

Management of acute pseudomembranous candidiasis with angular cheilitis in diabetic patient

Saka Winias¹, Priyo Hadi², Shakira Garini Prasetya³, Angelica Joyce Yokhebeth Sinaga⁴

^{1,2}Department of Oral Medicine, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia

^{3,4}Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia

ARTICLE INFO

Article history:

Received Jun 5, 2025

Revised Jun 10, 2025

Accepted Jun 18, 2025

Keywords:

Angular Cheilitis

Diabetes Mellitus

Oral Candidiasis

ABSTRACT

Diabetes mellitus (DM) is being increasingly documented even in developing countries. *C. albicans* infection is frequently found in diabetic patients. Diabetics and the 'poorly controlled patients are considered as immunocompromised, though it is not easy to characterise the immunologic deficiencies clearly. Since infection is mostly preceded by colonization. The risk factors that increased the risk of *Candida* carriage in diabetic patients with DM were a higher age and a higher HbA1c level (poor regulation of DM). *The purpose* of this study is to report the management of Acute Pseudomembranous Candidiasis with Angular Cheilitis in diabetic patients. A 51-year-old lady complained of dryness and pain in the corner of the mouth, recurrence within 2 years after she had been diagnosed diabetic, which had worsened in the last two weeks. The corner of the mouth showed a fissure with reddish area. Oral mucosa showed multiple yellow-white pseudomembranous. The patient was prescribed antiseptic mouthwash and an antifungal oral suspension, which should be applied to the lesion 3-4 times daily. Ketoconazole, as a systemic antifungal, was given 200 mg/day. The laboratory test showed an increase in leucocytes cells count, monocytes, and ESR. A direct mycological examination and culture observation *Candida albicans* was performed. Referral to an internist to manage her systemic condition. This study concludes that immune dysfunctions in diabetics is contribute to the pathogenesis of Oral Candidiasis and Angular Cheilitis, which may lead to optimum treatment.

This is an open access article under the [CC BY-NC](https://creativecommons.org/licenses/by-nc/4.0/) license.



Corresponding Author:

Saka Winias,

Department of Oral Medicine,

Faculty of Dental Medicine,

Universitas Airlangga,

Jl. Prof. Dr. Moestopo No. 47 Surabaya, East Java, 60132, Indonesia

Email: saka.winias@fkg.unair.ac.id

INTRODUCTION

Oral Candidiasis is an opportunistic infection of the oral cavity caused by excessive growth of *Candida spp* (Scully C, 2013). *Candida* species are commensal organisms commonly found in 80% of the mucosa of the oral cavity of healthy people (Dongari-bagtzoglou, 2005). Fungal opportunistic

infections occur mainly when the host's normal defense is decreased (*immunocompromised*) (Hashim & Mascellino, 2014).

Prevalence of Oral Candidiasis in Diabetes Mellitus (DM) patient was 13.7% to 64% and many cases were asymptomatic (Martinez et al., 2013). *Oral Candidiasis* is caused by an excessive growth or oral infection by a yeast-like fungus, *Candida* (Akpan & Morgan, 2002). *Yeast Candida albicans* is the most common pathogenic opportunistic fungus in humans (Hashim & Mascellino, 2014). Currently, more than 150 species of *Candida* are known. Although the frequency of isolation varies within 20-30 years, it has been determined that 95% of infections, pathogens include *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, dan *C. Krusei* (Yapar, 2014). *Candida* colonization in different areas including skin, the gastrointestinal tract and the surface of the vaginal mucosa are very common in healthy people. However, in responding to host defense environment changes, *Candida* may change from benign commensal to disease-causing pathogens.

The change of *Candida* from a harmless commensal into a pathogenic state can occur after the oral environment changes into an environment that supports the growth of *Candida* (Williams & Lewis, 2011). There is a relationship between *Oral Candidiasis* and the influence of local and systemic predisposing factors. Local predisposing factors may support the growth of *yeast* or affect the oral mucosal immune response. Systemic predisposing factors are often associated with immune status and individual endocrine status (Glick & Feagan Chair, 2015).

C. albicans normally resides in the oral cavity in the form of *yeast-like (blastophores)* cells that sometimes elongate to form *germ tubes* (pseudohifa). In the inactive state, the *yeast* is in a predominant form, but if pathological activity occurs the hyphae form is much clearer. This pseudohifa can be seen, not only superficial in the oral cavity, but also the penetration of the epithelium as far as the stratum granulosum (Field et al., 2003). In *immunocompromised* patient, *Candida* infections may affect the epithelial mucosa either the oral cavity, the gastrointestinal tract, the genital tract and infection in other organs.

The virulence of *Candida albicans* to the tissues resulting into an infection is strongly influenced by several factors. First, adhesion or attachment, the attachment of *Candida albicans* to mucosa is a very complicated process and complex, this adhesion uses several types of morphogenetic changes in the cell surface and proteins that bind to the mammalian cell's extracellular matrix, such as *fibronectin*, *laminin*, *fibrinogen* and collagen type I and IV. Factors that add *C. albicans* attachment includes surface hydrophobicity of fungal cells, pH, temperature, *microenvironment* and host immunity. Second, the transition morphogenesis between *yeast* cells and filament growth. *Candida* has the ability to grow in several stages of morphogenesis including *budding yeast* cells, pseudohifa (long chains of yeast cells) and also filaments of hyphae (Marsh & Martin, 2009). Third, the formation of biofilm which is a sequential process, including the *yeast* cell attachment to the substrate, *yeast* cell proliferation, hypha cell formation and accumulation of extracellular matrix material, and finally *yeast* cell dispersion of the biofilm complex. Hsp90's main *heat shock* protein is a key to control the dispersion in *C. albicans* biofilm, and is also necessary for antifungal drug resistance. Fourth, hydrolytic enzymes which are *Aspartyl proteinase* (SAP) and *phospholipases* (PL). SAPs are associated with *phenotypic switching* and enzyme *phospholipases* associated with invasion of host tissues that hydrolyze ester bonds of *glycophospholipids*. Focusing on *Candida* pathogenesis through biofilm formation and proteolytic enzyme activity offers practical therapeutic insights, as these mechanisms contribute directly to antifungal resistance and tissue invasion. Compared to immunological approaches, which highlight host susceptibility, targeting these microbial factors allows clinicians to choose antifungal agents and adjunct therapies more effectively to disrupt infection persistence and enhance treatment outcomes.

Acute Pseudomembranous Candidiasis (APC) is an acute infection, but may persist for several months or even years in patients taking topical corticosteroids or aerosols, in HIV-infected individuals, and in other *immunocompromised* patients. Symptoms of APC are burning sensation, changes in taste sensation, and difficulty swallowing. APC is characterized by white

pseudomembrane on the surface of the oral mucosa. These pseudomembranes can form layers that resemble milk curds. This pseudomembrane can be scraped and leaves the base of erythematous (Scully, 2013).

Angular Cheilitis is a typical inflammation seen in both commissures (corners) of the lips. This condition is often associated with other forms of Oral *Candididasis* (Marsh & Martin, 2009). These lesions are often coinfecting between *Candida albicans* and *Staphylococcus aureus*. Vitamin B12 deficiency, iron deficiency, and loss of vertical dimension have been associated with this disorder. Dry skin can trigger the development of fissure on the commissure, followed by invasion by microorganisms. This condition is usually persistent or recurrent, especially in patients with *immunocompromised* (Ghom, 2014; Scully, 2013). This case report contributes to bridging the clinical knowledge gap by highlighting the underrecognized co-infection of *Candida albicans* and *Staphylococcus aureus* in the oral cavity of a patient with type 2 diabetes mellitus (T2DM). While both pathogens are individually common in diabetic patients, their synergistic interaction and biofilm formation can exacerbate mucosal damage and complicate treatment outcomes. Some reports have written the process of occurrence of oral candidiasis or *Angular Cheilitis* in patients with DM separately, thus, please be noted the process of the occurrence of *Oral Candididasis* and *Angular Cheilitis* in patients with DM in order to provide proper management. Therefore this case report will discuss the management of APC with *Angular Cheilitis* in DM patients.

RESEARCH METHOD

First Visit, day 1

Female patient 51 years old came to Dental Hospital of Universitas Airlangga with the main complaint of right and left lip angle wounded and felt sore. The complaint arose since the patient did not use dentures about 2 years ago. The wound often appeared, and sometimes healed itself without any treatment. Starting from the lips felt tight, sore and bleed when she was waking up 22 - 3 days later the wound was widened. In addition, there were white patches on the tongue since 3 days ago. The white patches sometimes disappeared when she was eating and the next day it reappeared. Her tongue felt sore when she was eating spicy food. The patient has a medical history of DM in the last 5 years ago and she went to check her fasting blood glucose 230 mg/dL a month. The patients consumed Glibenclamide and Metformin drugs regularly. Extra oral clinical examination, in the corners of the mouth there were found multiple fissures, 2 mm, red color, clear boundaries, regular edges, coarse textures, bleed easily and painful. On intra oral examination of the upper labial mucosa, lower labial, left cheek, right cheek, maxillary gingiva, mandibular gingiva, tongue, and palate were found *pseudomembrane* surrounded by reddish color, multiple, 2-3 mm, white, clear boundaries, regular edges, smooth surface, no pain.

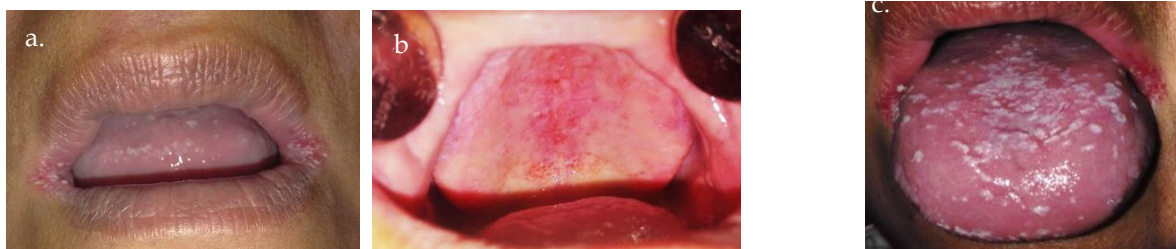


Figure 1. a. Fissure at the corners of the mouth b. Erythematous with pseudomembrane of the palatal mucosa, c. Pseudomembrane surrounded by a reddish area on the dorsum of the tongue

Second visit, day 7

On this visit the patient has been taking medication regularly. The pain in the corner of the lips started to decrease but there were still cuts, white patches in the oral cavity began to disappear

and decreasing, but it often appeared much especially in the morning. The patient consumed DM drugs regularly. On extra oral examination, the corners of the lips were found fissure, multiple, 2 mm, red, clear boundaries, regular edges, pain, rough texture. From intra oral examination of the lower labial mucosa, the buccal mucosa of the dextra and the sinistra, maxillary and mandibular gingivae, in tongue and palate were found pseudomembrane, multiple, 2-3 mm, white, surrounded by reddish areas, diffuse borders, irregular edges, soft textures, not painful from unstimulated saliva 0,1 ml/menit. From complete blood test, leukocyte results obtained 14.9 from the normal values of 3,6-11 $10^3/\mu\text{l}$, Monocytes 9 from the normal values of 3-6%, the blood precipitate rate 59 from the normal value of 1-30 mm, and the KOH examination - the spore fungus and positive hyphae.

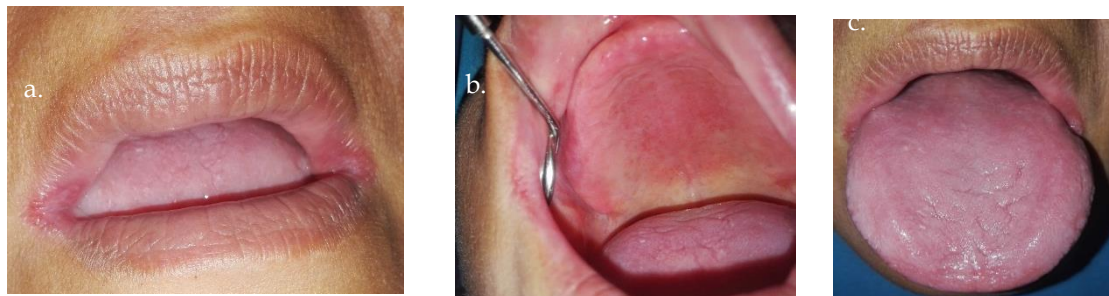


Figure 2. a. Fissure at the corners of the mouth, b. reddish erosion of the palatal mucosa, c. reddish erosion, accompanied by spreading pseudomembrane on the dorsum of the tongue

The patient's clinical diagnosis was *Acute Erythematous Candidiasis* with *Angular Cheilitis* in the healing process. The patient was prescribed with Nystatine oral soup. 100.000 IU/ml fl No.1 4 times a day. At the patient education the patient was instructed to use the medicine by rubbing it on the corner of the lips and dripping on the tongue for 3 drops and then flattening the entire mouth cavity and then vomiting (not swallowed), not eating/drinking for 30 minutes after taking the drug and increasing oral hygiene. The patient was referred to Clinical Pathology laboratory for fasting blood glucose examination, 2 hours PP, HbA1c and liver function (SGOT, SGPP) and kidney function (BUN, creatinine).

Third visit, day 21

The patient said the corners of the lips were not painful, white patches in the mouth disappeared in the morning, but sometimes it reappeared. And the medicine was still left for 4 days ahead. Medication is used regularly. The patient has checked herself to doctor of internal medicine and given 3 mg daily glimepiride drug which should be drunk in the morning.

On extra oral examination of the corner of the lips there was a reddish macular bounded diffuse and not painful. On Intraoral examination is found erythema, multiple pseudomembrane with diffuse boundary, irregular edge did not hurt on the palate.

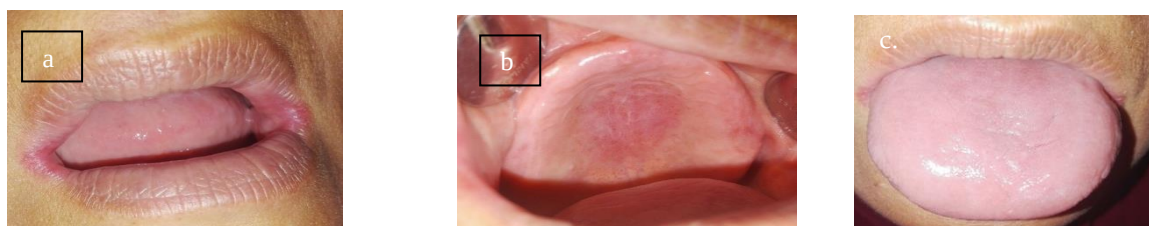


Figure 3. a. Fissure at the corners of the mouth b. Erythematous with pseudomembrane of the palatal mucosa, c. Normal mucosa dorsum of the tongue

The patient's clinical diagnosis was the healing process of *Acute Pseudomembranous Candidiasis*. From unstimulated saliva examination was obtained 0,2 ml/minute. The treatment given to the patient was to continue the nystatine drug, and ketoconazole 200 mg once daily for 10 days. At the patient education, the patient was instructed to maintain oral hygiene, taking prescribed medications regularly, taking DM medication regularly, and drink water 2 liters/day.

Fourth visit, day 43

On this visit the patient said her mouth cavity was healed and no more complaints. The patient has not used the mouthwash and have been drunk until every day once in the morning. The patient said that since this treatment was done onto her the wounds in the corner of the mouth and white patches in the mouth cavity never appeared again. On extra oral examination of the corners of the lips there was a diffuse macular. On intra oral lesions were not found. From unstimulated saliva examination was obtained 0.2 ml/min.

The patient's clinical diagnosis was that the *Acute Pseudomembranous Candidiasis* has healed. The drug was stopped and the patient was asked for check up if there was a complaint. At the patient education, the patient was required to increase oral hygiene, routine check up to a doctor of internal medicine to deal with her DM. The patient was advised to make dentures. Treatment complete. During the 43-day follow-up period, clinical improvement was assessed based on professional clinical judgment, including observable reduction in lesion size, resolution of erythema, and improvement in patient-reported symptoms such as discomfort.

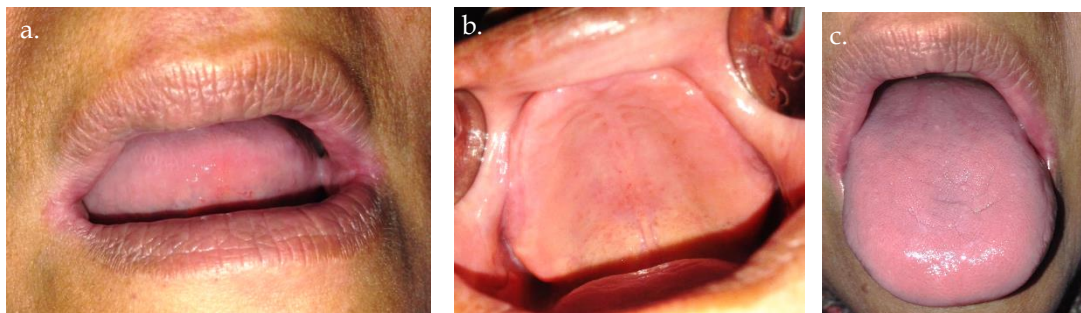


Figure 4. a. Normal mucosa at the corners of the mouth b. Normal mucosa at the palatal mucosa, c. Normal mucosa dorsum of the tongue

RESULTS AND DISCUSSIONS

Oral Candidiasis and other opportunistic fungal infections are some of the early signs of uncontrolled, but non-specific, DM. Carriage of *Candida* species and *Candida* growth density in the oral cavity is often claimed to increase in DM patient who contribute to the acquisition. *Oral Candididasis* in this patient (Adel et al., 2016).

Candida is known as commensal oral cavity organism. But in hyperglycemic states environmental changes in the oral cavity such as body immunity dysfunction, increased saliva glucose and the presence of acid production, thus supporting the transition of microorganisms from harmless commensants to pathogens (Deepa et al., 2014).

Normal glucose levels in saliva have no significant effect on oral hygiene or support the growth of microorganisms. However, high salivary glucose levels increase *Candida*'s attachment to buccal epithelial cells (Balan et al., 2015). Saliva glucose forms a reversible chemical product of glycosylation with proteins in tissues during hyperglycemic episode, leading to the accumulation of glycosylated products in buccal epithelial cells, which in turn can increase the number of receptors for *Candida* growth. (Sashikumar & Kannan, 2010) Glucose also serves as a nutrient for *Candida* microorganisms and decreases the phagocyte's ability of neutrophils (Geerlings & Hoepelman, 1999).

Host defense factors that can cause Oral Candidiasis infection in DM are the possibility of damage to neutrophil activity, especially in the presence of glucose.(de Souza Bastos et al., 2011) Phagocytosis, intracellular destruction, bactericidal activity and chemotaxis decreased especially in uncontrolled DM patient can make DM patients more susceptible to infection.(Lecube et al., 2011)

The patient has been taking metformin drugs for 5 years, it is known that the use of long-term metformin can stimulate decreased levels of B12 in the body. The most widely accepted mechanisms are metformin antagonists of calcium cation and interrupt calcium-dependent IF-vitamin B12 when binding to kubilin receptor ileum. Kubilin is a glycosylated protein expressed on the apical side of the enterocytes ileum. The IF-vitamin B12 complex binds to kubilin. This interaction requires calcium cations which can strengthen the function of complex affinity to the receptor.(Aroda et al., 2016; Hidalgo et al., 2010) Etiology of Multifactorial *Angular Cheilitis*. Vitamin B12 deficiency, iron deficiency, and loss of vertical dimensions have been linked to this disorder.(Shahzad et al., 2014) Dry skin may support the development of fissures on the commissures, followed by invasion by microorganisms. The microorganisms that cause *Angular Cheilitis* are mostly caused by the amount of *Candida albicans* and *Staphylococcus aureus* bacteria.(Al Maweri et al., 2013) The increase of *Candida* population is not only caused by DM condition, but also supported by local factors. *Angular Cheilitis* occurs in older people with a low vertical dimension. If the height of the vertical dimension is reduced due to tooth loss or the patient using inadequate denture will cause the corners of the mouth to fall and form folds at the corners of the mouth. The folds in the corners of the mouth will cause the stacking of saliva, thus creating an atmosphere suitable for the growth of infectious agent microorganisms. (Fajriani, 2017; Tucker, 2010) In patients with DM also increases the incidence of *Angular Cheilitis* lesions, as host defenses decrease from both low salivary production and the ability of body defense cells to decrease.(Belazi et al., 2005)

Candida fungus infection that occurs in the AC is not separated by the *Oral Candidiasis* (OC) in the oral mucosa. The relationship between these two occurs because AC which is also caused by *Staphylococcus aureus* bacterial infection of the skin, has a close relationship with *Candida albicans* fungi so that both can cause co-infection which eventually leads to AC. (de Souza Bastos et al., 2011) This is because the *Candida* has a special receptor that is suitable on its cell wall with *Staphylococcus aureus* bacteria which is *Adhesin Agglutinin-like Sequence Protein 3* (AIS3P) receptor. AIS3P is one of the *hyphaespecific* genes. In people with DM, the body defense systems decreased will affect the function and amount of macrophages and neutrophils, so that phagocytosis processes that can eliminate fungal and bacterial infections are inhibited. As a result, opportunistic infections of the fungus *Candida albicans* and *Staphylococcus aureus* bacteria which is the cause of AC, can be more easily occurred.(Peters et al., 2012)

The prevalence of hyposalivation and xerostomia in DM is present in uncontrolled type 2 DM patients. Salivary flow rates of the parotid glands are lower than those of controlled and normal patients.(Aitken-Saavedra et al., 2015) In a long term this condition will increase the chance of soft tissues in the oral cavity to be irritated easily, resulting in inflammation and pain. People with DM with xerostomia are more likely to have infections in the oral cavity. Because DM patients experience chronic complications such as neuropathy, micro-vascular damage and endothelial dysfunction which lead to the decreasing of microcirculation and the reducing production and salivary composition.(Al Maweri et al., 2013) Persistent hyperglycemia will also lead to changes in micro vascularization of the blood vessels, especially changes in the basement membrane in the salivary glands. This increase in the changes occur from the transport of glucose in the salivary gland duct cells, therefore triggers an increase in glucose production in saliva. Glucose is a small molecule that easily diffuses through a semipermeable cell membrane. Hence, large amounts of glucose can be found in saliva, when there is an increase in blood glucose in DM patients. Several studies on the condition of DM with elevated salivary glucose levels affect colonization of *C.albicans*. The growth of *C. albicans* is increased in DM patients due to high salivary glucose levels.

This statement is supported by the results of *in vitro* research conducted by Balan et al. (2015) in the saliva supplied by glucose may increase colonization of *C.albicans*.(Balan et al., 2015) In complete blood tests there was an increase in leukocyte of 14.9 from the normal values of 3.6 to 11 103/µl, Monocytes 9 from normal values of 3-6% and the rate of sedimentation of blood 59 from the normal value of 1-30 mm. An increase in leukocytes above 11,000 is a leukocytosis which is an indicator that there is infection or inflammation. Monocyte cells are one of the most active phagocytes, located in the peripheral blood. If blood tests show the increase of monocytes or monocytosis it indicates the presence of infection from microorganisms. The high and low values in the Erythrocyte Sedimentation Rate (ESR) are strongly influenced by the patient's body condition, physical condition, physiology, age etc., but the ESR increases as indicates acute inflammation/inflammation, acute and chronic infections or tissue damage.

The examination of oral lesions, the oral samples can be obtained by swabs. Microscopic examination directly added 10% KOH obtained positive spores and hyphae. The hyphae found from *Candida* indicates that the candida is pathogenic, the hyphae formation required by *Candida* to damage and invaded the tissue, and increase cell resistance to phagocytosis by *host* immune cells. Then, to detect the type of *Candida*, the culture is done on *Sabouraud Dextrose Agar* (SDA) and obtained *Candida albicans* type.

The principles of treatment on *Oral Candidiasis* are the identification and correction of predisposing factors and the provision of antifungal drugs to suppress the fungus. Considerations to select the antifungal therapy including patient's medical history, symptoms of *candida* infection, infection severity and possible side effects. The treatment in this patient is the administration of antifungal drugs group of the polien namely Nystatin oral drop. The polien group works by direct bonding with ergosterol on the cell membrane of the fungus. This bond triggers a cytoplasmic leak that alters the membrane permeability that ultimately leads to fungal cell necrosis. Nystatin is effective for the treatment of oral candidiasis in this patient. *Candida albicans* responds favorably to the administration of the polystyrene drug group which is Nystatin.(Bremenkamp et al., 2011)

The patient was prescribed with 0.2% Chlorhexidine gluconate mouthwash. This mouthwash has *chlorhexidine* molecules which has a positive charge (cation) and most of the fungus molecular charge is negative (anion). This causes a strong attachment of chlorhexidine to the mushroom membrane. *Chlorhexidine* will cause changes in the permeability of the mushroom membrane resulting in the release of cell cytoplasm and low molecular weight cell components from within the cell through the cell membrane causing death to fungal. *Chlorhexidine gluconate* 0.2% has a high degree of antifungal activity when binding to the fungal cell membrane component causes a change in the integrity of the fungal cell wall consisting of lipids. The change in the integrity of the cell wall causes the function of the fungal cell membrane to be lost. The chlorophenol ring in the structure of the 0.2% chlorhexidine gluconate formula is lipophilic by seeping into the cell wall so that it is readily accepted by the fungal cell membrane composed of lipids and causing a leakage of the intracellular component (Ryalat et al., 2011)(Cheung et al., 2012).

This patient was considered to use systemic antifungal because there was a history of DM of the patient causing the patient's condition to be immunocompromised, thus topical antifungal administration should be assisted with systemic administration which is ketoconazole from the azole group. The azole group is one of the most widely used antifungals in therapy. The azole group works by inhibiting the 14- α -demethylase lanosterole enzyme which is responsible for converting lanosterol to ergosterol. The loss of ergosterol which is an important component in the permeability of cell membranes will cause lysis and fungus death.(Patil et al., 2015). The decision to use a combination therapy involving topical nystatin, systemic ketoconazole, and chlorhexidine gluconate mouthwash was based on evidence-based practice that integrates clinical judgment, patient-specific factors, and literature support. Topical nystatin served as the first-line antifungal due to its effectiveness in localized oral candidiasis, while systemic ketoconazole was added to

address the more extensive infection and the risk of tissue invasion, especially in the context of immunocompromise and co-infection with *Staphylococcus aureus*. Chlorhexidine gluconate was used adjunctively to reduce overall microbial load and promote mucosal healing. This multi-modal approach aimed to enhance therapeutic efficacy in a complex clinical scenario.

CONCLUSION

Acute Pseudomembranous Candidiasis and *Angular Cheilitis* can occur in patients with Diabetes Mellitus. It needs careful diagnosis to ensure that patient gets proper management. Long-term therapeutic success in managing oral infections in patients with T2DM relies not only on pharmacological treatment but also on patient education. Emphasis on maintaining proper oral hygiene, adherence to antifungal therapy, and strict glycemic control is essential to prevent recurrence and support mucosal healing. In this case, the patient received targeted education as part of the overall management plan, aligning with evidence-based recommendations for chronic disease care. This case suggests the potential benefit of multidisciplinary approaches, future research could evaluate coordinated care models involving dental and medical professionals for complex infections in systemic patients.

References

- Adel, E., Khadijed, S., & Mohammad, M. (2016). *Oral cavity candidiasis as a complication of fungal diseases in diabetic patients in south-East of Iran*. 14(4), 1134-1138.
- Aitken-Saavedra, J., Rojas-Alcayaga, G., Maturana-Ramirez, A., Escobar-Alvarez, A., Cortes-Coloma, A., Reyes-Rojas, M., Viera -Sapiain, V., Villablanca-Martinez, C., & Morales-Bozo, I. (2015). Salivary gland dysfunction markers in type 2 diabetes mellitus patients. *Journal of Clinical and Experimental Dentistry*, 7(4), e501-e505. <https://doi.org/10.4317/jced.52329>
- Akpan & Morgan. (2002). Oral Candidiasis. *Postgraduate Medical Journal*, 78(922), 455-459. <https://doi.org/10.1136/pmj.78.922.455>
- Al Maweri, S. A. A., Ismail, N. M., Ismail, A. R., & Al-Ghashm, A. (2013). Prevalence of oral mucosal lesions in patients with type 2 diabetes attending hospital Universiti Sains Malaysia. *Malaysian Journal of Medical Sciences*, 20(4), 38-45.
- Aroda, V. R., Edelstein, S. L., Goldberg, R. B., Knowler, W. C., Marcovina, S. M., Orchard, T. J., Bray, G. A., Schade, D. S., Temprosa, M. G., White, N. H., & Crandall, J. P. (2016). Long-term Metformin Use and Vitamin B12 Deficiency in the Diabetes Prevention Program Outcomes Study. *The Journal of Clinical Endocrinology & Metabolism*, 101(4), 1754-1761. <https://doi.org/10.1210/jc.2015-3754>
- Balan, P., Castelino, R. L., & Fazil Areekat, B. K. (2015). Candida Carriage Rate and Growth Characteristics of Saliva in Diabetes Mellitus Patients: A Case-Control Study. *J Dent Res Dent Clin Dent Prospect*, 9(4), 274-279. <https://doi.org/10.15171/joddd.2015.048>
- Belazi, M., Velegaki, A., Fleva, A., Gidaraku, I., Papanau, L., Baka, D., Daniilidou, N., & Karamitsos, D. (2005). Candidal overgrowth in diabetic patients: Potential predisposing factors. *Mycoses*, 48(3), 192-196. <https://doi.org/10.1111/j.1439-0507.2005.01124.x>
- Bremenkamp, R. M., Caris, A. R., Jorge, A. O. C., Back-brito, G. N., Mota, A. J., Balducci, I., Brighenti, F. L., & Koga-ito, C. Y. (2011). Prevalence and antifungal resistance profile of *Candida* spp. oral isolates from patients with type 1 and 2 diabetes mellitus. *Archives of Oral Biology*, 56(6), 549-555. <https://doi.org/10.1016/j.archoralbio.2010.11.018>
- Cheung, H. Y., Wong, M. M. K., Cheung, S. H., Liang, L. Y., Lam, Y. W., & Chiu, S. K. (2012). Differential actions of chlorhexidine on the cell wall of *Bacillus subtilis* and *Escherichia coli*. *PLoS ONE*, 7(5). <https://doi.org/10.1371/journal.pone.0036659>
- de Souza Bastos, A., Leite, A. R. P., Spin-Neto, R., Nassar, P. O., Massucato, E. M. S., & Orrico, S. R. P. (2011). Diabetes mellitus and oral mucosa alterations: Prevalence and risk factors. *Diabetes Research and Clinical Practice*, 92(1), 100-105. <https://doi.org/10.1016/j.diabres.2011.01.011>
- Deepa, A. G., Nair, B. J., Sivakumar, T. T., & Joseph, A. P. (2014). *Uncommon opportunistic fungal infections of oral cavity: A review*. 18(2), 235-244. <https://doi.org/10.4103/0973-029X.140765>
- Dongari-bagtzoglou, A. (2005). Innate Defense Mechanism in Oral Candidiasis. In *Fungal Immunology* (pp. 14-34).

- Fajriani, F. (2017). Management of Angular Cheilitis in children. *Journal of Dentomaxillofacial Science*, 2(1), 1. <https://doi.org/10.15562/jdmfs.v2i1.461>
- Field, E. A., Longman, L., & Tyldesley, W. R. (2003). Tyldesley's Oral medicine. In *Oxford medical publications* (pp. xi, 243 p.).
- Geerlings, S. E., & Hoepelman, A. I. (1999). Immune dysfunction in patients with diabetes mellitus (DM). *FEMS Immunol Med Microbiol*, 26, 259-265. <https://doi.org/10.1111/j.1574-695X.1999.tb01397.x>
- Ghom, et al. (2014). *Text book of Oral Medicine* (3rd ed.). JaypeeBrothers Medical Publishers.
- Glick, M., & Feagan Chair, W. (2015). Burket's Oral Medicine. In *People's Medical Publishing House*. <https://doi.org/10.1007/s13398-014-0173-7.2>
- Hashim, I., & Mascellino, M. T. (2014). *Bacterial and Mycotic Infections in Immunocompromised Hosts : Clinical and Microbiological Aspects*.
- Hidalgo, S. F., De Paula, J. M. P., & Valdivieso, I. S. (2010). Metformina y deficiencia de vitamina B12. *Medicina Clínica*, 135(6), 286-287. <https://doi.org/10.1016/j.medcli.2009.04.055>
- Lecube, A., Pachón, G., Petriz, J., Hernández, C., & Simó, R. (2011). Phagocytic activity is impaired in type 2 diabetes mellitus and increases after metabolic improvement. *PLoS ONE*, 6(8), 6-11. <https://doi.org/10.1371/journal.pone.0023366>
- Marsh, P. D., & Martin, M. V. (2009). Oral Microbiology. In *Churchill Livingstone Elsevier-UK*.
- Martinez, R. F. F., Hernández-Pérez, F., Miguel, G. F. S., Jaimes-Avelaño, A., & Arenas, R. (2013). Portadores de Candida spp na cavidade oral: A sua prevalência em pacientes com diabetes Mellitus tipo 2. *Anais Brasileiros de Dermatologia*, 88(2), 222-225. <https://doi.org/10.1590/S0365-05962013000200006>
- Patil, S., Rao, R. S., Majumdar, B., & Anil, S. (2015). Clinical appearance of oral Candida infection and therapeutic strategies. *Frontiers in Microbiology*, 6(DEC), 1-10. <https://doi.org/10.3389/fmicb.2015.01391>
- Peters, B. M., Ovchinnikova, E. S., Krom, B. P., Schlecht, L. M., Zhou, H., Hoyer, L. L., Busscher, H. J., van der Mei, H. C., Jabra-Rizk, M. A., & Shirtliff, M. E. (2012). Staphylococcus aureus adherence to Candida albicans hyphae is mediated by the hyphal adhesin Als3p. *Microbiology (United Kingdom)*, 158(12), 2975-2986. <https://doi.org/10.1099/mic.0.062109-0>
- Ryalat, S., Darwish, R., & Amin, W. (2011). New form of administering chlorhexidine for treatment of denture-induced stomatitis. *Therapeutics and Clinical Risk Management*, 7, 219-225. <https://doi.org/10.2147/TCRM.S18297>
- Sashikumar, R., & Kannan, R. (2010). Salivary glucose levels and oral candidal carriage in type II diabetics. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology*, 109(5), 706-711. <https://doi.org/10.1016/j.tripleo.2009.12.042>
- Scully, C. (2013). *Oral and Maxillofacial Medicine The Basis of Diagnosis And Treatment* (3rd ed.). Elseiver Ltd.
- Shahzad, M., Faraz, R., & Sattar, A. (2014). Angular Cheilitis : Case Reports and Literature Review. 34(4), 597-599.
- Tucker, R. (2010). Angular cheilitis. *Pharmaceutical Journal*, 285(7621), 374.
- Williams, D., & Lewis, M. (2011). Pathogenesis and treatment of oral candidosis. *Journal of Oral Microbiology*, 3(2011), 1-11. <https://doi.org/10.3402/jom.v3i0.5771>
- Yapar, N. (2014). Epidemiology and risk factors for invasive candidiasis. *Therapeutics and Clinical Risk Management*, 10(1), 95-105. <https://doi.org/10.2147/TCRM.S40160>