

Case Report

Oral Management of Herpes-Associated Erythema Multiforme in A Microcytic Anaemia Patient

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Received date: January 7, 2025

Accepted date: July 22, 2025

Published date: August 5, 2025

KEYWORDS

Erythema multiforme, herpes simplex virus, HAEM, oral medicine



DOI : 10.46862/interdental.v21i2.10897

ABSTRACT

Introduction: One acute and self-limiting hypersensitivity reaction affecting the skin and/or other mucous membranes is known as Erythema Multiforme (EM). EM is considered to be associated with infections or medications. Infection with Herpes Simplex Virus types 1 and 2 (HSV-1 and HSV-2) is a well-known predisposing factor and the most prevalent cause of EM, also referred to as Herpes Associated Erythema Multiforme (HAEM).

Case: A 31-year-old female patient presented to RSGM Universitas Airlangga with red-black crusts, erosion, and bleeding on her lips, as well as erosion and sloughing of the oral mucosa. She had experienced fever and chills for a week, and three days later, lesions appeared on the lips and oral mucosa. The symptoms progressively worsened despite treatment.

Case Management: At the first visit, the patient was referred for serology tests, complete blood count, IgM and IgG Anti-HSV 1 and Anti-HSV 2, and total IgE. Positive serology for IgG Anti-HSV 1 confirmed the diagnosis, and microcytic anaemia was also detected. The patient was treated with steroid orabase and oral elixir, administered four times daily.

Discussions: The first line in treatment management is using antiviral therapy. Early treatment with oral antivirals may lessen the number and duration of lesions. Topical steroids can be given in dosage form, paste in orabase, ointment or elixir according to the involvement of the lesion area.

Conclusion: Management of HAEM must determine the etiology and symptoms. A prompt and correct diagnosis following by the right approach to oral management not only cure but also prevent recurrence and improve the quality of life.

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How to cite this article: Ayuningtyas NF, Sismiyan R, YasminMahdani F, Dewi GK. (2025). Oral Management of Herpes-Associated Erythema Multiforme in A Microcytic Anaemia Patient.. Interdental Jurnal Kedokteran Gigi 21(1), 335-40. DOI: 10.46862/interdental.v21i2.10897

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INTRODUCTION

One of the acute and self-limiting hypersensitivity reactions affecting the skin and/or other mucous membranes is known as Erythema Multiforme (EM). EM is considered to be associated with infections or medications. Infection with Herpes Simplex Virus (HSV-1 and HSV-2) is one of the predisposing factors and the most prevalent cause of EM, also known as Herpes-Associated Erythema Multiforme (HAEM).¹ HAEM can affect individuals of any age but typically occurs in teens and young adults who appear otherwise healthy. Several studies report that males are more commonly affected than females.²

According to reports, HSV infections account for the etiology of the majority of acute EM cases. Additionally, nonsteroidal anti-inflammatory drugs (NSAIDs), sulfonamides, antiepileptic drugs, and antibiotics have been associated with the development of HAEM.³ The initial onset of EM is typically mild or features no prodromal symptoms. Before the appearance of lesions, symptoms such as fever, lymphadenopathy, malaise, headache, cough, and sore throat may be present for up to one week.⁴ HAEM clinically presents as a polymorphous eruption consisting of macules, papules, bullae, and crusts. Lesions can occur on the skin, with or without involvement of the oral cavity or other mucous membranes.⁵

CASE

A 31-year-old female patient presented to RSGM Universitas Airlangga with red-black crusting, erosion, and bleeding on her lips, along with erosion and sloughing of the oral mucosa. She had experienced fever and chills for one week, and three days later, the lesions appeared on the lips and oral mucosa. Over the last six months, she frequently suffered from mouth ulcers that resolved after treatment. She had been using aloe vera extract gel; however, her current symptoms have progressively worsened and have not improved despite treatment. The patient is a breastfeeding mother with no history of allergies or other medical conditions. Recently, she has reported feelings of depression due to a long-distance marriage with her husband.

CASE MANAGEMENT

Based on the clinical examination, the patient's general condition was good. Extraoral examination revealed multiple red-black crusts on the upper and lower lips. These lesions were irregular in shape, bleed easily, had clear boundaries, a rough surface, surrounding redness, and were painful. Intraoral examination showed multiple erosions with sloughing on the right and left buccal mucosa. The erosions appeared whitish, surrounded by redness, had a rough surface, and were painful (Figure 1 and 2). No other lesions were observed on the skin or any other part of the body. Based on her history and clinical findings, the patient was diagnosed with Herpes-Associated Erythema Multiforme (HAEM), with differential diagnoses including pemphigus vulgaris and allergic stomatitis.

At the first visit (04/01/2023), management included debridement of the affected areas using 0.9% sodium chloride solution, asepsis with 10% povidone-iodine, and application of chlorine dioxide gel. She was prescribed triamcinolone acetonide paste in orabase and an oral elixir containing dexamethasone (0.5 mg/15 mL), to be taken four times daily. Laboratory investigations were performed, including serology tests, complete blood count, IgM and IgG antibodies against HSV-1 and HSV-2, ANA test, and total IgE levels.



Figure 1. Clinical appearance of the upper and lower lips on the first visit.



Figure 2. Clinical appearance of (A) right buccal mucosa and (B) left buccal mucosa on the first visit.

Complete blood count results (Table 1) showed a low hemoglobin level of 10.3 g/dL (normal range 12.0–17.4 g/dL), hematocrit of 32.1% (normal range 36%–52%), mean corpuscular volume (MCV) of 75.4 fL (normal range 80–96 fL), and mean corpuscular hemoglobin (MCH) of 24.2 pg (normal range 26–34 pg). Elevated values were observed in the sedimentation rate at 40 mm/hr (normal range 0–20 mm/hr) and IgG Anti-HSV-1 at 48.1. The positive serology for IgG Anti-HSV-1 confirmed the diagnosis of herpes-associated erythema multiforme (HAEM) accompanied by microcytic anaemia.

Table 1. Complete blood count and immunology test

Parameter		Value	Normal Range	Units	Information
Haemoglobin	L	10.3*	11.7-15.5	g/dL	Woman
Leukocytes		8.7	3.6-11.0	$10^3/\mu\text{L}$	Woman
Erythrocyte		4.26	3.8-5.2	$10^6/\mu\text{L}$	Woman
Thrombocyte		362	150-440	$10^3/\mu\text{L}$	Woman
Haematocrit	L	32.1	35-47	%	Woman
Sedimentation rate	H	40	0-20	mm/hour	Woman
Eosinophil		0	2-4	%	Woman
Basophil		0	0-1	%	Woman
Neutrophil		55	50-70	%	Woman
Lymphocytes		33	25-40	%	Woman
Monocyte	H	12	2-8	%	Woman
MCV	L	75.4	80-100	fL	Woman
MCH	L	24.2	26-34	pg	Woman
MCHC		32.1	32-36	g/dL	Woman
RDW	H	15.8	11.5-14.5	%	
Immunology					
Total IgE		23.3		IU/mL	>15 years : < 100
ANA Test		Negative			
IgM Anti-HSV 1		2.7			< 9 : negative 9-11 : grey zone > 11 : positive
IgG Anti-HSV 1		48.1*			< 9 : negative 9-11 : grey zone > 11 : positive
IgM Anti-HSV 2		2.0			< 9 : negative 9-11 : grey zone > 11 : positive
IgG Anti-HSV 2		2.4			< 9 : negative 9-11 : grey zone > 11 : positive

L: Low
H: High

Later, she was given multivitamins, zinc, iron, and folic acid, and referred to a lactation consultant. Topical treatment was continued, and over the course of one week, the lesions on the lips and oral mucosa gradually improved. On the 12th day of treatment, the patient was followed up via telemedicine, and the lesions on the lips and buccal mucosa had completely resolved.



Figure 3. Clinical appearances of upper and lower lips (A and B) and dextral and sinistra buccal mucosal (C and D) on telemedicine at the 12th day.

DISCUSSION

Erythema Multiforme (EM) is considered one of the acute and self-limiting hypersensitivity reactions that affect the skin and/or other mucous membranes. EM is considered to be associated with infections or medications. Herpes Simplex Virus (HSV-1 and HSV-2) infection is one of the predisposing factors and the most prevalent cause of EM, also known as Herpes Associated Erythema Multiforme (HAEM).¹ The lesions that appear in HAEM have several forms, so they are called 'multiforme'. This condition represents a type IV hypersensitivity reaction (cell-mediated hypersensitivity reaction) to infectious agents (in the majority of cases) or drugs.⁶⁻⁹

In general, EM is classified as minor EM if there is less than 10% skin involvement and little or no mucous membrane involvement, while major EM appears as a more widespread condition, but still characterized by skin and oral cavity and other mucous membranes.⁶ As in this case, it is included in minor EM type because the lesions are only found on the oral mucosa and not found on other parts of the body. Minor EM lesions are limited to the oral

mucosa and lips, and tend to bleed. Extraoral lesions, in this case, is on the upper and lower lips. There are crusts, red-black, multiple and bled.

The pathogenesis of HAEM is a hypersensitivity reaction type 4 or also known as delayed-type hypersensitivity. Starting from transferring HSV virus DNA fragments to certain parts of the lips through peripheral blood circulation with mononuclear cells. The viral DNA fragment then expressed in keratinocytes, resulting in movement of HSV-specific CD4⁺ Th-1 cells which are included in the cellular immune system. The CD4⁺ cells then provide a response to HSV virus antigens by producing the cytokine interferon-gamma (IFN- γ), which then initiates an inflammatory cascade and causes tissue damage.⁶

HSV antibodies of the IgM indicate an acute infection, while antibodies of the IgG indicate previous exposure.⁷ Positive serology test IgG Anti HSV-1 confirmed the diagnosis of HAEM with the hypothesis that HSV-1 can determine more cross-reactions and induce autoimmune responses than HSV-2.¹⁰⁻¹⁵

The patient had prodromal symptoms, fever and chills for a week and 3 days later, the lesions appeared on the lips and oral mucosa. In the case of HAEM, the first line of treatment management is using antiviral therapy. Early treatment with oral antivirals may lessen the number and duration of lesions.^{8,12,13,15} Acyclovir 1000 mg a day in divided doses or valaciclovir 500 mg a day may be given for at least 7 days or 6 months to prevent the recurrence in severe cases.³ But in this case, the patient was a breastfeeding mother who was unwilling to get any drugs without approval from her lactation consultant. Topical steroids can be given in dosage form, paste in orabase, ointment or elixir according to the involvement of the lesion area. In this case, she was prescribed triamcinolone acetonide paste in orabase and oral elixir (dexamethasone 0.5 mg/15 mL). At the first visit, the patient's lips are given chlorine dioxide gel as an antimicrobial therapy and helps the healing process.¹⁶

The common type of anaemia with low mean corpuscular volume (MCV) is microcytic anaemia caused by iron deficiency. It can also caused by GIT disease or another chronic disease.^{17,18} The body can't make enough

material in red blood cells to transport oxygen and nourishment to cells in the body if there is insufficient iron. Clinical oral symptoms of iron insufficiency can occur independently of anaemia. Epithelial tissues have high iron requirements because of rapid growth and turnover rates and thus are affected in many patients with iron deficiency. Non-hematologic effects of iron deficiency include impaired immunity and infection resistance, diminished exercise tolerance and work performance, delayed wound healing, and various behavioural and neuropsychologic disorders. The treatment of this disease can be carried out by a multidisciplinary approach.¹⁹⁻²¹

Treatment for patient with iron deficiency anaemia is to restore iron storage. It can accelerate the healing of lesions by bringing haemoglobin levels back to normal and improving general condition. An iron supplement of 100 mg per day can be given to patients, and a blood transfusion can be given immediately in more severe cases.^{20,21}

The patients must maintain adequate hydration and nutritional intake. Inadequate nutritional intake, dehydration, and debilitation are conditions that arise as a result of difficulty eating and drinking, which ultimately require the patient to be hospitalized.^{22,23}

During the Covid-19 pandemic, telemedicine has become important in reaching patient during the outbreak. Telemedicine is very helpful in following up on a patient's condition. However, the limitations of this method are less able to get more accurate clinical examination results. The collaboration between doctors and patients is the key to the success of telemedicine.²⁴

CONCLUSION

Management of HAEM should focus on identifying the underlying etiology, especially when prodromal symptoms are present. A prompt and accurate diagnosis, followed by an appropriate oral management approach, not only facilitates healing but also helps prevent recurrence and improves the patient's quality of life. Generally, HAEM has a good prognosis and typically resolves within 2 to 4 weeks.

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