

## The management of herpes labialis, oral thrush and angular cheilitis in cases of oral diabetes

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### ABSTRACT

**Background:** As reported in several studies, prolonged or uncontrolled cases of diabetes mellitus (DM) may induce a more extreme inflammatory response. Mucosal lesions can be observed in patients who present this systemic condition. **Purpose:** The purpose of this study was to elaborate the management of herpes labialis, oral thrush and angular cheilitis as oral manifestations of diabetes.

**Case:** A 49-year-old male complained of having experienced painful lip ulceration for the preceding seven days. The anamnesis of the patient revealed that, prior to lip ulceration, he had experienced high fever and malaise in addition to frequent urination at night and a tingling sensation in the toes and fingertips on waking. **Case management:** The patient was referred to undergo blood count, fasting blood glucose and oral glucose tolerance tests. The blood test result confirmed the patient to be suffering from DM and anemia. The immunocompromised condition of the patient prompted the occurrence of herpes labialis, oral thrush and angular cheilitis. **Conclusion:** Multidisciplinary treatment for herpes labialis resulting in oral candidiasis in DM patients is indispensable. Concurrent infection with HSV and candidiasis necessitates a more prolonged healing process. Consequently, it is essential to treat the hyperglycemia which induces an immunocompromised state in diabetic patients.

**Keywords:** angular cheilitis; diabetes mellitus; herpes labialis; management; oral thrush

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### INTRODUCTION

Diabetes mellitus (DM) constitutes a chronic disorder induced by the inability of the body to produce insulin or to produce it in adequate quantities. Characterized by a high blood glucose level, DM is classified into two types where the first (type 1) is induced by genetic and autoimmune factors, while the second (type 2) is due to lifestyle.<sup>1</sup> The Basic Health Survey of 2018 revealed an increased prevalence of DM from 6.9% to 8.5% in Indonesia during the preceding five years. This resulted in Indonesia ranking sixth in the world in terms of the occurrence of DM.<sup>2</sup>

Prolonged or uncontrolled DM may cause a stronger inflammatory response as reported in previous studies.<sup>3</sup> Hyperglycemia demonstrates a direct interrelation with the development of inflammatory conditions by enhancing pro-inflammatory cytokine expression such as IL-6, and

TNF- $\alpha$ . DM is also notable as an inflammatory disease in which the production of reactive oxygen species (ROS) is intensified.<sup>3,4</sup> An increase of ROS in the inflammatory stage of the diabetic healing process will lead to inevitable results such as a prolonged healing process in the oral mucosa.<sup>4,5</sup>

Pathological symptoms in the soft tissues, including; a reduction in salivary flow, xerostomia and taste disorders may often be identified in patients suffering from DM. Mucosal lesions resulting from fungal infection (oral candidiasis and angular cheilitis), bacterial infection (gingivitis and periodontitis), viral infection (herpes labialis and herpes zoster) and other lesions (oral lichen planus, lichenoid reaction, recurrent aphthous stomatitis) can also frequently be observed.<sup>6,7</sup>

This case report seeks to elaborate the management of herpes labialis, oral thrush and angular cheilitis as

oral manifestations in diabetic patients. Treatment of the symptoms of oral diabetes requires significant time and a collaborative approach from the internist to refine the blood glucose level. In order to achieve successful results, the two conditions should be controlled and managed concurrently.

## CASE

A 49-year-old male patient presented painful lower lip ulceration the first symptoms of which had appeared seven days previously. Three days prior to lip ulceration, high fever and malaise were indicated by the anamnesis results of the patient who reported pain while eating, speaking and tooth-brushing. This individual had merely self-administered paracetamol and applied honey once a day to reduce the extreme discomfort. A history of consistently experiencing tingling sensations in the toes and fingertips on awakening from sleep were highlighted together with the need to urinate more than three times during the night.

## CASE MANAGEMENT

During the initial consultation (day 1), an extraoral examination revealed painful bilateral palpable submandibular lymph nodes firm in consistency. The lower lip presented symptoms including a painful erythematous crust, erosion and ulceration (Figure 1). Intraoral examination illustrated painless erythematous erosion on the lower lip mucosa. The provisional diagnosis was one of herpes labialis due to the appearance of the lips and coated lesion on the tongue (Figure 2). The drugs prescribed for a period of seven days comprised aloclair to be gargled and applied topically to the lower lip three times a day, two 400 mg caplets of acyclovir to be taken three times a day, one 400 mg caplet of ibuprofen to be taken three times a day and one caplet of neurobion forte to be taken once a day. Excessive urination occurring more than three times at night, a tingling sensation in the toes and fingertips invariably present on

awakening from sleep, together with malaise constituted requisite symptoms to the conducting of a complete blood count and fasting blood glucose and oral glucose tolerance tests at a clinical pathology laboratory.

During the second consultation (day 6), anamnesis revealed that drugs had been regularly consumed and a test was conducted at a clinical pathology laboratory. A complete blood count produced a result of haemoglobine 7.4 g/dL (13-17.5 g/dL), erythrocyte 3.53 million/uL (4.5-6 million/uL), leukocyte 11.000/uL (4700-10500/uL), hematocyte 23.5% (40-50%), trombocytes 815000 (150000-350000/uL), lymphocytes 8.6% (25-40%), neutrophils 80.8% (33-66%), MCV 66.6 fL (80-97 fL), MCH 21.0 pg (27-32 pg), MCHC 31.5 g/dL (32-40 g/dL) and RDW-CV 16.8% (11.5-14.7%). A fasting blood glucose test produced a result of 170 mg/dL (70-110 dL), while an oral glucose tolerance test one of 140 mg/dL (<125 mg/dL). Based on these clinical pathology laboratory test results, the patient was diagnosed with DM and anemia which were subsequently referred to an internist.

Elimination of lower lip pain resulted from anamnesis. However, the patient reported having to frequently scratch his lower lip in order to relieve the irritation experienced. Extraoral examination indicated painless palpable submandibular lymph nodes of a firm consistency. Meanwhile, the lower lip region was diagnosed as suffering from erythematous erosion, drying crust and itchiness (Figure 3), although the tongue was no longer coated (Figure 4). Recommended therapies comprised aloclair to be applied three times a day, two 400 mg caplets of acyclovir three times a day, one capsule of sangobion once a day and one 10 mg cetirizine tablet per day. All the drugs mentioned above were prescribed for a period of seven days.

During the third consultation (day 13) with the internist, the patient was prescribed one 500mg metformin tablet to be taken daily for 30 days. The anamnesis result confirmed the elimination of lip pain and itchiness, although soreness and a burning sensation on the dorsal of the tongue was reported by the patient. Extraoral examination demonstrated normal submandibular lymph nodes. Although no erosion of the



**Figure 1.** Painful, itchy, erythematous ulceration, erosion and crust on the lower lip.



**Figure 2.** Presentation of a painless, scrapable, brownish white plaque lesion on the tongue.

lips was observed, painful white erosion and fissures were present on the lateral commissures (Figure 5). Intraoral examination confirmed the presence of a painful, burning, scrapable, white yellowish plaque lesion on the tongue (Figure 6). Herpes labialis therapy was terminated and the patient was subsequently diagnosed with oral thrush and angular cheilitis, the prescribed drugs for which consisted

of 1 mL nystatin oral suspension applied three times a day and one capsule of sangobion once a day. All drugs were prescribed for a period of seven days and the patient was instructed to clear plaque from the surface of the tongue and the commissures of the lips prior to the application of nystatin. The patient was not allowed to eat, drink or gargle for 30 minutes after application.



**Figure 3.** Presentation of itchy erythematous ulceration and drying crust on the lower lip.



**Figure 4.** Normal condition of the tongue with no presentation of coated tongue.



**Figure 5.** Painful white erosions and fissures at the commissures of the mouth. Lips exhibiting the absence of erosive lesion.



**Figure 6.** Tongue presenting a painful, scrapable, burning, yellowish white plaque lesion.



**Figure 7.** Lower lip presenting itchy and painful erythematous erosion, both lateral commissures of the mouth and tongue exhibiting normal condition.



**Figure 8.** Normal presentation of lower lip devoid of erosion, pain or itchiness.



During the fourth consultation (day 23), no pain or burning sensation was reported during the most recent anamnesis. However, the patient complained of itchy and painful ulceration on his lower lip, despite the medication regime prescribed by the doctor having been fully adhered to. Extraoral examination confirmed both normal and painless bilateral commissures of the mouth combined with itchy painful erythematous erosion on the lower lip and mucosa. Intraoral examination confirmed a normal tongue devoid of plaque (Figure 7). The patient was diagnosed with herpes labialis, prescribed drugs including two caplets containing 400mg of acyclovir three times a day, one 10mg tablet of cetirizine once a day and instructed to gargle with aloclair three times a day. All drugs were prescribed for a period of seven days.

During the fifth consultation (day 30), anamnesis confirmed that the patient had observed a regular intake of drugs. Extraoral examination of the lower lip confirmed it to be normal without the presence of erosion, pain or itchiness (Figure 8) and the patient was declared to have been healed.

## DISCUSSION

The patient complained of lower lip ulceration and fever which had commenced three days prior to the appearance of the lesion and was subsequently diagnosed as herpes labialis. A painless scrapable yellowish white plaque on the surface of the tongue had concurrently developed resulting in a diagnosis of coated tongue. This constituted a differential diagnosis of oral thrush since no pain and burning sensation accompanied the coated tongue lesion.<sup>8</sup> In this case, a history of a burning sensation and pain reported by the patient, allied with clinical examination results indicating the presence of white plaque which could be scraped off leaving a reddish area, oral thrush was recorded.

Another patient experienced malaise, a tingling sensation in the toes and fingertips accompanied by frequent urination at night leading to a diagnosis of DM and was referred for a complete blood count test, fasting blood glucose test and oral glucose tolerance test at a clinical pathology laboratory.

The results of a clinical pathology laboratory test confirmed the patient to be suffering from DM and he was subsequently prescribed with metformin. This drug is categorized within the guanidine group which may enhance sensitivity to insulin, inhibit glucose formation in the liver, and reduce low density lipoprotein (LDL) and the level of triglyceride. Its ability to suppress appetite renders it the first drug of choice. Metformin is commonly prescribed in cases of an initial diagnosis of DM.<sup>1,9</sup>

In the case described here, the patient was suffering from both DM and anemia. These conditions are induced by an increase in proinflammatory cytokine expression among

diabetic patients with anemia compared to those suffering only from DM. Anemic individuals are characterized by increased interleukin-6 (IL-6) production and B cell activity which enhances the link between IL-6 and anti-erythropoietic action. Furthermore, patients with DM and anemia demonstrate high levels of C-reactive protein and ultra-sensible ferritin. In contrast, low iron levels are present in those patients where the increase in ferritin is interconnected with the chronic inflammatory process evident in cases of diabetes.<sup>3,9</sup>

Anemia can cause degradation of cellular immunity, reduced bactericidal activity in polymorphonuclear leukocytes, inadequate antibody response and abnormality in epithelial tissues. This condition can reduce the activity of mitochondrial enzymes due to oxygen and nutrition transport being disrupted. It leads to the inhibition of epithelial cell differentiation and growth. The terminal differentiation process in the epithelial cells of the stratum corneum will be impeded resulting in loss of normal keratinization and atrophy. As a result, the oral mucosa tissue will become thinner and easily ulcerated.<sup>10</sup> In anticipation of the development of anemia, the patient was prescribed with Sangobion, a supplement containing 250 mg ferrous (Fe) gluconate, 0.2 mg mangan sulfate, 0.2 mg copper sulfate, 50 mg vitamin C, 1 mg folic acid, and vitamin B12. Fe gluconate is an iron compound crucial to the energy metabolism process. At the same time, the presence of mangan sulfate and copper sulfate as iron transporting compounds is essential, while vitamin C assists the absorption of iron by the intestines to be subsequently transported by blood serum around the circulatory system. Moreover, vitamin B12 and folic acid act as pivotal cofactors in blood cell deoxyribonucleic acid (DNA) synthesis.<sup>11</sup>

The patient initially complained of lower lip ulceration accompanied by fever which was diagnosed as herpes labialis. He was prescribed acyclovir which can prevent virus replication through three mechanisms: phosphorylation of acyclovir to phosphate derivatives within the cell via viral thymidine kinase, inhibition of DNA polymerase by acyclovir activation, and termination of chain elongation by eliminating cyclic sugar from acyclovir triphosphate.<sup>12</sup> Acceleration of the wound healing process and prevention of secondary infection in herpes labialis were managed by prescribing topical aloclair to be gargled and topical application to the lower lip region. Due to its aloe vera extract content, aloclair can accelerate wound healing through stimulation of and increase in anti-inflammatory cell activity which enhances the reepithelization process.<sup>13</sup>

Acyclovir intake was consistently managed by the patient during a period of two weeks. An antiviral drug was administered to resolve the herpes infection resulting from the immunocompromised condition of the patient who was eventually declared to have been cured of herpes labialis. Nevertheless, this positive development was followed by the occurrence of oral thrush on the surface of the tongue

and angular cheilitis on the lateral vermilion border of the lips. In order to manage these conditions, the patient was subsequently prescribed nystatin oral suspension.

Considered the most common therapy in dentistry, the application of topical nystatin plays an essential role in oral and systemic candidiasis prophylaxis among immunocompromised patients. This drug is primarily recommended for the treatment of oral candidiasis because of its high efficacy, low cost and less serious side effects. The colony of candida species adheres to the oral mucosa via epithelial cells, germ tube formation and the hydrophobicity of cell surfaces. Absorption of topical drugs by the oral mucosa is crucial to the elimination of hyphae. Nystatin, one of the topical drugs used in candidiasis treatment, can be prescribed for between one and six weeks.<sup>14,15</sup>

Following administration of nystatin during a period of ten days, the patient was cured of oral thrush and angular cheilitis. However, the recurrence of herpes labialis induced extreme irritation in the lower lip which was managed by the patient immediately being prescribed a combination of cetirizine and acyclovir. Several studies posit that viral infection may induce exacerbation of acute urticaria as indicted by the appearance of a herpes simplex lesion. The chronic urticaria presented by the patient was instigated through recurrent herpes simplex infection.<sup>16</sup>

Reversible dysfunction of T lymphocyte can occur as a result of a hyperglycemic condition. Several studies have identified the seropositivity of the herpes simplex virus (HSV) as a risk factor for diabetes due to chronic inflammation or immune activation. Hyperglycemia can potentially induce T-cell inhibition against HSV, thereby enabling viral escape from immune control. Viruses are exclusively localized in the neuron. The paramount importance of herpes virus latency located in the ganglion is related to reactivation and clinical manifestations. DNA will be maintained in a heterochromatin state rendering gene expression silenced. Despite this, latency associated transcripts (LATs) are produced which increase the efficiency of latency establishment and reactivation because of their ability to promote both neuronal apoptosis and lytic gene expression inhibition. LATs may impede superinfection by other strains of the same herpes virus or by other herpes viruses.<sup>17,18</sup>

This case presents a recurrent infection of herpes labialis coinciding with oral thrush induced by the presence of candida biofilm which may act as a persistent reservoir not only for fungal cells, but also infectious viruses. These viruses might be preserved and protected within the biofilm. Representing an additional health risk factor, Candida biofilm is reported as entrapping viral particles, thereby protecting the virus from conventional antiviral treatment. Anti-candida effector function was inhibited by HSV infection. It was protected by *Candida* biofilm that encompassed HSV inactivation resulting from acyclovir treatment.<sup>18,19</sup> It can be concluded from the foregoing discussion that multidisciplinary management of herpes labialis co-occurring with oral candidiasis in DM patients is

indispensable. Concurrent infection of HSV and candidiasis in diabetic individuals will require a more protracted wound healing process. Therefore, stabilizing the hyperglycemic level which induces an immunocompromised condition in DM patients is pivotal.

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