*

Zavod za oralnu medicinu Stomatološkog fakulteta Sveučilišta Chulalongkorn, Bangkok, Tajland  
Oral Medicine Department, Faculty of Dentistry Chulalongkorn University, Bangkok, Thailand

#### Sažetak

*Erythema multiforme* (EM) rijetka je akutna upalna bolest kože i sluznica obilježena ulceracijama. Može nastati kao reakcija na lijekove, mikrobnе uzročnike ili alergene. Nekoliko je oblika te bolesti – može se manifestirati kao težak oblik koji obično zahvaća kožu, a patognomičan znak je hemoragična krusta na usnici. Tipične prstenste lezije mogu se i ne moraju pojaviti. Ako ih nema, diferencijalna dijagnoza u odnosu na druge slične bolesti vrlo je složena. *Erythema multiforme* povezan s herpesom (engl. *herpes associated erythema multiforme* – HAEM) rijetko je stanje uzrokovano infekcijom virusom *herpes simplex*. Opisan je slučaj HAEM-a kod 28-godišnje trudnice s bolnim lezijama. Inače, od te bolesti trudnice rijetko obolijevaju, pa klinički nalaz, dijagnoza i liječenje dosad nisu opisani.

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#### Adresa za dopisivanje

Kobkan Thongprasom  
Chulalongkorn University  
Faculty of Dentistry  
Oral Medicine Department  
Bangkok 10330 Thailand  
kobkan.t@chula.ac.th

#### Ključne riječi

multiformni eritem; Herpes simplex virus; fluokinolon acetamid; trudnice

#### Uvod

*Erythema multiforme* (EM) akutni je samoograničavajući imunosni poremećaj koji zahvaća kožu i/ili sluznice. Smatra se reakcijom preosjetljivosti povezanom s određenim infekcijama ili lijekovima (1, 2). EM je obilježen tipičnim prstenastim promjenama, a povremeno zahvaća samo oralnu šupljinu. Predisponirajući čimbenik za tu bolest je infekcija virusom *herpes simplex* (HSV) i tada je riječ o *Erythema multiforme* povezanom s herpesom (engl. *herpes associated erythema multiforme* – HAEM). Najčešći uzročnik upravo je infekcija HSV-om (HSV-1 i 2) (1, 3, 4).

Imunopatogeneza uključuje odgođenu reakciju preosjetljivosti. DNK fragmenti HSV-a prenose se cirkulirajućim mononuklearnim stanicama CD34 (prekursor Langerhansovih stanica) na keratinocite, što aktivira HSV specifične CD4+ Th1 stanice koje proizvode interferon  $\gamma$  (IFN- $\gamma$ ) i posljedično razaraju epidermis (1, 5). Sistemske kortikosteroide smatraju se prvim izborom u terapiji EM-a (6). Međutim, HAEM u trudnoći nije uobičajen. U radu se raspravlja o izazovnoj dijagnozi i liječenju složenog slučaja.

#### Introduction

Erythema Multiforme (EM) is an acute and self-limiting immune-mediated disorder affecting the skin and/or other mucous membranes. EM is considered to be a hypersensitivity reaction associated with certain infections or medications (1,2). EM is characterized by skin target lesions, and occasionally EM may only involve the oral cavity. One predisposing factor for EM is an infection with herpes simplex virus (HSV), called herpes associated erythema multiforme (HAEM) and the most common trigger for the development of EM is HSV (HSV-1 and HSV-2) infection (1, 3, 4).

The immunopathogenesis of HAEM is consistent with a delayed hypersensitivity reaction. HSV DNA fragments are transported by circulating peripheral blood mononuclear CD34+ cells (Langerhans cell precursors) to keratinocytes, leading to the recruitment of HSV-specific CD4+ Th1 cells, which produce interferon  $\gamma$  (IFN- $\gamma$ ), and subsequent epidermal damage (1, 5). Systemic corticosteroids are considered to be the first-line treatment modality for EM (6). However, HAEM is very uncommon in pregnant women. Challenges in diagnosis and treatment of a severe case of HAEM are discussed in this paper.

## Prikaz slučaja

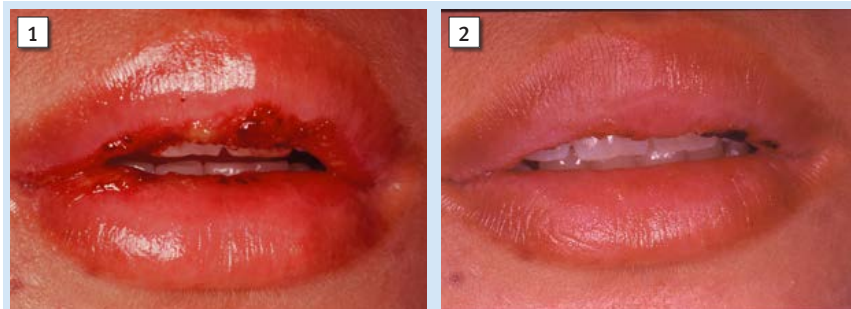
Pacijentica u dobi od 28 godina došla je u Kliniku za oralnu medicinu Stomatološkog fakulteta Sveučilišta Chulalongkorn zbog bolnih ulceracija na bukalnoj sluznici i hemoragičnih krusta na usnicama. Žalila se da već mjesec dana ne može jesti niti piti. Iz medicinske anamneze bilo je jasno da je prije godinu dana tijekom ljeta imala slične lezije koje su liječene antibioticima, prednisolonom i antivirusnim lijekovima. Mjesec dana poslije postupno su se počele povlačiti, no ponovno su se pojavile u prvom mjesecu trudnoće. Pacijentica se obratila liječniku koji je obavio dijagnostičke pretrage kako bi se otkrilo je li riječ o virusnoj infekciji. Iako je laboratorijski nalaz krvi pokazao da se radilo o infekciji virusom *herpes simplex* s titrom i imunoglobulinom G (HSV IgG) 1 : 2560, HSV IgM-a bio je negativan. Tzanckovim testom nisu otkrivene multinuklearne gigantske stanice. Propisana joj je terapija antivirusnim lijekom famciklovirom, ali nije pomogao – lezije su se progresivno čak pogoršavale. Pacijentica je zatim došla u našu Kliniku za oralnu medicinu u potrazi za alternativnom terapijom jer je bila zabrinuta za trudnoću i šteti li to stanje plodu.

Kliničkim pregledom ustanovljeno je da su joj submandibularni limfni čvorovi obostrano bili blago povećani i osjetljivi, ali nije bilo lezija na koži. Intraoralnim pregledom pronađene su mnogobrojne ulceracije na lijevoj i desnoj strani bukalne sluznice te nepravilne ulceracije s hemoragičnim krustama na gornjoj i donjoj usnici (slika 1.). Na temelju kliničkog nalaza hemoragičnih krusta, oralnih ulceracija s otežanim otvaranjem usta i laboratorijskog nalaza, postavljena je dijagnoza – *erythema multiforme* povezan s herpesom (HAEM). Propisan je potentni topikalni steroid, 0,1-postotni fluocinolon-acetonid u orobazi (FAO) za usnice i 0,1-postotna otopina fluocinolon-acetonida (FAS) za primjenu na oralnoj sluznici tri puta dnevno. Radi ublažavanja boli također je propisana otopina benzidamin-hidroklorida za ispiranje (0,15 %), prema potrebi 15 ml (oko 1 jušna žlica) svaki sat i pol do tri sata. Tjedan dana nakon početka liječenja znatno se poboljšalo stanje usnica i sluznice (slika 2.), a i bolovi su se smanjili. FAO i FAS (0,1 %) također su se primjenjivali na zahvaćenim područjima sve dok se lezije nisu postupno povukle do potpuno normalnog nalaza nakon mjesec dana. U sklopu telefonske kontrole nakon osam mjeseci obavijestila nas je da je rodila sina. I najvažnije – nisu zabilježene nuspojave ni kod pacijentice ni kod njezina novorođenog djeteta.

## Case Report

A 28-year-old female patient presented to the Oral Medicine clinic at the Faculty of Dentistry, Chulalongkorn University complaining of extensive painful ulcers and a hemorrhagic crust on her lips. She reported having experienced pain due to oral ulcers on her lips and buccal mucosa and she said that she had been unable to eat any food for 1 month. She said she had drunk only water. Her medical history suggested that a year before, during the summer, she had lesions similar to her current lesions and they were treated with antibiotics, prednisolone, and antiviral drug. One month after that, the lesions showed a gradual improvement. These oral lesions recurred after she had been pregnant for 1 month. The patient went to her doctor for treatment of those severe painful lesions. Her physician tested her for viral infection, and although the Herpes blood tests showed herpes simplex virus immunoglobulin G (HSV IgG) with a titer of 1: 2560, HSV IgM was negative. Tzanck's test did not reveal any multinucleated giant cells. Her physician treated her lesions with an antiviral drug– Famciclovir, however, the lesions did not improve; instead, they became progressively worse. The patient then came to our Oral Medicine clinic in order to seek alternative treatments because she was concerned about risks to her fetus.

Clinical examination revealed that her bilateral submandibular lymph nodes were slightly enlarged and tender; however, no skin lesions were present. In contrast, her oral examination revealed severe oral ulcerations on both right and left buccal mucosae and irregular ulcerations with a hemorrhagic crust on the upper and lower lips (Figure 1). Based on the clinical findings of hemorrhagic crust, severe oral ulceration with difficulty in opening her mouth, and the previous laboratory report, the diagnosis of herpes associated erythema multiforme (HAEM) was made. A potent topical steroid, Fluocinolone Acetonide Orabase (FAO), 0.1% was prescribed for lips and Fluocinolone Acetonide in solution (FAS), 0.1% was prescribed to be applied to the buccal mucosae three times a day. Benzzydamine hydrochloride, 0.15% w/v mouthwash was also prescribed, 15 ml (approximately 1 tablespoonful) every 1½ to 3 hours as required for pain relief. One week after the treatment, her both buccal mucosae and lips showed marked improvement (Figure 2) with a dramatic reduction in pain. FAO and FAS 0.1% were still applied to the affected areas until the lesions gradually resolved to a normal appearance after 1 month of treatment. Moreover, at the



**Slika 1.** Hemoragične kruste na gornjim i donjim usnicama kod 28-godišnje pacijentice trudne mjesec dana

**Figure 1** Hemorrhagic crust on the upper and lower lips of one-month pregnant 28-year-old female.

**Slika 2.** Tjedan dana nakon liječenja 0,1-postotnim fluocinolon-acetonidom u orobazi i potentnim topikalnim steroidom, lezije HAEM-a vidljivo su se povukle

**Figure 2** One week after the treatment with fluocinolone acetonide orabase 0.1%, a potent topical steroid, the HAEM lesions showed marked improvement.

## Rasprava

HAEM koji zahvaća samo usnu šupljinu nije uobičajen u trudnoći i dosad ne postoje izvješća o teškim slučajevima na usnicama i u usnoj šupljini tijekom toga stanja. Planiranje liječenja pacijentice u opisanom slučaju bilo je otežano i zahtijevalo je detaljnu procjenu mogućih neželjenih učinaka lijekova na plod.

Prije početka bilo kakve terapije bilo je nužno postaviti točnu dijagnozu. Zato je korisno uzeti detaljnu anamnezu kako bi se ustanovilo jesu li se i prije pojavljivale slične lezije. Na temelju povijesti bolesti, kliničkog nalaza i laboratorijskih pretraga potvrđeno je da je već postojala infekcija virusom *herpes simplex*. Zato je postavljena dijagnoza HAEM-a. Naša pacijentica imala je tešku infekciju virusom *herpes simplex* prije godinu dana i lezije su bile potaknute sunčevom svjetlošću tijekom ljeta. Jaka bol tipičan je simptom te bolesti. Zato je u ovom slučaju postavljena dijagnoza HAEM-a.

Farthing i suradnici izvijestili su da su 82 pacijenta bolovala od rekurentnog EM-a te da su se oralne lezije ili zahvaćene usnice pojavile u 70 posto, odnosno u 13 posto slučajeva (7). Nadalje, u više od 60 posto slučajeva stanje se manifestiralo nakon infekcije virusom *herpes simplex*. Mnogi pacijenti s EM-om u anamnezi su naveli raniju HSV infekciju. Lezije se tipično pojavljuju na oralnoj sluznici i usnicama (8), a u ovom slučaju bile su slične kao u već opisanim prikazima slučajeva.

Ne postoji specifična terapija HAEM-a, ali obično se propisuju analgetici i tekuća dijeta. Sistemske steroidi prva su linija obrane u terapiji EM-a, a u liječenju HAEM-a mogu se koristiti antivirusni lijekovi (9). No u prikazanom slučaju nije bio ordiniran prednisonol kako bi se izbjegle moguće nuspojave. U jednom izvješću preporučuje se primjena antivirusnih lijekova u slučaju HAEM-a kako slijedi: na prvi znak lezije – 200 mg aciklovira 5x/dan, 5 dana, 4x/dan 400 mg 6 mjeseci, ili kontinuirano liječenje valacicloviro 2x/dan 500 mg kao profilaksa (10). U našem slučaju antivirusnu terapiju odredio je obiteljski liječnik, ali lezije se nisu povukle. Potentni topikalni steroidi FAO i FAS (0,1 %) bili su učinkoviti u liječenju HAEM-e i bez nuspojava kod ove trudne pacijentice koja je na kraju rodila zdravog sina.

## Zaključak

U prikazanom slučaju HAEM je dijagnosticiran na temelju anamneze, kliničkog nalaza i specifičnog laboratorijskog nalaza. Benzidamin-hidroklorid (0,15 %) može biti koristan u smanjenju bolova. Dodatno, FAO i FAS (0,1 %) pokazali su se učinkovitim u liječenju ulceracija. To su jeftini, sigurni i učinkoviti lijekovi bez nuspojava u ovom slučaju. Kratkoročna terapija s tim potentnim topikalnim steroidom sigurna je i u liječenju HAEM-a u trudnoći.

8-month telephone follow-up, she informed us that her newborn son was in a healthy condition. Importantly, no side effects were found in this patient or her newborn son.

## Discussion

HAEM involving the mouth alone is uncommon in pregnant women. There have been no previous reports of any severe cases of HAEM arising on the lips and oral cavity during pregnancy. The management of HAEM in this case was quite difficult and required full consideration of adverse effects to the fetus caused by any medications given to this patient.

A definitive diagnosis was of prime importance before beginning any treatment of this patient. Therefore, taking a thorough history to determine if similar lesions had previously erupted was useful, and together with the oral findings and laboratory tests of previous herpes simplex infection, the diagnosis of HAEM was made. Our patient had a severe herpes simplex infection a year before and the lesions were precipitated by sunlight during the summer. The most common symptom of this disease is severe pain. Hence, the diagnosis of HAEM was made in this case.

Farthing et al. reported that in 82 recurrent EM patients, oral lesions and affected lips were present in 70% and 13%, respectively (7). Moreover, in more than 60% patients, those attacks followed an episode of herpes simplex virus infection. Many patients with EM had a history of preceding HSV infection and the patients with EM typically presented with oral mucosal and lips lesions (8). Oral mucosal lesions and lip involvement in the present case were similar to those described in previous reports.

Regarding the treatment of HAEM, there is no specific treatment; however, analgesics and a liquid diet are needed. Systemic steroids are the first line therapy in EM and antiviral agents may be used in treating HAEM (9). However, in the present case, prednisolone was not prescribed by her physician to avoid serious side effects. One report recommended that antiviral agents may be indicated in individuals with HAEM; a 5-day course of acyclovir 200 mg 5 times/day at the first sign of lesions, 400 mg, 4 times/day for 6 months, or a continuous treatment with valacyclovir, 500 mg, twice a day, is useful for prophylaxis (10). In our case, antiviral therapy was prescribed by her physician to treat the lesions, however, the lesions did not improve. FAO and FAS 0.1%, the potent topical steroid, was effective in treating HAEM with no side effects on this pregnant patient who gave birth to a healthy son.

## Conclusion

In the present case, HAEM was diagnosed based on history taking, clinical findings, and the specific laboratory report. Benzidine hydrochloride 0.15% w/v mouthwash was found to be useful for pain reduction. In addition, the use of FAO and FAS, 0.1% was effective in treating the patient's severe painful oral ulcerations. Moreover, FAO and FAS, 0.1%, are low cost, safe, effective, and did not have any adverse effects on the patient. Short-term use of potent topical steroids, under the supervision of a doctor, is indicated for the treatment of HAEM in pregnant patients.

**Sukob interesa**

Autor ne navodi sukob interesa.

**Zahvala**

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**Conflict of interest**

The author declared no potential conflict of interest.

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**Abstract**

Erythema Multiforme, (EM) is an uncommon, acute inflammatory disease of the skin and mucous membranes characterized by ulcerations caused by hypersensitivity to drugs, microbial agents or other allergens. An EM outbreak can result in more severe forms of EM involving the skin, and there are several types of EM manifestations. A hemorrhagic crust on the lip is a pathognomonic sign of this disease. Target lesions may or may not be present in EM cases. When target lesions are not present on the skin, it is very difficult to make a definitive diagnosis of EM. Herpes associated erythema multiforme (HAEM) is an uncommon lesion caused by herpes simplex virus infection. A case of severe painful lesions in a 28-year-old pregnant patient with HAEM is presented here. HAEM is rarely found in pregnant women, and its clinical findings, diagnosis and treatment have not previously been reported.

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**Address for correspondence**

Kobkan Thongprasom  
Oral Medicine Department  
Faculty of Dentistry  
Chulalongkorn University  
Bangkok 10330 Thailand  
kobkan.t@chula.ac.th

**Key words**

Erythema Multiforme; Herpes Simplex; Fluocinolone Acetonide; Pregnant Women

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