Sriwijaya Journal of Dentistry

Sriwijaya Journal of Dentistry (SJD)
Volume 2 Issue 1 2021 : 22-30
https://jurnalkedokteranunsri.id/index.php/SJD/index

Acute Pseudomembran Candidiasis In A Patient With Osteogenic Sarcoma And Anemia

Zara Alviometha[1], Ade Puspa Sari[2], Siti Rusdiana Puspa Dewi[1*]

[1]Dentistry Program, Faculty of Medicine, Sriwijaya University, Palembang, Indonesia

[2]Central General Hospital Dr. Mohammad Hoesin, Palembang, Indonesia

[*]Correspondence author email: sitrus.pd@gmail.com

Abstract

Introduction: Acute pseudomembranous candidiasis is an opportunistic infection caused by the overgrowth of *Candida spp*. *Candida spp* can become pathogenic in a weak immune response. There is a clear relationship between oral candidiasis and patients with malignant disease (cancer) and hematological disorders, such as anemia. Anemia is a complication that often occurs in patients with malignancy. **Purpose:** This paper reports a case of acute pseudomembtane candidasis caused by osteogenic sarcoma and secondary anemia. **Case presentation:** A 12-year-old male patient was hospitalized for osteogenic sarcoma and anemia. Intraoral examination showed white plaque that could be wiped out on the tongue dorsum. *Candida albicans* was identified by oral microbial tests. Antifungal therapy was applied for 14 days and it showed improvement. **Conclusion**: The successful management of this patient involves control of predisposing factors, plaque control, and DHE.

Keywords: Acute pseudomembrane candidiasis; Anemia; Osteogenic sarcoma

Introduction

Acute pseudomembranous candidiasis (oral thrush) is classified as primary oral candidiasis and is recognized as the most common candida infection.[1] *Candida albicans (C. albicans*) is the primary causative agent in oral candidiasis. Candida spp is a commensal microorganism or normal flora in the mouth without causing symptoms.[2] The transformation from a commensal organism to a pathogen depends on different predisposing factors that modify the microenvironment in the oral cavity to become an opportunistic infection.[3] Proliferation of *Candida spp* in the oral cavity can occur. A weak immune system is able to precipitate infectious disease by opportunistic pathogens.[2]

Osteogenic sarcoma is a primary malignant bone tumor characterized by the direct formation of immature bone or osteoid tissue by the tumor cells.[4] The incidence was 3.4 per million people per year.[5] Osteogenic sarcoma is a rare sarcoma that has the histological findings of osteoid production in association with malignant mesenchymal cells.[6] Etiology of osteogenic sarcoma is unknown. It could be suggested that osteogenic sarcoma can be induced by viruses, ionizing radiation, and genetic factors.[7] The diagnosis of osteogenic sarcoma can be performed by clinical examination and additional testing. The additional evaluation can be made by

radiography, computed tomography (CT), magnetic resonance imaging (MRI), angiography, and dynamic bone scintigraphy.[6,7]

Anemia is a complication that often occurs in patients with cancer, which is caused by many factors.[8] Tu *et al*, 2018 reported that there was a decrease of Dynamic Hb and ΔHb > 7.6 found in patients with osteogenic sarcoma and anemia.[9] Anemia can be caused by impaired red blood cell (RBC) production, increased RBC destruction, excessive blood loss, and bone marrow neoplasms.[10] Madu and Ughasoro 2017 reported that malignant tumor is one of the most frequent conditions associated with anemia.[11] Osteogenic sarcoma related to anemia may occur as a direct effect of malignant sarcoma, by the sensitization of the immune system, or as a result of the cancer treatment whether surgery, radiotherapy, or chemotherapy.[12] The secretion of cyclo-oxygenase-2 and the production of cytokines such as interleukin-1, interferon-*γ*, interleukin-6, and tumor necrotizing factor-*α* decreased production of red cells, inhibiting the synthesis of endogenous erythropoietin, and causing impair erythropoiesis.[13] Tumor invasion by malignant cells leads to the obstruction and destruction of the bone marrowas pathogenetic processes to anemia.[11,13]

Candida species commonly reside as commensal organisms in the oral cavity. The changes in the oral environment, such as alterations in normal microbiota or compromised local immune defenses, is able to be pathogenic.[14] Osteogenic sarcoma and anemia lead to a decrease in the immune system.[15] Many putative virulence factors play important roles in *Candidal* infections. One of them is the invasion of hypha formation.[16] The weakened immune systems suppress the secretion of cytokines and chemokines in epithelial cells as a response to *Candida* albicans invasion. As a result oral candidiasis invaded in the oral cavity.[17]

Candidiasis treatment leads to the identification of the underlying factors of the disease through clinical examination and patient history.[3] Controlling or correction of candidiasis predisposing factors such as patients with osteogenic sarcoma and anemia is needed so that the proper treatment can be reached. The drug of choice drug depends on the patient's history and symptoms that occur in the oral cavity. The purpose of this article is to report a case of acute pseudomembtane candidasis caused by osteogenic sarcoma and secondary anemia.

Case report

A 12-year-old male patient, transferred from oncological pediatric of Central General Hospital Dr. Mohammad Hoesin, Palembang, Indonesia, with the medical history of osteogenic

sarcoma of the lower extremity and a secondary diagnosis of anemia, complained of yellowish-creamy *white* curd-*like plaques* that spread on the dorsum of tongue with painful surface since ± 8 months ago. The lesion was soft, could be peeled off when scraped, and leave the underlying surface redness. The clinical features of white lesions can be diagnosed as acute pseudomembranous candidiasis (Fig 1A). Differential diagnosis may include a white-coated tongue, lichenoid reactions, and leukoplakia. Supportive examination in the form of microbiological testing of fungal culture with the tongue swab method was carried out. Examination of the swab taken from the mucosa on the dorsum of tongue. Microbiological culture with potassium hydroxide (KOH) staining was observed. KOH's staining preparations are commonly used for the rapid detection of candidal infection in specimens. The candidal elements are visible during direct microscopic investigations.[18] The result showed that it was a large, ovoid, pseudohyphae yeast cell (+) with *Candida spp.* The diagnosis was made based on history, clinical and microbiological examination, and investigations.

Antifungal therapy was applied by giving Nystatin oral drops with a recommended use of 1 mL (100,000 units) 4 times daily for 14 days. The preparation should be applied to the dorsum of the tongue and retained in the mouth as long as possible before swallowing. The first control (on the 7th day), showed improvement in the healing of the lesion. The painful surface of the tongue was reduced and the yellowish-white plaque layer on the tongue dorsum had degraded without further complications (Fig 1B). In the second control (14th days), it was found that the lesion had totally healed. The oral symptoms and plaque layers were resolved (Fig 1C). The patient was instructed to stop antifungal therapy and continue to consult his predisposing factors (osteogenic sarcoma and anemia), plaque control, and dental health education.

Figure 1. Oral Candidiasis on tongue dorsum. A. Before treatment; B. After 7th day treatment; C.After the 14th day of treatment.

Discussion

Acute Pseudomembranous Candidiasis is an opportunistic infection in the oral cavity that causes pathogenic conditions in certain circumstances, especially due to immune suppression.[16] *Candida spp* is microorganisms or normal flora in the mouth and found about 20-75% in the general population without causing any symptoms.[19] It is potentially able to be pathogenic and cause infection if there are predisposing factors.[20] Predisposing factors that cause oral candidiasis are local factors including the use of dentures, smoking, use of inhaled and topical steroids, hyperkeratosis, imbalance of oral microflora and saliva quality and quantity; and general factors include immune deficiency disorders, malignancy (cancer), chemotherapy, endocrine diseases, drugs that suppress the immune system, and hematinic deficiency.[21] In this case, the predisposing factor was malignancy and anemia. This predisposing factor can then lead to the mechanism of candida infection through two microbial phenomena, (1) genetic control of the process of changing the yeast cell form to hyphae form and (2) the ability of the organism to attach (adhesion) to the mucous membrane.[22] The pathogenicity of *C. albicans* is significantly based on its ability of surface molecules, such as mannoproteins and complement receptors to modulate phagocyte responses.[23] *Candida* will adhere to the epithelial surface and invade the mucosal layer. Yeast penetration of epithelial cells is facilitated by the production of candida-produced lipases.[22, 23] Overgrowth of the fungus then leads to the formation of a pseudomembrane.

The clinical appearance of acute pseudomembrane candidiasis was yellowish-white creamy plaques resembling milk curds, which can be scraped off by wiping gently and leaving underlying erythematous in oral mucous.[24] The plaque material consists of hyphae invading the depth of the stratum spinosum, desquamated epithelial cells, fibrin, debris, and necrotic material.[25]

This appearance is similar to the coated tongue, lichenoid reactions, and leukoplakia. However coated tongue is often related to oral hygiene. It can be removed easily and does not leave an underlying erythematous surface.[26] The white plaques consist of debris.[27] While the clinical presentation of lichenoid reaction is white reticular striae to painful erythema and erosions.[28] The clinical appearance of leukoplakia is white plaques that cannot be wiped out

because it consists of keratocytes cell or dysplasia.[29] Microbiological examination of these differential diagnoses were yeast cell negative.[2]

Osteogenic sarcoma is a malignant primary bone cancer that influences upper and lower extremity bones.[5] Tumor cells induce the secretion of cyclo-oxygenase-2 enzyme, vascular endothelial growth factor, interleukin-6, interferon- g, TNF-α, and also stimulate macrophage activation.[7] Proinflammatory cytokines, ROS, macrophage activation, cause the liver synthesis of hepcidin.[30] Hepcidin is a glycoprotein that has function to manage the mobilization of iron in the body.[31] The increased hepcidin leads the functional iron deficiency by involving impaired erythropoietin production and increased resistance of erythropoietic precursors to erythropoietin.[32] This condition may cause inducing ferritin synthesis, enhance degradation, and phagocytosis of red cells, elevate intracellular iron by stimulation of DMT-1, inhibition of ferroportin, stimulate nitric oxide production, and inducible nitric oxide synthase mRNA expression.[7, 32] The decreased lifespan of circulating red blood cells results in various physiological complications such as impaired tissue oxygenation, impaired organ function, fatigue, prone to bleeding due to thrombocytopenia and impaired quality of life and maintaining oral hygiene is reduced. [33] As hepcidin increases, the growth differentiation factor 15 (GDF-15) is also elevated. This inhibitor of leukocyte integrin is associated with tumor metastasis and hemopoiesis.[34] Madu *et al* reported that the serum level of GDF-15 is correlated with the degree of anemia in patients with cancers.[35]

Secondary anemia related to cancer pathophysiologically can be divided into several mechanisms, (a) The alterations in the production of several pro-inflammatory cytokines, including interleukin (IL)-1, IL-6, tumor necrosis factor-alpha (TNFα), the interferons (IFN) and hepcidin; (b) blood loss due to hemolysis; (c) miscellaneous etiologies; (d) uncertain etiologies.[8] Those mechanisms can be overlapped. The prevalence of underlying causes of anemia due to cancer was 30%-77%.[34] The pathogenetic processes entangled active protection expressed by the immune system in eliminating invading iron cells, is an essential nutrient for the proliferation of both cancer cells and pathogens.[35] These processes primarily include bone marrow invasion by tumors or infective agents, alteration of iron metabolism and diversion of body iron, haemophagocytosis, reduction in erythropoiesis, and diminished response to erythropoietin stimulation.[31] The pathogenetic mechanisms are mediated through the actions of cytokines (tumor necrosis factor (TNF) and interleukins (IL)-1 and −6, and interferon (IFN)), as well as the acute-phase protein hepcidin.[35] They inhibit iron release from the marrow

macrophages to the progenitors of erythroid, modulate the translation/transcriptions of genes involved in iron homeostasis.[31, 34, 35]

Anemia affects the adequate immune response in the body. The ability in producing immune cell proliferation, lymphocytes, monocyte/macrophage differentiation is decreased.[11, 15] Lymphocytes are mostly associated with the generation of a specific response to infection, while macrophages as a cofactor for the execution of important antimicrobial effector mechanisms.[36] The suppression of the immune system causes the change of oral cavity. Oral pathogens are more capable to survive and evade detection by the host immune defense, such as *Candida albicans*.[37]

Candida may attempt to activate a protective host immune response that allows its survival. Underlying acquired immunity to the candida is usually present in immunocompetent adults and is thought to prevent progression from mucosal colonization to symptomatic infection.[1] Normally the integrity of the mucosa prevents the penetration of pathogens as well as macromolecules, which may be antigenic.[37] The lower immune response of mucous is the best way for the colonization of oral pathogens. Gravina *et al* reported that oral candidiasis is a frequent complication in children and young adults with malignant disease, as *C. albicans* is the main etiological agent.[38] Jayachandran et al revealed that there was a connection of certain symptoms with the isolation of *Candida* among cancer patients. It could be caused by the pathophysiology process itself or due to the radio or chemical-therapy.[39]

The management of this patient was giving antifungal drugs, control of plaque, and DHE, control once a week. Besides that, the patient should continue to control and consult oncological pediatric in the general hospital to treat his osteogenic sarcoma and secondary anemia. The antifungal drug given was one bottle of 12 ml Nystatin oral drops with a recommended use of 1 mL (100,000 units) 4 times daily for 14 days was applied to the dorsum of the patient's tongue for 14 days. Nystatin is a broad-spectrum antifungal compound that has significant toxicity to candidal infection.[40] It is available in various forms, such as oral suspension, topical cream, and oral pastille. The topical use of nystatin is considered the most common route of administration in dentistry because systemic exposure is minimal.[41] It can be used as prophylaxis of oral and systemic candidiasis in immunocompromised patients because the interaction of the drug administration is minimal.[40] Nystatin absorbs into the oral epithelium and kills yeast hyphae growing within the tissue. Its mechanism of action is driven by forming pores on membrane lipid composition and underlie the cytotoxic effect of pathogens.[42] Bohbot

reported that Nystatin is the first line of topical treatment for local candidiasis.[43] After 14 days of treatment, therapy has been adequately successful in healing lesions.

Conclusion

Based on the anamnesis, clinical examination, and laboratory examination, the diagnosis of the lesion in the patient was acute pseudomembranous candidiasis. The management of this patient was to control the predisposing factors for candidiasis (Osteogenic sarcoma), control of plaque and DHE, administration of antifungal drugs, and control once a week.

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