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**NECROTIZING ULCERATIVE GINGIVITIS AS A COMPLICATION OF FEBRILE  
 NEUTROPENIA IN ACUTE MYELOID LEUKEMIA PATIENT**

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**ABSTRACT**

**Background:** Necrotizing ulcerative gingivitis (NUG) is a periodontal disease characterized by gingival pain, interdental gingival necrosis, and bleeding. NUG is closely related to immunosuppression, smoking, poor oral hygiene, malnutrition, and stress. Acute myeloid leukemia (AML) is a bone marrow malignant neoplasm. Chemotherapy as the treatment for AML often causes febrile neutropenia which results in immunosuppression conditions and is a risk factor for NUG. This case report aimed to discuss NUG as a complication of febrile neutropenia. **Case:** A 22-year-old woman was referred from hemato-oncology with acute myelomonocytic leukemia (AML-M4) and febrile neutropenia due to her oral complaints. She had undergone one cycle of chemotherapy and developed febrile neutropenia. Intra-oral showed ulcers covered with white-grayish plaques on the gingival region 35 to 45 and 15 to 25. There were white plaques that could be removed leaving an erythematous area on the dorsal tongue. Blood laboratory tests showed pancytopenia and severe neutropenia. The diagnoses were necrotizing ulcerative gingivitis and pseudomembranous candidiasis. **Case management:** Debridement using 1.5% hydrogen peroxide solution, rinsing with 0.2% chlorhexidine gluconate, as well as cleaning teeth and tongue 2 times daily. The internal medicine department gave meropenem. The lesions and gingiva were healed after three weeks of therapy. **Conclusion:** Febrile neutropenia due to chemotherapy reduces the body's ability to fight infection, oral homeostasis is disturbed therefore bacterial growth increases, neutrophils carry out phagocytosis forming reactive oxygen species which causing necrotic cells and then NUG occurred. Appropriate, adequate, and immediate therapy is needed to avoid further complications.

**Keywords:** Acute myeloid leukemia, Febrile neutropenia, Necrotizing ulcerative gingivitis

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**INTRODUCTION**

Leukemia is a malignant disorder where leucocyte counts increase in the blood and/or bone marrow.<sup>1</sup> GLOBOCAN data 2020 showed new cases of leukemia in Indonesia are in the ninth highest position of all cancers with 14979 cases.<sup>2</sup> Based on the rapidity of its proliferation, leukemia is classified into acute and chronic while based on the cell of origin, leukemia is divided into myeloid and lymphoid.<sup>1</sup> Acute myeloid leukemia (AML) is the most common type of acute leukemia in adults.<sup>1,3</sup> AML is defined as a heterogeneous hematological malignancy characterized by clonal expansion of myeloid blast cells in the peripheral blood, bone marrow, and/or other tissues. Risk factors that are suspected to be

related to AML i.e. exposure to ionizing radiation (people working in the nuclear industry, exposure to atomic bombs), benzene, formaldehyde, smoking, cytotoxic chemotherapy, pesticides, and a high body mass index.<sup>3,4,5</sup>

AML therapy has not changed much in recent years. Briefly, AML treatments consist of induction, remission, and post-remission chemotherapy, targeted therapy, and hematopoietic stem cell transplantation.<sup>6,7</sup> But unfortunately, chemotherapy often causes complications such as febrile neutropenia (FN). Febrile neutropenia is a serious complication of chemotherapy that can lead to delayed treatment and decreased doses of chemotherapy which in turn will affect the efficacy of therapy. Approximately 1% of

patients receiving chemotherapy develop febrile neutropenia, this condition contributes to morbidity and mortality.<sup>8</sup>

Febrile neutropenia is characterized by an oral temperature  $> 38.3^{\circ}\text{C}$  or two consecutive readings  $> 38.0^{\circ}\text{C}$  for 2 hours and an absolute neutrophil count of fewer than  $500 \text{ cells/mm}^3$  in 48 hours period.<sup>9,10</sup> Neutrophils have an important role in the innate immune system. Neutrophils respond directly to pathogens, either bacterial cells or fungal hyphae, and release cytokines to recruit inflammatory response at the site of infection. Quantitative or qualitative neutrophil deficits put patients at risk for infection caused by organisms, particularly bacteria, and fungi. Many cytotoxic chemotherapeutic agents act on bone marrow myeloproliferative cells, in addition to the desired tumor cell targets, resulting in neutropenia.<sup>10</sup>

The oral cavity is a very diverse microbial habitat, more than 700 species of bacteria are found on the hard surfaces of teeth and soft tissues as biofilms. The microbes prevent colonization and overgrowth of opportunistic and pathogenic microorganisms. Studies showed that treatment with myelosuppressive chemotherapy-induced changes in the oral microbiome.<sup>11</sup> Healthy oral tissue has a balance between symbiotic bacteria and innate immune system cells, especially neutrophils. Neutrophils act as a barrier against dysbiotic bacteria. However, when neutrophils are insufficient, bacteria will develop lead it to periodontitis and inflammatory disease that can damage the teeth-supporting tissues.<sup>12</sup>

Necrotizing ulcerative gingivitis (NUG) is a periodontal disease characterized by gingival pain, interdental gingival necrosis, and bleeding. Several risk factors for NUG related to immune system function and opportunistic bacteria can predispose to NUG. These factors include malnutrition, poor sleeping time, emotional stress, poor oral hygiene, chemotherapy, and systemic diseases. NUG often occurs in immunosuppression patients along with opportunistic bacteria including Spirochaeta and anaerobic subgingival flora.<sup>4</sup> Immunosuppression conditions, accompanied by chemotherapy cause neutropenia that initiates the occurrence of NUG. NUG therapy is carried out in several stages, i.e. acute phase therapy, improving pre-existing conditions, treating sequelae of the disease, and transitioning to a supportive or maintenance phase. Treatment in this acute phase includes debridement using substances that can release oxygen, as well as plaque control with 0.2% chlorhexidine gluconate.<sup>13</sup> The purpose of this case report is to discuss necrotizing ulcerative gingivitis as a complication of neutropenic febrile in patient with leukemia.

#### CASE REPORT

A 22-year-old woman was referred from the hemato-oncology division of Dr. Hasan Sadikin

Bandung to the Department of Oral Medicine complaining of discolored and bleeding easily gum. The patient was diagnosed as AML M4 and currently had febrile neutropenia. The Internal Medicine treated her with granulocyte colony stimulating factor (G-CSF), paracetamol, and meropenem. Chemotherapy was administered with a regimen of daunorubicin and cytarabine. Blood laboratory test results showed pancytopenia, i.e. hemoglobin 8.2 g/dL, hematocrit 24.0%, erythrocytes  $2.51 \times 10^6/\mu\text{L}$ , leukocytes  $0.75 \times 10^3/\mu\text{L}$ , platelets  $81 \times 10^3/\mu\text{L}$ , segment neutrophils 41%, 3% rod neutrophils, and absolute neutrophil count 330.

Chemotherapy had been carried out in one cycle for seven days, one week later the patient got fever. Her gingiva was pain, bleeding if she brushed her teeth, felt discomfort in her mouth, as well as bad breath. The complaints of discomfort and pain made her difficult to open her mouth and she could only eat porridge. The gum was bleeding during she brushed her teeth 5 days ago, therefore she did not clean her teeth and tongue. Intra-orally, an ulcer covered with a grayish-white plaque that could not be scrapped off and tended to bleed was found on the gingiva regio 15 to 25 and 35 to 45 accompanied by halitosis. There was a white plaque that could be scrapped off leaving an erythematous area on the entire dorsum of the tongue (Figure 1).



**Figure 1.** The clinical appearance of the patient's oral cavity (first visit)

The Oral Medicine diagnosed her as necrotizing ulcerative gingivitis regio 15 to 25 and 35 to 45 and pseudomembranous candidiasis. The management were pharmacological and non-pharmacological therapy. Non-pharmacological therapy including giving instructions to maintain oral hygiene, cleaning the teeth and tongue using gauze which was soaked in 0.9% NaCl twice a day, in the morning after breakfast and at night before going to bed. The pharmacological therapy were debridement using mouthwash containing substances that can release oxygen, i.e. 1.5% hydrogen peroxide solution, and then rinsing with 0.9% NaCl as well as plaque control by gargling 0.2% chlorhexidine gluconate 10 ml, 3 times a day.

During the first visit, the patient could not open her mouth widely. The management started with debridement using 1.5% hydrogen peroxide and 0.9% NaCl and plaque control with 0.2% chlorhexidine gluconate. The first control was carried out on the next day, and the lesions on the anterior gingiva of the mandible and dorsum of the tongue had already improved (figure 2). Three days later her condition generally improved so that she could go home and continue as an outpatient.

We advised her to keep cleaning her teeth and tongue using a gauze soaked in 0.9% NaCl and routinely gargling 0.2% chlorhexidine gluconate 3 times a day. The next follow up was scheduled one week later, but she came three weeks later. The lesions on the gingiva of the maxilla and mandible had already improved, and no more ulcer which was covered with grayish-white plaques as well as white plaque on the dorsum of the tongue (figure 3).



**Figure 2.** The clinical appearance of the patient's oral cavity (control on the next day)

She had also been able to open her mouth and eat as usual. The blood laboratory results still showed low platelet level of 58,000/ $\mu$ L therefore scaling and root planning could not be done because it may provoke bleeding.



**Figure 3.** Three weeks after the first visit; no more ulcer lesions which was covered with gray-white plaque and white plaque on the tongue.

## DISCUSSION

Acute myeloid leukemia is a myeloid disorder of the hematopoietic system and is characterized by the accumulation of immature blood cells in the peripheral blood and bone marrow.<sup>15</sup> The early manifestations of AML that can be found in the oral cavity are gingival bleeding, oral ulceration, and gingival hyperplasia.<sup>16</sup>

Conventional therapies for AML that are still being carried out is chemotherapy in the induction phase, followed by the consolidation phase and allogeneic stem cell transplantation. Generally, cytotoxic chemotherapy has pharmacological effects by causing damage to DNA cells either specifically or nonspecifically. Damage to the DNA of cancer cells by chemotherapeutic agents demonstrates their ability to kill cancer cells. Many chemotherapeutic agents suppress the bone marrow, resulting in neutropenia, and may eventually lead to an increased risk of infection.<sup>17</sup> These neutropenic complications are associated with morbidity and mortality, disrupt the course of therapy, and increase the treatment costs. Neutropenia usually occurs about 1 week after the administration of cytotoxic chemotherapy.<sup>10</sup> Chemotherapy-induced neutropenia is characterized by decreased in the absolute neutrophil count (ANC)  $< 2000$  cells/ $\text{mm}^3$ . The degree and duration of neutropenia determine the risk of infection. The National Cancer Institute classifies neutropenia into 4 grades; grade 1 ANC 1,500–2,000 cells/ $\text{mm}^3$ , grade 2 ANC 1,000–1,500 cells/ $\text{mm}^3$ , grade 3 ANC 500–1,000 cells/ $\text{mm}^3$ , and grade 4 ANC  $< 500$  cells/ $\text{mm}^3$ .<sup>18</sup> Neutrophils are the first line of defense against infection. Neutropenia decreases the inflammatory response to infection, allowing bacterial multiplication and invasion.<sup>19</sup>

Fever is one of the manifestations of several signs of the release of pro-inflammatory cytokines (including interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-alpha) as a result of infection or inflammation.<sup>11</sup> Fever that occurs during cytotoxic cancer therapy that causes neutropenia, also called febrile neutropenia (FN), is a medical emergency. FN that occurs during the first cycle of chemotherapy is much higher (23%-36%) compared to that in later cycles.<sup>18</sup> Febrile may be the only indication of a severe infection because the signs and symptoms of inflammation are usually weakened this condition. This circumstance makes the infection can quickly develop into life-threatening complications such as sepsis and septic shock, therefore febrile neutropenia must be treated immediately.<sup>10,11</sup> Initial therapy for this condition is the administration of broad-spectrum empiric antibiotics intravenously because the risk of sepsis is very high, while patients with low risk can be given oral antibiotics.<sup>9</sup> The antibiotics cefepime, imipenem, meropenem, or piperacillin-tazobactam in the National Comprehensive Cancer Network guideline are the first choice for patients with FN.<sup>20</sup> Meropenem belongs to the carbapenem group which has a broad-spectrum antibacterial effect with extended-spectrum

beta-lactamase resistance (ESBL), effective for Gram-negative and Gram-positive anaerobes.<sup>8</sup>

Oral homeostasis occurs due to the complex interactions between the host and the resident microorganisms. The presence of cancer, myelosuppressive chemotherapy, as well as drugs, including antibiotics, disrupt the balance of the oral ecosystem through direct and indirect mechanisms, thereby contributing to the occurrence of complications in the oral cavity.<sup>11</sup> The normal flora prevents colonization and overgrowth of opportunistic and pathogenic microorganisms. Studies showed that treatment with myelosuppressive chemotherapy-induced changes in the oral microbiome. Research conducted by Dawood et al on the buccal mucosa of rats treated with cytarabine showed that the salivary glands were shrinkage and atrophy in the mucous salivary glands, decreased zymogen granules in the cytoplasm of serous gland cells, reduced interlobular and lobular salivary duct diameters, vacuolation of stratified squamous epithelium, and interstitial edema.<sup>21</sup> This is thought to cause hyposalivation in patients undergoing chemotherapy. Saliva has a key role in maintaining a stable oral ecosystem because it contains peptides and proteins that have antibacterial, antifungal, and antiviral effects as well as lubricating, buffering, remineralizing, and playing a role in digestion. This lack of salivary defense mechanisms may contribute to oral dysbiosis which leads to the increased incidence and severity of oral mucosal infections.<sup>11</sup>

Neutrophils are the first line of defense against infection and inflammation. Neutropenia decreases the inflammatory response to infection, allowing bacterial multiplication and invasion.<sup>19</sup> The inflammatory response following tissue injury is a dynamic process consisting of sequential steps aimed at tissue recovery. Depending on the type of tissue injured, there are three possible strategies for neutrophils in repairing damaged tissue. First, as phagocytes, neutrophils can remove tissue debris at the site of injury. The debris removal mechanism appears to be very effective since cell remnants are usually rare under physiological conditions. Second, mature neutrophils have more than 700 proteins including growth factors or pro-angiogenic factors stored in the nucleus and granules. Many proteins can be released quickly after activation and thus directly contribute to regeneration and revascularization. Third, the most studied mechanism of neutrophil contribution to tissue repair is that neutrophils become apoptotic and are cleared by macrophages.<sup>22</sup> The presence of neutrophils in overcoming infection makes it very important, therefore the reduction of neutrophils in the state of neutropenia leads the body susceptible to infection.

NUG is caused by several factors, including gingival infection by periodontopathic bacteria, especially *Spirochaeta* and fusiform bacilli, impaired host immune response, and other predisposing factors

such as physical and emotional stress, as well as malnutrition.<sup>23</sup> NUG is characterized by gingival necrosis, gingival bleeding, and pain. Other common features, but not pathognomonic of NUG, are the presence of pseudomembranes, cervical lymphadenopathy, and halitosis.<sup>23</sup> Neutropenia is a potentially fatal and common complication in myelosuppressive chemotherapy.<sup>18</sup> The low immune response associated with neutropenia and the specific microflora of the dentogingival plaque may play an important role in initiating NUG. Bacteria colonize and invade the periodontal tissues, and the host uses various defense mechanisms to maintain a dynamic balance with the oral microbial flora.<sup>24</sup>

Besides NUG, this patient also had candidiasis. Candidiasis is the most common opportunistic fungal infection of the oral mucosa and is caused by fungi of the genus *Candida*.<sup>26,27</sup> *Candida spp.* is a normal flora that lives as commensal microorganisms in the oral mucosa, digestive tract, urogenital tract, and skin, but in some circumstances can become pathogenic.<sup>27</sup> The transition to pathogenicity in candida is related to several factors; i.e. the use of broad-spectrum antibiotics, immunosuppression, neutropenia, hematological malignancies, chemotherapy, cancer, diabetes, corticosteroid therapy, and HIV.<sup>27,28</sup> Malignancy and related therapeutic interventions such as chemotherapy and radiotherapy can lower the immune system which plays a role in controlling fungal infections. This cancer therapy can induce hyposalivation and xerostomia causing proliferation, colonization, and fungal infection.<sup>28</sup> Neutropenia is also associated with the overgrowth of candida because neutrophils are the first line of defense of mucous membranes against candida.<sup>27</sup> Neutrophils have an important role in the initiation of cellular and humoral immunity by releasing mediators such as IL-1, IL-6, or TNF- $\alpha$ . The function of neutrophils on fungal infections is to inhibit the spread of fungi, block candida filaments, modify the composition of the fungal cell wall in the interaction between fungi and polynuclear neutrophils, and release proteins that inhibit candida growth.<sup>27</sup>

NUG therapy in the acute phase has two main goals; to stop the disease process and tissue damage and to reduce discomfort and pain in the oral cavity.<sup>13</sup> Debridement with chemical agents containing substances that can release oxygen, plaque control, and cleaning the calculus with an ultrasonic scaler are the first things to do.<sup>29</sup> Because of the medical complexity of the patient with leukemia, it is necessary for the dental care of leukemia patients to be integrated into a multidisciplinary framework. This is because this patient's medical complexity may affect the selection of priorities and the amount of time available for dental therapy. Bleeding, bruising, and opportunistic infection may develop if the treatment if dental treatment does not consider the patient's condition.<sup>30</sup> In this case report,

the patient was treated with hydrogen peroxide irrigation because it is an oxidizing agent that has been widely used in the treatment of necrotizing ulcerative gingivitis. Hydrogen peroxide will release oxygen, removing debris or necrotic tissue in areas that cannot be reached by mechanical cleaning. It is also used as an antiseptic by damaging membrane lipids, DNA, and other important cellular components.<sup>31</sup> Hydrogen peroxide is also effective for removing the pseudomembrane of the NUG and has been shown to reduce bleeding.<sup>31</sup> Chlorhexidine gluconate is used because it can reduce bacterial colonization and reduce gingival infection.<sup>32</sup> A study by Daniel et al showed that chlorhexidine with concentration of 0.2% had significant antifungal activity compared to ketoconazole.<sup>32</sup> 0.2% Chlorhexidine gluconate is a broad spectrum antimicrobial mouthwash against a variety of organisms, including *C. albicans*. Chlorhexidine has the ability to prevent candidal adherence to inert and biological surfaces. It has fungicide and fungistatic effect, causing alterations in cell walls and the coagulation of nucleoproteins, which may allow cytoplasmic components to escape via the plasmalemma.<sup>33</sup> Rinsing the mouth with normal saline is recognized as the most preferable method for oral wound care. It is an affordable and nontoxic way to provide a moist environment to facilitate the healing of oral wounds.<sup>34</sup> It was seen in this patient that the use of 0.2% chlorhexidine gluconate can cure pseudomembranous candidiasis. Antibiotics are usually given in the management of NUG because NUG is caused by periodontopathic bacteria, especially *Spirochaeta (Treponema spp)*, *Fusobacterium nucleatum*, *Prevotella spp*, and *Peptostreptococcus*.<sup>35</sup> Meropenem have been administered by the Internal Medicine as the antibiotic to treat FN. The broad spectrum of antibacterial makes meropenem an empiric antibiotic in serious bacterial infections. The mechanism of action is by interfering with the synthesis of the bacterial cell wall, causing cell death. In vitro studies have shown good effectiveness of meropenem against anaerobic bacteria that cause NUG such as *Prevotella spp* and *Peptostreptococcus*.<sup>21</sup> Meropenem also has bactericidal activity (99.9%) against *Fusobacterium nucleatum*.<sup>21</sup> It made the use of this drug was sufficient to treat febrile neutropenia as well as NUG.

After three weeks of therapy from the Oral Medicine Department, the gingiva and tongue were improved, halitosis was reduced, the patient was able to eat solid food as usual, and the oral cavity also felt much more comfortable. Follow-up therapies to get rid of local factors such as calculus and the remaining tooth roots could not be carried out considering that the blood laboratory test results still show pancytopenia and low platelet counts. The patient was instructed to maintain her oral hygiene by cleaning the teeth and tongue at least twice a day, hoping it can reduce the occurrence of infections in the oral cavity, especially in the

immunosuppressive state. Chemotherapy in acute myeloid leukemia causes febrile neutropenia which can reduce the body's ability to fight infection so that oral homeostasis is disrupted. Overgrowth of normal flora causes neutrophil reaction as the first line of defense against infection by phagocytosis and the formation of reactive oxygen species forming necrotic cells and if it occurs in the gingiva causes NUG. Proper, adequate, and immediate therapy is urgently needed to avoid further complications. Maintaining oral hygiene is important to minimize the occurrence of infections, especially in immunosuppression conditions such as acute myeloid leukemia undergoing chemotherapy.

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