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RESEARCH ARTICLE

Herpes-associated erythema multiforme in a postmenopausal woman

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ABSTRACT

Herpes-associated erythema multiforme (HAEM) is an acute inflammatory mucocutaneous disease which is characterized by ulcerative lesion on oral mucous membrane with or without skin involvements. The etiology of erythema multiforme (EM) is probably hypersensitivity reaction to human herpes simplex virus tipe 1 (HSV-1). Lesions on lips with HAEM can be treated by corticosteroid and acyclovir topically and/or orally. The objective of this study was to report the case of HAEM with painful ulcers accompanying with crust on lips. A 55 years old woman complained painful ulcers with crust on lips since the last five months. She had visited a primary health care service and received several medications such as antibiotic (ciprofloxacin), anti-inflammatory drug (corticosteroid), analgesic (mefenamic acid) but her complaint was never healed completely because it was always recurring. The lesion on her lips got worse when she ate hot and spicy food and after she went out for outdor activities. She had a history of herpes virus infection seven months before but it was completely healed after treated by acyclovir topically and amoxicilin orally. An extra oral examination found black brown crust on her upper lip vermillion, well-demarcated, irregular margin, rough surface, erythematous surrounding area, accompanied with pain. An intra oral examination identified ulcers, yellowish, 4-5 mm in size, well-demarcated, irregular margin, redness in surronding area, accompanied with pain. A complete blood count examination, serology test for HSV-1 (IgM and IgG) were taken and the result showed that only IgG was reactive. The therapies given to the patient were topical medications with a combination of corticosteroid, chloramphenicol and moisturizer, followed by methyl prednisolone and acyclovir orally. After 6-week treatment, the lesions were completely healed.Herpes-associated erythema multiforme (HAEM) caused by hypersensitivity reaction to herpes simplex virus type 1 (HSV-1) may have a characteristic of painful ulcers accompanied with crust on the lips. The combination of both anti-inflammatory and antiviral drugs can be a choice for the therapy.

Keywords: crust; herpes-associated erythema multiforme (HAEM); herpes simplex virus type 1 (HSV-1); lip ulcer

INTRODUCTION

Erythema multiforme (EM) is a mucocutaneous inflammatory disease that may be acute or chronic and has manifestations on the skin, oral mucosa, or genital mucosa. Erythema multiforme is a self-limiting disease, mild in nature, and can be severe.[1–3] There are two classifications of EM in general, namely minor type and major type. Minor EM may have lesion less than 10% of body surface with minimal mucosal involvement or no mucosal involvement, but EM can occur only in one location such as the oral mucosa.[2] Erythema multiforme is usually found in young adults around the age of 20-40 years old, more common in men than women. Twenty percent EM can be found in children.[3]

In terms of etiology, EM may be caused by several factors including drugs such as sulfonamides, (cotrimoxazole), cephalosporins, aminopenicillins, quinolones, chlormezanone, barbiturates, non-steroidal anti-inflammatory oxicam, anticonvulsants, protease inhibitors, allopurinol, and corticosteroids. The etiology of EM may also be genetic factor. Erythema multiforme is associated with the involvement of human leukocyte antigen (HLA) - B15 (B62), HLA-B35, HLA-A33, HLA-DR53, HLA-DQB1*0301. Meanwhile HLA DQ3 is a genetic factor involved in HAEM.[3]

Majalah Kedokteran Gigi Indonesia. April 2021; 7(1): 51 – 59
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Other causes of EM are bacteria, fungi, parasites, chemicals, or foods. Erythema multiforme can also be caused by the herpes simplex virus (HSV), varicella zoster virus, cytomegalovirus, Epstein-Barr virus, adenovirus, enterovirus (coxsackievirus B5, echovirus), viral hepatitis (A, B, C), influenza, paravaccinia, parvovirus B19, poliomyelitis, vaccina and variola. However, most minor EM may be caused by virus.[3]

Herpes-associated erythema multiforme (HAEM) is a variant of EM caused by the herpes simplex virus (HSV) type 1. The development of HAEM is usually preceded by herpes simplex virus infection. This is supported by evidence that there are 36-81% of HSV DNA in HAEM lesions. The HSV type 1 is involved in about 66% of HAEM especially in the case of EM with lesions on the lips. Twenty eight percent HAEM is caused by HSV-2.[3] Herpes-associated erythema multiforme (HAEM) is an immune reaction-mediated disease against the HSV DNA fragments. The HSV DNA fragments persist on the skin or mucosa after previous infection of HSV type 1. A study showed that there is DNA polymerase (PoL) and accumulation of CD4 T cells in the epidermal suprabasal cell layer of lesions that have healed after three months. The DNA fragment induces the formation of Th1 cells and produces interferon (IFN) gamma which is the main proinflammatory cytokine in the delayed hypersensitivity reaction and induces the expression of adhesion molecules in keratinocyte cells. The expression of IFNγ will increase the immune response by stimulating the production of other cells such as cytotoxic cells and natural killer cells (NK). Those cells may damage oral epithelium.[3]

Previous HSV infection is one important history to diagnose HAEM. Other symptoms such as burning and painful lesions are usually preceded or not preceded by prodromal symptoms (i.e malaise and fever). An objective examination can find reddish macules with clear borders and papules. There are enlarged papules or plaques of which the middle part is darker and brownish; there is also purpura. The lesions on the skin are characterized by target lesions that resemble the iris of the eyes because they have a rounded pattern with a dark center, surrounded by a more pale area and a ring-like reddish border. Skin lesions are found in the extremities such as the hands and feet, but lesions can only be found on the oral mucosa.[4] Mucosal lesions can be found in the lip mucosa and they are present as swelling, cracking, and crusting. Crusts in minor EM are often found on the lips.[3] The lesions of EM may be recurrent with variations of 2 to 24 episodes a year. The serum Immunoglobulin (Ig) tests M and G against HSV may confirm the presence of HSV infection to support the Diagnosis of HAEM. The lesion biopsy is not needed if the clinical signs of EM have been found. Besides, histopathological examination of EM lesions can have variation including the interpretation.[3,4] Erythema multiforme may have differential diagnosis such as autoimmune disease, drug eruptions, lupus erythematosus, pityriasis rosea, polymorphic light eruption, Steven Johnson syndrome, toxic epidermal necrolysis, urticaria vasculitis, viral exanthema, and hypersensitivity reactions.[4]

Some studies have found HAEM cases in children with an average age of 8 years,[5] but it can also be found in the age range of 10 to 21 years.[6–10] Most HAEM have clinical signs on both the oral mucosa and on the skin. HAEM cases in the age of 50 years or older are rarely reported. However, there was one HAEM case report in a 57-year-old woman with ulcers in the lip vermillion border accompanied by hemorrhagic crusts and ulcers on the buccal mucosa, gingiva, and tongue.[11] Although EM can heal spontaneously, some cases can be recurrent so it requires treatment. There is no specific treatment for EM. Antiviral (acyclovir) can effectively treat HAEM with the dose of 200 mg five times a day for 5 days. The treatment of HAEM can also use topical corticosteroids or systemic corticosteroids, and antibiotics to relieve inflammation.[3,12]

METHODS

A 55-year-old woman came to the Oral Medicine Clinic at Dental Hospital, Universitas Airlangga

with a complaint of painful mouth ulcers on her lips which easily bled. The lip lesions had been recurrent since the last five months. This complaint was recurrent and the pain got worse after eating spicy and hot foods as well as after doing outdoor acitivities. The patient had visited a primary health center because of her complaint and she was given mefenamic acid and vitamins. The patient was prescribed the same drugs by her doctor two months prior to visiting this dental hospital. Five days prior to visiting this dental hospital, the patient went to the general practitioner and was given ciprofloxacin 500 mg twice daily, ketoconazole 200 mg once daily, gom and steroid topically. Besides, she had taken herbal medicines as well. The drugs were taken three days prior to visiting this hospital, but it had no effect. She had her blood sugar and blood pressure examined, and the results were normal. However, her cholesterol and uric acid levels were high. The patient did not consume foods that could aggravate the recurrence of bleeding on the lips. The patient had history of herpes virus infection on her neck seven months prior to visiting this dental hospital. She was then given acyclovir topically and amoxicillin by her doctor and she healed after seven days, but she felt that the lesion on her lips got worse two weeks before coming to this hospital, precisely after she went out without a face mask.

Her general conditions were as follows: body weight 50 kg, height 137 cm, blood pressure 110/90 mm Hg. An extra oral examination showed that there was an irregular crust on her upper lip vermilion, clear margin, black brown crusts, with normal surrounding area, accompanied by pain. On the lower lip there are multiple ulcers with a diameter of 4-5 mm, clear margin, irregular border, yellowish, with erythematous surrounding area, accompanied by pain (Figure 1). The working diagnosis was EM with a differential diagnosis of actinic cheilitis. The result of an intra-oral examination: the dorsal tongue had white pseudomembrane, diffuse, irregular edges, without pain, normal color of the surrounding area, and can be scraped off (Figure 1) and diagnosed as coated tongue.

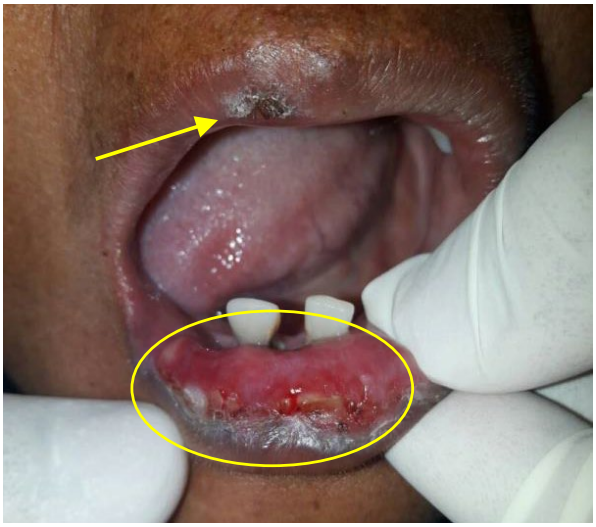

Figure 1. Hemorrhagic crust (arrow) and ulcers with erythematous surrounding area on lip vermilion area (circle)

The treatment plan included lesion asepsis, application of topical anti-inflammatory drugs, and prescription of topical drugs which consisted of hydrocortisone (0.125 gr), kemicetine (0.125 gr), lanoline (0.25 gr), vaselin (5 gr). The drugs should be used three times a day applied to the lesions of the upper and lower lips after meal, isoprinosine two times daily, multivitamin (10 tablets) once a day. A complete blood test, immunoglobulin (Ig) G and IgM of HSV type 1 were performed. The result of the complete blood test showed the value of erythrocytes sedimentation rate (ESR) was 50-103 (normal value: ≤15/hour), neutrophil segmen was 64 (normal value: 54-62), serum IgG for HSV type 1 was reactive (39.58), IgM for HSV type 1 was non reactive (0.81). Other parameters such as liver and blood glucose regulations (HbA1c) were normal. The patient was informed and educated that the possible cause of the disease was HSV type 1 that previously infected her and caused erythema multiforme. The lesions were treated with topical anti-inflammatory drugs to relieve inflammation of the lips and vitamin to accelerate the lesion healing. She was also advised to maintain oral hygiene, continue to wear a face mask when going out, and avoid consuming spicy and hot foods.

After two weeks treated by a combination of topical steroid and antibiotic, the lesions were still

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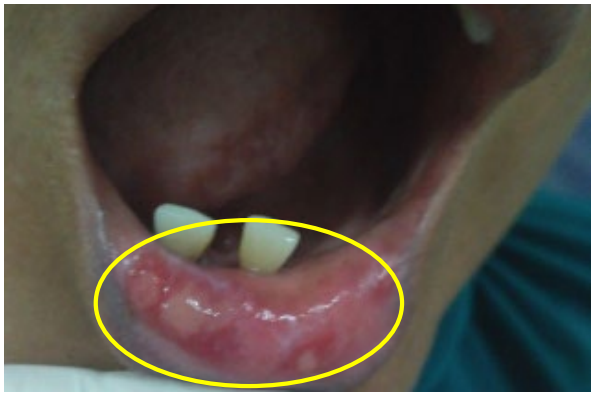

Figure 2. multiple yellowish ulcers with erythematous surrounding area on lower labial mucosa

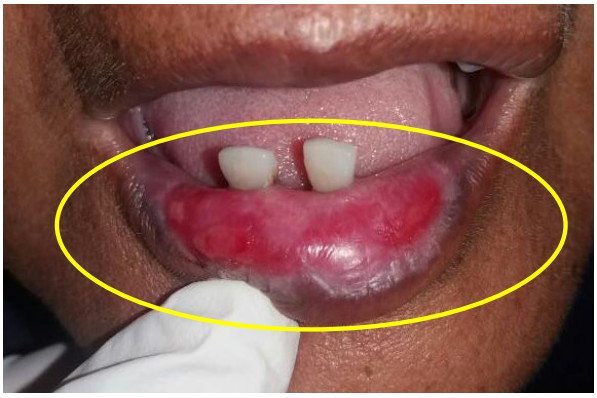

Figure 5. Erythematous area on the lower labial mucosa

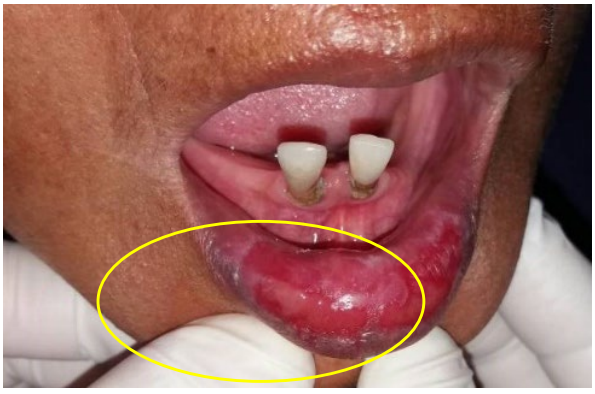

Figure 3. Multiple yellowish ulcers with erythematous surrounding area on the lower labial mucosa

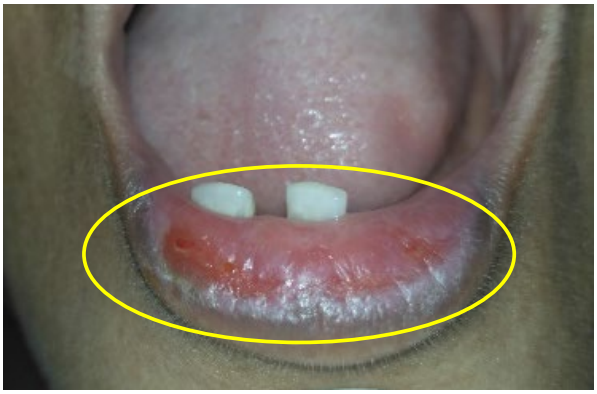

Figure 6. Yellowish crust with normal surrounding area on the lower labial mucosa

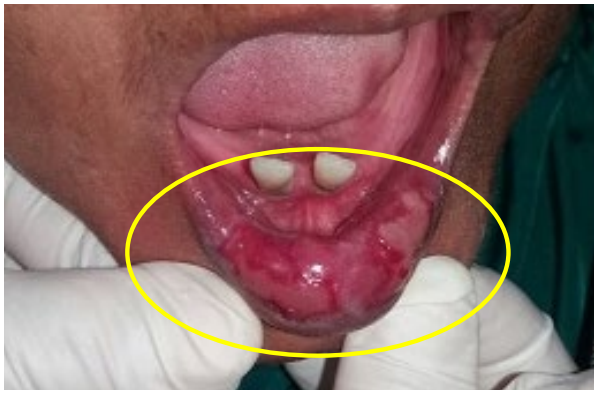

Figure 4. Multiple ulcers with erythematous surrounding area on the lower labial mucosa

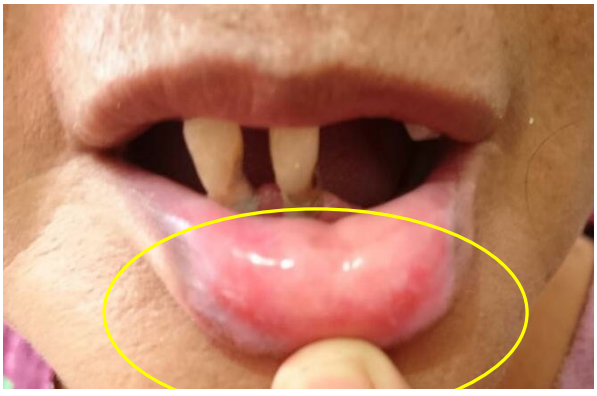

Figure 7. Lower labial mucosa with normal colour

present, but the pain reduced (Figures 2 and 3). The treatment was then continued by prescribing systemic steroid (methyl prednisolone) 4 mg three time daily for two weeks and antiviral drug (acyclovir 200mg) orally five times daily for two weeks and analgesic (methampyrone 500 mg) with diazepam 2mg for five days once daily; the lesions and the pain decreased (Figures 4

and 5). The lesions decreased after treated by methyl prednisolone orally two times daily for one week (Figure 6) and completely healed one week later (Figure 7).

DISCUSSION

This case came with a complaint of pain on the upper and lower lips due ulcers that had not healed for the past five months. The clinical examination found yellowish ulcerative lesions on the lower lip vermilion, and there was black brown crust on the upper lip vermilion. Those clinical signs were some signs of EM. Minor EM is one type of EM that involves less than 10 percent of the body area and may only have lesions on the oral mucosa[13] or diagnosed as oral EM.[2] Oral EM lesions can be found only on the lips with ulcerative lesions, erosion, cracking, bleeding accompanied by the formation of hemorrhagic crust on the lips. The lesions of this current case were only found on the upper and lower lips without lesions on the skin surface, indicating minor erythema multiforme.[2,3] The subjective examination showed that there was history of similar lesions for five months on the lips which never completely healed and may be recurrent. In fact, these lesions may also be a chronic feature.[2]

Minor EM can be caused by several factors, one of which is HSV type 1 which has caused approximately more than fifty percent of EM cases.[4] In this study, the diagnosis of EM caused by the HSV type 1 was supported by the subjective examination revealing a history of herpes virus infection in the neck which healed after given topical acyclovir medication by a general practitioner. The history of herpes simplex virus infection prior to the onset of mucosal lesions is very important to diagnosis HAEM.[4] The diagnosis of HAEM was also supported by the results of the serological examination, showing reactivity of immunoglobulin (Ig)G against HSV type 1, but non-reactivity of Ig M against this virus. The reactivity of IgG against HSV-1 indicated that the patient had a history of HSV-1 virus infection. The IgM was not reactive because IgM will appear in the first 7-10 days after the first exposure or early HSV infection.[1,14] The IgG in this case was reactive because IgG will appear in individuals who have been infected after about two to three months after infection and IgG will be non-reactive in primary HSV infection.[15] Therefore this case was diagnosed as HAEM.

The differential diagnosis in this case was actinic cheilitis. The allergic contact cheilitis can be ruled out because there was no history of allergies and the lesions did not associated with the patient's habits such as the use of drugs, cosmetic, and certain foods. The differential diagnosis of actinic cheilitis was chosen based on the history of ulcerative lesions that recurrent after outdoor activities. Hence, there was a possibility that the lesions on the patient's lips were due to sun exposure. In addition, this case had clinical similarities with Actinic cheilitis becasue the ulcerative lesions were only limited to the upper and lower lip vermilion in which the lesions on the lower lip vermilion were wider than those on the upper lip vermilion. However, actinic cheilitis lesions may be different from with ulcerative lesions, may be accompanied by cracked lips, crusting, prolonged pain, and involve the lip vermilion border especially on the lower lip,[16,17] whereas ulcerative lesions in this case were not only on the lower lip and did not involve the lip vermilion border.

Herpes-associated erythema multiforme is a cell-mediated hypersensitivity reaction to DNA polymerase (Pol) HSV fragments in the skin or oral mucosa. Herpes simplex virus DNA found in the oral mucosa will stimulate Th1 cell-mediated delayed-type hypersensitivity. There is accumulation of Th1 CD4 cells, mononuclear cells in active HAEM lesions. Macrophages will phagocyte HSV which results in DNA fragmentation including DNA polymerase (Pol). Peripheral blood mononuclear cell carrying HSV fragments are then recognized by intercellular adhesion molecule (ICAM)-1 in endothelial cells and deposited in the epithelium. Expression of HSV DNA on keratinocytes will stimulate Th1 CD4 T cells in response to HSV DNA. The presence of specific T cells against HSV will produce interferon (IFN)γ. Interferon (IFN)γ will stimulate other cytokines such as tissue growth

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factor (TGF)β, which then will increase the number of T cells in the oral mucosa in response to HSV DNA including cytotoxic T cells, natural killer (NK) cells, leukocytes, and monocytes. The accumulation of cytotoxic T cells, NK cells, and TGFβ will damage the mucosal epithelium.[3,18] There is a difference between the pathogenesis of herpes labialis and HAEM. The herpes simplex virus in herpes labialis is not detected on peripheral blood mononuclear cell (PBMC), which means transient viremia occurs when HSV virus reactivation in herpes labialis. Meanwhile in HAEM, HSV DNA fragments are still detected in PBMCs and remain in the epithelium. This might be caused by the inability of HAEM to eliminate the HSV from the epithelium, whereas in herpes labialis the virus will completely disappear, leaving no DNA fragments in the epithelium after the lesions dissapear.[19] The crusts found in this case indicated vasculitis. Erythema multiforme vasculitis can occur due to the presence of type three hypersensitivity reactions, caused by antigen-antibody complexes. When phagocytic cells such as macrophages cannot eliminate the complex, the antigen-antibody complex then enters the blood circulation and deposited on the surface of the blood vessel wall resulting in an increase in blood vessel permeability. This complex will then bind to inflammatory cells through Fc and C3b receptors and cause the release of vasoactive mediators and cytokines then trigger an inflammatory reaction.[20]

The treatment of EM is topical corticosteroid in the first two weeks to relieve inflammation of ulcers and the pain. In addition to topical corticosteroids, methyl prednisolone can also be given orally. Methyl prednisolone is an anti-inflammatory drug which is often prescribed in oral ulcer lesions in HAEM.[3] Topical corticosteroid has also been given in several cases of HAEM such as dexamethasone elixir,[7,10,13] triamcinolone in orabase.[8] and systemic or oral (methyl prednisolone/prednisolone).[3,21] Corticosteroids have an anti-inflammatory action by reducing the number and ability of polymorphonuclear leukocytes and monocytes to attach to the endothelium in the inflammatory area. Besides, these drugs may reduce NK cells and immune cells, inhibit the release of phospholipase A2 which is involved in the production of prostaglandin, leukotriene in the synthesis pathway of arachidonic acid. Corticosteroids may reduce T cell production to increase T cell apoptosis, decrease adhesion molecules such as intracellular adhesion molecule-1 (ICAM-1) from the endothelium. Corticosteroids also inhibit transcription factors such as activator protein -1 (AP-1) and nuclear factor kappa beta (NFkB) which are needed in activating the proinflammatory gene. In addition, corticosteroids will inhibit the production of IL 1, IL-2, and granolocyte-monocyte stimulating factor (GMSF), and inhibit cyclooxygenase and nitric oxide (NO) which are inflammatory vasodilators. Topical hydrocortisone is a corticosteroid that has short acting with a low potency that can be used for long periods of time.[22]

The other drugs prescribed in this case were methampyrone or metamizole (500 mg), an analgesic with a combination of diazepam (5 mg). Methampyrone is a non-opioid analgesic drug that can be prescribed for acute and chronic pain, from mild to moderate pain. Methampyrone has an activity in the central nervous system by reducing the synthesis of prostaglandin E2 (PGE2) in the central nervous system and the sensitivity of peripheral nociceptors. Besides, methampyrone has an anti-inflammatory effect which inhibits cyclooxygenase-1 (COX-1) and COX-2 but the effect is very weak.[23] Diazepam is a type of anxiolytic drug that can be used to reduce anxiety usually in dental patients, only given for 1-7 days with a minimum dose of 2-5 mg.[24]

The multivitamins prescribed in this case consisted of vitamin B1, B2, B12, folic acid, niacin (B3), pantothenic acid, vitamin C, vitamin E, and zinc. Vitamin B1 is a coenzyme in energy metabolism through the Krebs cycle which aims to produce energy and plays a role in nerve tissue. Vitamin B2 is a coenzyme for carbohydrate metabolism, protein, and fat release for cellular energy and plays a role in the maintenance of mucous membranes. Vitamin B3 (niacin) is a coenzyme in energy formation (ATP) and along with riboflavin (Vitamin B2), it plays a role in glucose production and metabolism and is involved in fat

and protein metabolism. Niacin plays a role in the maintenance of mucous membranes. Pantothenic acid also plays a role in the metabolism of carbohydrates, fats, and proteins, and plays a role in the synthesis of triglycerides, phospholipids, hormones, and nerves. Vitamin B12 is a vitamin that contains minerals (cobalt) which functions as a coenzyme with folic acid in nucleic acid synthesis. This vitamin functions in catabolism of amino acids and fatty acids. Vitamin B12 plays a role in the formation of red blood cells and myelin nerve synthesis. Vitamin C functions as a coenzyme and has an ability as an antioxidant that functions in the synthesis of collagen and hyaluronate and plays a role in wound healing and decreases the degradation of extracellular matrix mediated by enzyme matrix metalloproteinase (MMP). Vitamin C also increases capillary integrity, helps in the formation of red blood cells by increasing iron absorption in the intestine, and increases fibroblast proliferation. This vitamin also helps the use of vitamin B12 and folic acid by the body. Vitamin E is a vitamin that is involved in the cellular defense system. As an antioxidant, vitamin E functions in maintaining and stabilizing the integrity of cell membranes by protecting cells from oxidation. Vitamin E also plays a role in the nervous system.[25,26] Zinc is a coenzyme of more than 300 enzymes involved in cell proliferation, DNA replication, and signal transduction. Zinc is an integral part of several enzymes such as oxidoreductase, transferase, hydrolase, lyase, isomerase, and ligase. Zinc also plays a role in the body's immune system including mucosal immunity and is involved in the proliferation of T and B cells, in the production of immunoglobulins and cytokine.[27] Zinc is a co-factor for DNA polymerase and RNA polymerase.[25]

In addition, this patient was treated with isoprinosine which is a type of immunomodulator. Treatment with immunomodulators is usually given in severe cases of HAEM.[3] Isoprinosine is a synthetic drug that contains p-acetamido benzoate salt of N N-dimethyamino-2-propanol and inosine which has immunomodulatory and antiviral effects. Isoprinosine has been known to be used in the treatment of infections by the herpes virus in the oral cavity. Isoprinosine has the ability to stimulate differentiation of T cells into cytotoxic T cells and helper T cells and increase the production of IL-1 and IL-2, and improve NK cell function. In addition, isoprinosine increases the response of humoral immunity by increasing antibody production. Isoprinosine also has the ability as an anti-viral agent and has been used as one of the treatments for herpes infections in the oral cavity. The effectiveness of isoprinosine resembles oral acyclovir in the treatment of recurrent herpes labialis and recurrent genital herpes. Nevertheless, isoprinosine has a side effect, namely increasing uric acid in the blood due to isoprinosine metabolism into purine compounds, but the effect is reversible after the treatment is stopped.[28] This was also found in the case of this study, namely after taking isoprinosine on the second visit, the patient had a symptom of stiffness in the knee joint but the symptom did not persist after the cessation of isoprinosine.

We added chloramphenicol ointment combined with hydrocortisone. Chloramphenicol antibiotics have the ability to inhibit protein synthesis and have a broad spectrum of gram-positive, gram-negative, and anaerobic bacteria and these antibiotics are effective for several bacteria such as Spirochetes, Rickettsia, Chlamydia, and Mycoplasmas. Chloramphenicol can be bacteriostatic but can be bactericidal against Streptococcus pneumonia and Nisseria meningitis. Chloramphenicol prevents infection in vermilion lesions and can be prescribed for Staphylococcus bacteria.[29] Although chloramphenicol has side effects such as aplastic anemia but these side effects do not occur in topical use.[30] A previous study showed that one of the bacteria found in the lips which caused infection in the perioral and lip regions was Staphylococcus.[31]

On the third visit, we added acyclovir (200mg) five times a day for two weeks (14 days) until the lesion disappeared. Other case reports also used acyclovir at the same dose as a drug in HAEM but with a short duration,[7,11,13] but in a different case, 200 mg of acyclovir five times a day was

given up to 14 days.[10] Administration of acyclovir in oral diseases caused by HSV infection can be given for up to 14 days.[32] Acyclovir is an anti-viral drug which is a guanosine acrylic analog which is a potent inhibitor of HSV-1, HSV-2, and varicella zoster which has low toxicity in normal body cells. Acyclovir selectively undergoes phosphorylation into monophosphate derivatives in cells infected with the virus by the enzyme thymidine kinase. The binding of acyclovir to HSV thymidine kinase is stronger than the binding to human cell thymidine kinase. Kinase enzyme changes the form of acyclovir monophosphate to diphosphate and then forms acyclovir triphosphate. Acyclovir triphosphate will inhibit virus DNA polymerase so viral replication does not occur.[33]

CONCLUSION

Herpes-associated erythema multiforme (HAEM) may have hemorrhagic crust accompanied by ulcerative lesions on the lip vermilion. The treatment of HAEM may be a combination of corticosteroid and anti-viral drugs topically and orally to accelerate lesion healing.

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