Successful Treatment of Persistent Oral Ulcers in Patients with HIV / AIDS

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Abstract

Oral ulceration is a common condition found in patient with HIV/AIDS. The ulcerations may be fungal/bacterial/viral infection-associated or non-infection-associated. The standard treatment protocol for these oral ulcers includes the elimination of etiologic factors, pain reduction, healing acceleration and prevention of recurrent episodes. However, challenges may be applied when dealing with a patient with HIV/AIDS. A 39 years old male with a diagnosis of AIDS, was referred to Oral Medicine Clinic in Cipto Mangunkusumo Hospital. He initially presented with necrotizing stomatitis on the upper lip and tongue. Standard treatment protocol for oral ulcers was done, however due to his anemic condition, the healing was delayed and accompanied with occurrence of another necrotizing stomatitis lesions on the right retromolar pad, on uvula extended to soft palate, and major stomatitis on the posterior lateral of tongue.

The management included debridement using antiseptic, application of topical metronidazole as well as improvement of his systemic conditions with a blood transfusion, antiretroviral therapy, and systemic antibiotics. The success of treatment of this case is determined by lesion management, patient's compliance, and improvement of systemic condition that includes improving nutrition intake, therapy of anemia, and correcting CD4 count that was achieved with teamwork of different specialties.

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Introduction

Human Immunodeficiency Virus (HIV) is a virus that attacks human immune system. HIV can progress into Acquired Immunodeficiency Syndrome (AIDS) when CD4 counts in an infected patient is below 200 cell/ml.[1] There are seven oral lesions strongly associated with HIV/AIDS including oral candidiasis, hairy leukoplakia, linear gingival erythema, necrotizing ulcerative gingivitis (NUG), Kaposi's sarkoma, necrotizing ulcerative periodontitis (NUP), and Non-Hodgkin lymphoma.[2]

Recurrent aphthous stomatitis (RAS) is a common oral ulcer found in humans. In people with AIDS, RAS is more severe with longer duration, more painful, causes dysphagia, and leads to mucosal scarring.[3] Necrotizing ulcerative stomatitis (NUS) occurs more frequently in patients with HIV seropositive compared to immunocompetent population. NUS is a necrotic, deep painful ulcer, localised, and may extend to contiguous site. NUS can develop as a progression of NUG/NUP or as an entirely different lesion located distinct from periodontium.[4,5]

This case report describes successful treatment of oral ulcers consist of several NUS and major RAS accompanied with delayed healing in patient with HIV/AIDS.

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Case Report

A 39 years-old male patient with AIDS was referred to Oral Medicine Clinic in Cipto Mangunkusumo Hospital (CMH). The chief complaints were swollen upper lip, painful ulcer on the upper lip and on the left side of his tongue that caused difficulties in eating and drinking. In clinical examinations, we found three ulcers consisted of necrotizing ulcer on the upper labial

mucosa (15 mm), necrotizing ulcer on the left side of tongue (20 mm), and a shallow round ulcer (3 mm) on the midline of lower labial mucosa. We diagnosed the necrotizing ulcers based on clinical ground as NUS. During treatment, another necrotizing stomatitis occured on the right retromolar pad (10 mm) and palatal mucosa contiguous with the retromolar pad (5 mm), and on the uvula extended to soft palate (25 mm), respectively. The patient was experiencing difficulties in eating, drinking, and swallowing that caused inadequate nutrition intake. Another RAS lesion occured on the posterior lateral and dorsum of tongue (Figure 1). All of the lesions showed delayed healing.

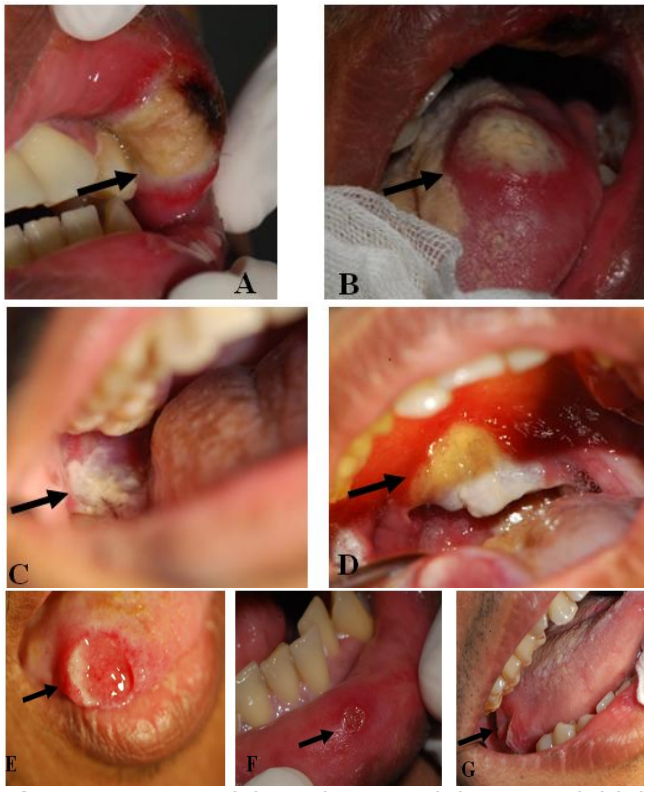

Figure 1. Necrotizing ulcer on (A) Upper labial mucosa; (B) Left side of tongue; (C) Retromolar pad; (D) Uvula extended to soft palate. Recurrent aphthous ulcer on (E) tongue; (F) Lower labial; (G) Right side of tongue.

The necrotic lesions were treated locally with debridement using 3% hydrogen peroxide, 0.2% chlorhexidine, and application of topical metronidazole on the lesions. After necrotic lesions subsided, we gave doxycyline rinse. Since doxycycline did not give significant benefits in ulcer healing, we decided to discontinue doxycycline and use sucralfate rinse. Sucralfate acted as coating agent that facilitate the patient to eat, drink, and swallow. We also prescribed systemics antibiotics consisted of metronidazole and clindamycin to erradicate infections.

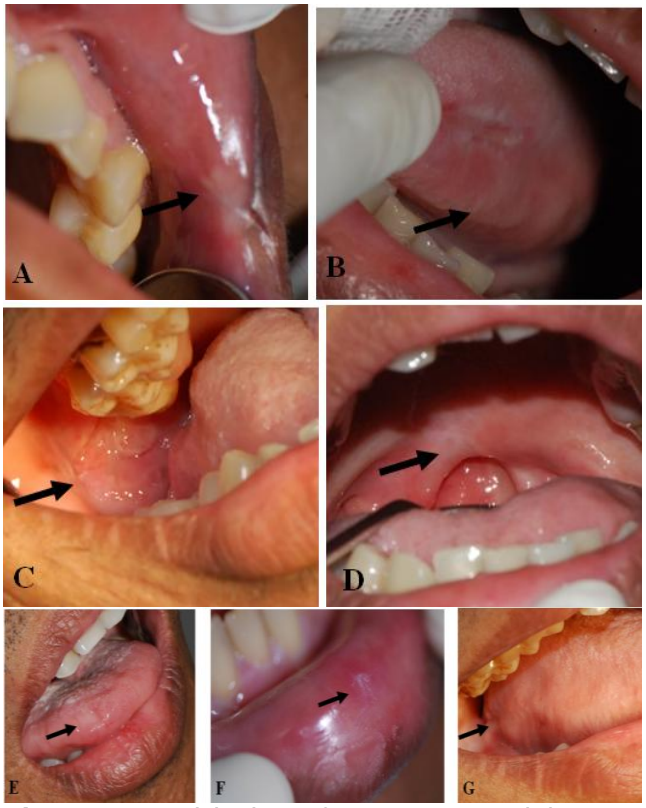

Figure 2. Oral lesion after treatment: (A) upper labial mucosa; (B) Left side of tongue; (C) Retromolar pad; (D) Uvula extended to soft palate; (E) Tongue; (F) Lower labial mucosa; (G) Right side of tongue.

Component	Jan	Feb	Mar 4th	Mar 31st	April	May	June
Hb (g/dL)	11.5	8.3	7.4	7.9	9.9	8.9	11.1
Ht (%)	32.4	23.7	22.0	23.8	30.5	27.7	33.2
Leukocytes (10^3/µL)	1.23	2.85	2.33	2.25	1.46	2.35	4.67
Thrombocyte (10^3/µL)	185	239	421	418	445	354	257
CD4 %	2	3	-	-	-	5	5
CD4 absolute (cell/ µL)	20	56	-	-	-	53	98

Table 1. Haematologic and CD4 counts from initially referred to follow up after treatment completed.

The patient had been diagnosed with HIV since 2014 and treated with antiretroviral (ARV) therapy. The patient's systemic conditions were monitored by hematological examinations (Table 1). CD4 counts when the patient was referred were 20 cell/µL. The patient also had anemia that caused delayed healing of the oral ulcers. The patient was then referred back to HIV / AIDS Clinic in CMH for management of anemia.

Before the patient had oral ulcers, he had received ARV in combination of lamivudine / zidovudine and lopinavir / ritonavir and still consumed the medications during treatments of his oral lesions. Anemia was suspected due to the adverse effects of lamivudine / zidovudine.

Lamivudine / zidovudine was discontinued and subsequently replaced with the combination of emtricitabine / tenofovir disoproxil fumarate.

The patient also received blood transfusion because his hemoglobin (Hb) counts had fallen into 7.4 g/dl. In this condition, we suspected his anemic condition was not only because of adverse effects from previously used ARV, but also because of deficiency of nutrition intake that caused malnutrition and led to worsen of anemia.

Necrotizing ulcer on the uvula extended to soft palate caused difficulties for the patient to eat, drink, and swallow and eventually led to inadequate nutrient intake. The patient also referred to Ear, Nose and Throat (ENT) Clinic for management of dysphagia and throat swab to examine bacteria resistency. Throat swab examination revealed two isolates of *Pseudomonas aeruginosa* and *Klebsiella pneumonia*. According to the results of bacteria resistency test, the patient was prescribed systemic antibiotics of 500 mg ciprofloxacin twice a day for two weeks.

The patient was suggested to consume diets contain high of calories and proteins. Oral lesions resolve significantly after nutritions intake were optimal and systemic conditions improved (Figure 2).

Discussion

Ulcerative lesions in patients with HIV/AIDS may be associated with recurrent aphthous stomatitis (RAS), herpes simplex (HSV), cytomegalo virus (CMV), varicella zoster (VZV), dan necrotizing ulcerative stomatitis (NUS).[6] In the present case, the patient experienced NUS and RAS. NUS can develop as a progression of NUG/NUP or as an entirely different disease.[4] In the case reported here, NUS was not associated with NUG or NUP, because we did not find any of the necrotizing periodontal diseases during clinical examination. NUS is a common ulcerative lesion found in patients with HIV/AIDS. That is probably because the depletion of Langerhans cells in oral mucosa of patients with HIV/AIDS may reduce local immune response on the oral mucosa and increase the susceptibility to develop NUS.[5]

In this case report, NUS occured on the upper labial mucosa, on the dorsal surface of tongue, on the left retromolar pad, and on the uvula extended to soft palate. NUS was diagnosed based on clinical grounds. The lesions were deep, ulcerated, varied shapes, size ranged from 10 – 20 mm, and covered with thick white-yellowish fibrin layer.[7]

CD4 counts when the patient referred was 20 cell/µL which is a severe immunosuppresion according to Centers for Disease Control and Prevention (CDC) classification. CD4 counts is useful to predict the severity of HIV and low CD4 counts may prone to development of oral lesions.[8] The role of T-cells in wound healing is still unknown, however there was an increase counts of CD4 found in hypertropic scar tissue in burn patients that may increase collagen synthesis.[9] Decreased number of CD4 may not affect wound healing, but it can impair neutrophils and monocytes infiltration into the wound.[10] The impairement to neutrophils infiltration might have a role in development of NUS and delayed eliminations of those necrotic tissues.

In this case report, NUS was treated locally and systematically. Initial local treatment for NUS was done by lesion debridement using 3% hydrogen peroxide, 0.2% chlorhexidine, and topical application of metronidazole gel on the lesion. After necrotic tissues were eliminated, doxycycline rinse was administered to facilitate healing and tissue regeneration. Doxycycline was given with considerations for its anti collagenase properties and was expected to accelerate wound healing, however apparently it did not give significant benefits.[11] Doxycycline rinse subsequently was replaced with sucralfate rinse.[12,13] Sucralfate is a coating agent that binds to protein on the base of ulcer. The patient was instructed to rinse with sucralfat before meals to facilitate eating and drinking.[3]

Systemic antibiotics of metronidazole (3 x 500 mg), clindamycin (3 x 300 mg), and ciprofloxacin (2 x 500 mg) was given for two weeks each, respectively. Metronidazole and clindamycin were given empirically but did not work as expected in erradicating infections. The patient was referred to ENT Clinic to do throat swab for bacteria resistance test. Two isolates of

bacteria were found on the oral lesion, consist of *Pseudomonas aeruginosa* and *Klebsiella pneumonia*. *P. aeruginosa* and *K. pneumoniae* are bacterias in the digestive system and normally do not exist in the mouth of an immunocompetent individual. *P. aeruginosa* may cause oral infections such as NUG, NUP, or NUS in immunocompromised patients.[14] Many oral ulcers containing biofilm of *P. aeruginosa* that protects this bacteria from phagocyte activity by polimorfonuclear leukocytes showed delayed healing.[15] We could not find any literature that showed the involvement of *K. pneumonia* in NUS, however this bacteria also may cause necrotizing infections such as in necrotizing fasciitis.[16] According to the results of bacteria sensitivity test, one of the antibiotics that were sensitive for both of the bacteria was ciprofloxacin. With consideration to the results, clindamycin was discontinued and replaced with ciprofloxacin. After two weeks of using ciprofloxacin, the necrotic lesions were erradicated.

The other lesion in this patient wasmajor type RAS that occured with longer duration, more painful, and resolved with scarring.[3] The lesion was diagnosed as RAS according to anamneses that reveals history of recurrent ulcers and clinical findings (round shape and white ulcer base with erythematous edge). RAS occured on the right lateral surface of tongue resolved in eight weeks, on the right posterior of tongue in seven weeks, and the lower labial mucosa in three weeks. RAS was treated simultaneously with NUS because the therapeutic agents indicated for NUS were also the same regiments for RAS.

During treatments for oral lesions, the patient's systemic condition were monitored every month. The patient had anemia with the lowest Hb count was 7.4 g/dl and we suspected that this may be one of the factors responsible for delayed healing of the ulcers. Hb is a molecule of blood cell protein required for oxygen transport into the tissues. In the process of wound healing, there are increasing demands for energy that lead to increase of oxygen demand as well. Anemia decrease oxygenation to injured tissue and subsequently led to insufficient oxygen needed for oral ulcer to heal.[17] Anemia in this patient was suspected due to adverse effects of ARV (lamivudine / zidovudine) and malnutrition. Lamivudine / zidovudine were known to cause anemia by supressing bone marrow, however it remains unclear whether they only disrupt erytrocyte formations or the entire hematopoietic cells.[18,19]

The patient experienced difficulties in eating and completely lost the appetite. Deficiency of nutrition intake caused malnutrition, led to decrease of body weight and anemia. Anemia was treated with blood transfusion and replacing ARV from lamivudine / zidovudine to emtricitabine / tenofovir disoproxil fumarate. However, those treatments were insufficient to improve Hb counts significantly while nutritions intake were still inadequate. The patient was suggested to modify his meal to soft diet, improve intake of high-protein high-calories diet, and was prescribed for multivitamin.

Malnutrition can have profound impacts that may cause delay in wound healing. Nutrients such as carbohydrate, proteins, fats, vitamins and mineral are required in healing process. Glucose is the primary source of fuel to create cellular ATP that provides energy for angiogenesis and establishing new tissues. Protein deficiency may impair capillary formation, fibroblasts proliferation, proteoglycans and collagens synthesis, and wound remodelling. It may also affect the immune system by decreasing leukocytes phagocytosis activity and increasing susceptibility to infection. Fats are required to fulfill energy demand for wound healing and tissue formation. Vitamin A (retinol), C (L-ascorbic acid), and E (tocopherol) also have antioxidant and anti inflammatory effects. Minerals like magnesium, iron, and zinc are important in tissue healing and collagen synthesis.[15]

The use of antibiotics that sensitive for the bacterias found on the oral ulcers had eradicated the necrotic layers on the ulcers. The use of sucralfat also gave benefits that the patient was able to eat more easily so nutrition intake was improved. After the patient was able to eat and maintain his nutrition intake, oral lesions healed significantly within two weeks.

Conclusions

Oral ulcers are common in patients with HIV/AIDS. Lesion management was done with standard protocol indicated for oral ulcers diagnosed in this case. Succesful treatment in this case report was achieved by debridement in

every visit, proper use af antibiotics sensitive to the bacterias involved, correction of anemic state of the patient, and improvement of nutrition intake.

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Declaration of Interest

The authors report no conflict of interest.

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