e-GiGi 2026; Volume 14, Nomor 1: 190-197
DOI: https://doi.org/10.35790/eg.v14i1.64361
URL Homepage: https://ejournal.unsrat.ac.id/index.php/egigi

Management of Herpes-Associated Erythema Multiforme in a Young Male: A Case Report

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Received: October 3, 2025: Accepted: November 2, 2025; Published online: November 5, 2025

Abstract: Erythema multiforme (EM) is an acute mucocutaneous hypersensitivity reaction often triggered by infections or medications. The most common infectious cause is herpes simplex virus (HSV). Herpes-associated erythema multiforme (HAEM) typically presents with sudden, painful oral ulcers and hemorrhagic crusts on the lips. This case report highlights the clinical presentation, diagnosis, and management of a young adult with HAEM. A 20-year-old male presented with multiple painful oral ulcers and lip crusting following a febrile episode. Clinical examination revealed multiple, variably sized ulcers with erythematous borders and yellowish centers. A diagnosis of HAEM was established based on clinical findings and serological tests showing reactive HSV-1 IgG. The patient was hospitalized due to severe pain, dehydration, and inability to eat. Treatment included systemic acyclovir, intravenous fluids, analgesics, and supportive topical therapy with aloe vera extract mouthwash for intraoral lesions and hydrocortisone ointment for lip crusts. The ulcers and pain progressively improved, with complete recovery achieved by the third follow-up visit. This case emphasizes the importance of timely recognition and combined systemic–topical therapy in HAEM. Early antiviral intervention with supportive care can prevent complications, restore nutritional intake, accelerate healing, and improve quality of life.
Keywords: herpes-associated erythema multiforme; herpes simplex virus infection; oral ulcer; acyclovir; supportive therapy

INTRODUCTION

Erythema multiforme (EM) is an acute, self-limiting inflammatory mucocutaneous disorder characterized by distinctive target-like skin lesions that often involve the oral mucosa.[1,2] This EM is typically classified into two main forms: minor and major. The EM minor is limited to the skin, generally affecting less than 10% of the body surface area, whereas the EM major involves both the skin and mucous membranes. In more severe cases, mucosal involvement can lead to ulceration and significant discomfort.[1,3,4] A subset of EM cases may exclusively affect the oral mucosa without any accompanying skin manifestations, demonstrating the wide clinical variability of the condition.[1] EM can be triggered by multiple factors, primarily infections and medications. The most well-established infectious cause is the herpes simplex virus (HSV), particularly HSV-1, although HSV-2 can also contribute to EM.[3,5] In herpes-associated erythema multiforme (HAEM), approximately 90% of EM episodes are linked to HSV infections.[3,5–7]

HAEM is a clinically significant condition that demands prompt attention because of its severe impact on the quality of life, particularly oral health and systemic well-being. It often causes extensive oral ulcerations, leading to considerable discomfort and impairing essential functions such as eating and speaking. The rapid progression of symptoms from initial fever to severe ulcerative lesions within days underscores the need for timely medical intervention and comprehensive treatment strategies.[8,9] In this case, the patient developed multiple painful ulcers in the oral cavity after an episode of fever, suggesting an immunological response to HSV infection. Such cases of HAEM can be complex to manage due to the potential recurrence of herpes infections and the severe oral involvement that limits nutrient intake and quality of life.[9] Without effective and prompt treatment, HAEM can lead to complications including malnutrition, dehydration, and systemic infections, as observed in this patient's hospitalization.

Previous studies have explored various therapeutic modalities for HAEM, including systemic antiviral medications like acyclovir, corticosteroids to control inflammation, and supportive care for symptomatic relief. For instance, corticosteroids such as methylprednisolone have been used to alleviate inflammation, while antivirals like acyclovir target the viral etiology.[10] However, the effectiveness of these approaches varies depending on patient-specific factors such as immune status and the timing of intervention.

Recent reports emphasize the role of combination therapy, involving both systemic and topical agents. Topical treatments such as aloe vera extract and chlorine dioxide mouthwash has shown promise in reducing mucosal inflammation and promoting faster healing, thereby complementing antiviral therapy.[11] Additionally, individualized treatment plans that consider patient stress levels and immune responses are crucial for optimizing outcomes. The HAEM management requires a multidisciplinary approach combining timely antiviral, anti-inflammatory, and supportive therapies to effectively control symptoms and prevent complications.

This study presents a case of HAEM in a young adult, highlighting the progression of symptoms and treatment interventions, while also reviewing existing literature and recent therapeutic advances. Understanding these aspects is essential for improving care and prognosis in patients with HAEM.

CASE REPORT

A 20-year-old male presented to the Dental Hospital of the Faculty of Dentistry, Airlangga University, with the chief complaint of painful oral ulcers on the lower lip, buccal mucosa, ventral tongue, and gingiva, which had been present for four days. The pain was severe, with a VAS score of 7 at rest and 10 during meals. It was causing significant difficulty in eating and drinking, even at rest. Initially, the patient attempted self-management with warm salt water and povidone-iodine mouthwash.

The onset of symptoms was preceded by a fever, for which the patient received an intramuscular injection of metamizole sodium administered by a nurse at his dormitory. The following morning, two oral ulcers appeared, which rapidly increased in number by the second day.

The lesions remained confined to the oral cavity, with no skin or other systemic involvement. The patient had no history of similar symptoms. He reported taking antibiotics three times daily for three days, although the specific drug was unknown. Symptomatic relief with paracetamol, mefenamic acid, and methylprednisolone had been prescribed by a general practitioner at his dormitory. The patient denied smoking, alcohol use, or betel chewing, and had no parafunctional habits. He reported an allergy to seafood and an imbalanced diet. Psychological assessment (DASS-42) revealed mild depression, severe anxiety, and a normal stress level. The patient was a third-semester student at the Faculty of Economics and Business, experiencing a heavy academic workload.

Extraoral examination revealed stable general condition with blood pressure of 120/80 mmHg and a body temperature of 36.7°C. The submandibular glands were palpable, soft, and tender. The vermilion border of the lips showed multiple hemorrhagic crusted lesions of various shapes and sizes, black-brown coloration, rough surfaces, irregular edges, and surrounding erythema. Intraoral examination revealed multiple ulcers on the buccal and labial mucosa, and on the dorsal and ventral surfaces of the tongue. The ulcers varied in shape and size, with whitish centers, erythematous borders, smooth surfaces, and irregular margins. The surrounding mucosa appeared erythematous and painful. The gingiva was swollen, reddened, and painful. A clinical diagnosis of herpes-associated erythema multiforme was made, with differential diagnoses including allergic stomatitis and pemphigus vulgaris (Figure 1).

Figure 1. The initial visit: hemorrhagic crusting on the upper and lower lips with multiple ulcers on the labial mucosa, ulcerative lesions on the dorsal and ventral surfaces of the tongue, multiple ulcers on the buccal mucosa and gingiva, with swelling and erythema.

The initial management plan aimed to control symptoms and promote healing. Debridement was performed using normal saline (0.9% NaCl) and sterile gauze, followed by 1% povidone-iodine and topical application of chlorine dioxide mouthwash. The patient was prescribed aloe vera extract mouthwash to be used four times daily for intraoral lesions and a topical hydrocortisone ointment for lip lesions. A referral was made for laboratory testing, including serologic assay for HSV-1 and HSV-2 to confirm the diagnosis.

The first follow-up visit was conducted at Universitas Airlangga Hospital. The patient reported that two days earlier he had been hospitalized due to severe weakness and an inability to eat for several days (Figure 2). During hospitalization, the patient presented the results of his serologic examination, which showed a reactive HSV-1 IgG titer of 19.62 (Table 1). This positive result confirmed the diagnosis of HAEM.

During admission, the patient was treated in collaboration with an internist and received comprehensive supportive care, including intravenous fluids such as 0.9% NaCl and 5% glucose to address nutritional deficits and dehydration. Additional treatments included metamizole sodium 500 mg/2 mL IV, paracetamol 1 g/100 mL infusion, diphenhydramine 10 mg/1 mL IV, and lansoprazole 30 mg IV. Oral acyclovir 400 mg twice daily was given to target the viral component of his condition. Laboratory investigations, including a complete blood count and electrolyte analysis, revealed increased monocytes and decreased eosinophils and basophils (Table 2). Intraoral management at this visit consisted of debridement with sterile saline and gauze, along with continuation of the previous prescriptions. Additional education was provided, and the patient was instructed to return for a follow-up appointment.

Figure 2. The first follow-up visit: resolution of hemorrhagic crusts on the upper and lower lips, healing of ulcers on the dorsal tongue and labial mucosa, resolution of ulcers on the buccal, labial mucosa and gingiva

Table 1. Serologic test results for HSV of the patient

Immunology investigation	Result	Normal
IgM anti HSV 1	1.79	Non-Reactive: <9; Equivocal: 9-11; Reactive: >11
IgG anti HSV 1	19.62*	Non-Reactive: <9; Equivocal: =>9-<11; Reactive: >=11
IgM anti HSV 2	0.79	Non-Reactive: <9; Equivocal: 9-11; Reactive: >11
IgG anti HSV 2	0.85	Non-Reactive: <16; Equivocal: =>16-<22; Reactive: >=22

Note: *Out of reference range

Table 2. Hematology and electrolyte test results of the patient

Hematology tests	Result	Normal
Hemoglobin	14.4	13.2 - 17.3 g/dl
Leukocyte	7.43	6.0 - 12.0 10^3 µL
Erythrocyte	4.86	4.4 - 5.9 10^6 µL
Hematocrit	41.9	40 – 52 %
Thrombocyte	257	150 - 440 10^3 µL
MCV	86.2	80 – 100 fL
MCH	29.6	26 – 34 pg
MCHC	34.4	32 – 36 g/dl
RDW	12.2	11.5 – 14.5 %
MPV	9.1	6.8 – 10 fL
Lymphocyte %	31.0	25 – 40 %
Monocyte %	14.4*	2 – 8 %
Eosinophil %	1.9*	2 – 4 %
Basophil %	0.3*	0 – 1 %
Neutrophil %	52.4	50 – 70 %
PCT	0.23	0.2 – 0.36 %
Electrolytes		
Natrium	136	135 – 147 mmol/L
Kalium	3.9	3.5 – 5 mmol/L
Chloride	100	98 – 108 mmol/L

Note: *Out of reference range

During the second follow-up visit, the patient reported significant improvement, stating that he was now able to eat and experienced much less discomfort. He had been using the prescribed topical and mouthwash treatments regularly. Upon examination, multiple ulcers were still present in various areas of the oral cavity, including the buccal mucosa and tongue, with a whitish-yellow appearance and defined margins. The hemorrhagic crusts on the lips, as well as gingival swelling and redness, had improved (Figure 3). Management during this visit, included continued debridement with normal saline using sterile gauze, application of aloe vera extract spray for symptom relief, and continuation of previous prescriptions.


Figure 3. The second follow-up visit: significant improvement of hemorrhagic crusts on the lips and healing of ulcers on the dorsal and ventral surfaces of the tongue


Figure 4. The third follow-up visit: significant improvement and complete healing of ulcers on the gingiva as well as the upper and lower lips

At the third follow-up visit, the patient presented with no active complaints, indicating a substantial improvement and resolution of symptoms. Upon examination, some desquamation was observed on the vermilion border of the lower lip, with an irregular surface, but the remainder of the oral cavity appeared normal, with no new ulcers or erosions (Figure 4). Treatment during this visit included asepsis with 1% povidone-iodine. The patient was advised to return if any new complaints or symptoms developed. The overall treatment consisting of antiviral therapy and supportive care with symptomatic relief and topical application, successfully promoted healing and resulted in complete recovery by the third follow-up visit.

DISCUSSION

The diagnosis of HAEM was based on the patient's medical history and clinical features observed during the initial examination.[3,10] Typically, nonspecific prodromal symptoms in HAEM, such as fever, headache, malaise, lymphadenopathy, cough, and sore throat, last for 3-10 days.[12] Hemorrhagic crusting of the lips and ulceration primarily affecting the non-keratinized mucosa were noted, which are typical characteristics of oral lesions associated with HAEM.[9,10,13] When HAEM affects the lips, it leads to erosions or serum-hemorrhagic crusts (sanguinolent), presenting as pathognomonic blood-stained crusts on swollen lips. These lesions can hinder phonation and feeding, and they limit oral movement due to severe pain. Management often requires a combination of antiviral and corticosteroid therapy to reduce inflammation and accelerate healing.[13,14] Intraoral lesions associated with HAEM are most commonly found in the anterior regions, with the tongue and buccal mucosa being the most frequently affected. Although any site can be involved, the hard palate and gingiva are typically spared, with involvement observed in only 16% of patients.[10,13]

In this case, HAEM was limited to the lips and oral mucosa, with no skin involvement. The observed lesions included ulcers on the buccal mucosa, labial mucosa, and the dorsal and ventral tongue, as well as hemorrhagic crusts on the lips, all accompanied by significant pain. This presentation aligns with several case reports indicating that HAEM can exclusively affect the oral mucosa without skin involvement.[9,15,16]

When HAEM involves the skin, typical lesions appear as target or bull's eye lesions, usually found on the hands, feet, or trunk. These lesions can manifest as macules, papules, or vesicles with a necrotic center, giving a distinctive appearance. Oral lesions, meanwhile, may present as ulcers, erythema, or hemorrhagic crusts on the lips, similar to this case and other reports.[9,17] In more severe cases, such as erythema multiforme major, multiple mucosal sites (oral, genital, and conjunctival) may be affected, with skin lesions being more extensive.[18,19] Compared with these types, HAEM restricted to the oral mucosa appears less severe than the major form. Management of cases without skin involvement typically focuses on topical corticosteroids, mouth antiseptics, and antiviral agents like acyclovir, all of which were used here.[9,15]

Serology has proven valuable for establishing the etiology of erythema multiforme, especially when HSV infection is suspected. Serology, together with clinical features, particularly in cases

with typical oral or skin lesions, can confirm HSV as the trigger.[11,20] In this case, serological tests for HSV-1 showed positive (reactive) IgG and negative IgM, indicating a past or recent HSV infection.[21,22] A complete blood count also revealed changes in blood cells. Monocytosis is common in chronic infections, while eosinopenia and basopenia are often found during physical stress, reflecting suppression of eosinophil and basophil production. Stress-induced glucocorticoid release inhibits their mobilization from the bone marrow. An experimental study in mice showed that acute physical stress alters leukocyte distribution, including eosinophils and basophils, through neuro-immune mechanisms.[23,24] The patient reported experiencing psychological stress, as indicated by his DASS-42 scores. Both physical and psychological stress can compromise immunity, potentially triggering HSV reactivation and HAEM.[22,25,26] The decline in immune function due to cortisol secretion during stress contributes to HSV reactivation. Endogenous corticosteroids suppress immune-cells populations, such as interleukin-6 (IL-6), tumor necrosis factor- α (TNF-α), B lymphocytes, NK cells, and monocytes, all crucial in controlling HSV. Therefore, patients experiencing stress are more susceptible to HAEM recurrence.[22]

The pathogenesis of HAEM is consistent with a delayed hypersensitivity reaction. HSV DNA fragments are transported by peripheral blood mononuclear CD34+ cells (Langerhans cell precursors) to keratinocytes, leading to the recruitment of HSV-specific CD4+ Th1 cells. The inflammatory cascade is initiated by interferon-γ, released from CD4+ cells in response to viral antigens, triggering immune-mediated epidermal damage.[27]

Severe or extensive mucosal involvement may reduce oral intake, necessitating hospitalization for intravenous fluids and electrolyte repletion. In this case, hospitalization was required due to difficulty eating and a deteriorating general condition. Hospital care ensures adequate hydration and electrolyte balance, which can be disrupted by feeding difficulties.[3,28]

The management of erythema multiforme depends on its etiology and severity.[3] In HSV-induced erythema multiforme, acyclovir is the first-line treatment, while corticosteroids are used to control inflammation.[3,15,22] In this case, the patient received acyclovir 400 mg twice daily during hospitalization.[3,15] Acyclovir inhibits viral DNA replication, preventing viral proliferation.[29,30] Topical hydrocortisone ointment was applied to lip lesions, consistent with literature supporting corticosteroid use for reducing inflammation and promoting ulcer healing.[22] In this case, hydrocortisone was administered in an ointment formulation, an ointment is a semi-solid dosage form, typically an emulsion that contains one or more medicinal ingredients dissolved in a suitable base. The ointment formulation is intended to provide a cooling effect and moisturize the skin.[31,32]

Debridement with 0.9% NaCl was performed to remove necrotic tissue and exudate enhancing penetration of topical therapies.[33] Normal saline irrigation is widely used because it safe, inexpensive, and non-toxic to healthy tissue. This solution helps reduce bacterial contamination of the wound surface and supports wound healing through irrigation.[34]

Supportive care, including hydration and symptom relief, was emphasized. Chlorine dioxide mouthwash and aloe vera extract were used to reduce mucosal inflammation and accelerate healing. Chlorine dioxide solutions often contain additional agents such as xylitol and zinc acetate. Chlorine dioxide reduces gingival and plaque indices within two weeks, thereby lowering microbial contamination and preventing secondary infection of oral ulcers. [22,35] Zinc acetate acts as a deodorizer and helps maintain mucosa moisture, while xylitol provides antimicrobial activity. Stabilized chlorine dioxide assists in maintaining oral pH.[22] Aloe vera extract mouthwash provides comfort and pain relief by forming a protective barrier on lesions. Its hyaluronic acid and aloe vera content support mucosal repair.[22]

During hospitalization, intravenous fluids and parenteral analgesics were also administered to manage dehydration and severe pain, underscoring the importance of supportive measures in extensive cases.[36] The patient expressed satisfaction with the treatment results, noting a significant pain reduction and oral healing. At the second follow-up, he reported being able to eat and experiencing much less discomfort, indicating that the combination of antiviral therapy, topical treatments, and supportive care effectively resolved the condition.

CONCLUSION

The patient with herpes-associated erythema multiforme (HAEM) showed significant improvement following a combination of debridement, povidone-iodine application, topical hydrocortisone, chlorine-dioxide mouthwash and aloe vera extract. Systemic acyclovir effectively targeted the underlying herpes simplex virus infection. Complete recovery was achieved by the third follow-up visit, underscoring the importance of early intervention to relieve symptoms and prevent complications. Based on this case, it is recommended that clinicians consider a combined topical corticosteroid and systemic antiviral therapy, together with patient education on stress management and oral hygiene, to accelerate recovery and reduce the risk of recurrence in HAEM.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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