Oral Opportunistic Infections in Patient with HIV Wasting Syndrome

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ABSTRACT

Background: Human immunodeficiency virus (HIV) wasting syndrome is a condition in which weight loss, fever, and chronic diarrhea occur for more than 30 days without any causes other than HIV infection. HIV causes an immunocompromised condition resulting in susceptibility to infection. The opportunistic infections are oral candidiasis, herpes simplex virus (HSV), and tuberculosis. This study aims to explain oral opportunistic infections in a patient with wasting syndrome. Case Report: A 20-year-old female, who was 165 cm in height and 33.75 kg in weight, with wasting syndrome, pulmonary tuberculosis, oral candidiasis, and angular cheilitis was referred from an internist in Hasan Sadikin Hospital. Extraoral examination showed a yellowish brownish crust on the lips. Intraoral examination showed multiple ulcers covered by a yellowish membrane on the labial mucosa. The white plaques were scrapable, and an erythematous was found on the dorsum of the tongue, buccal mucosa, and palate. Laboratory results revealed a decrease in hemoglobin, hematocrit, leucocyte, erythrocyte, basophil, neutrophil, lymphocyte, albumin, reactive anti-HSV IgG, CD4 16 cell/µl, mycology culture test, chest x-ray, and sputum. On the basis of anamnesis, clinical features, and laboratory examination, the patient was diagnosed with stomatitis herpetica and oral candidiasis. Chlorhexidine gluconate 0.2%, nystatin oral suspension, vitamin B₁₂, folic acid, and vaseline album were administered on the lips. Clinical recovery of oral candidiasis was accomplished after five weeks of therapy. Conclusion: Opportunistic infections in patient with wasting syndrome are oral candidiasis, herpetic stomatitis, and tuberculosis.

Keywords: opportunistic infections, wasting syndrome
Background

Human immunodeficiency virus (HIV) wasting syndrome is defined as a condition where weight loss, fever, and chronic diarrhea that have lasted for more than 30 days without any causes other than HIV infection. HIV wasting syndrome or multifactorial cachexia was a result of insufficient calorie intake, malabsorption, and alteration of metabolism. These interactions can cause weight loss and increase the energy requirements to 50% to 100% more than normal. Weight loss that accompanied by diarrhea can increase morbidity and mortality in HIV wasting syndrome. Unwittingly, HIV infection and malnutrition can have a negative impact on the development of Acquired Immunodeficiency Syndrome (AIDS) itself. AIDS sufferer have a weak immune system that can aggravate infections in general and make the pathogens easily adapted to the patient. Chronic infections can add the severity and prolonged the recovery of the patient. Immunocompromised patients are susceptible to opportunistic infections, such as oral candidiasis, herpetic stomatitis and tuberculosis.

Immunosuppression in HIV/AIDS can develop to opportunistic infections in the oral cavity, such as oral candidiasis, hairy leukoplakia, linear gingival erythema, necrotizing ulcerative gingivitis, necrotizing ulcerative periodontitis, and non-hodgkin lymphoma. Oral candidiasis is the most common opportunistic fungal infection among immunocompromised patients, and is usually caused by Candida albicans. Candida is a normal microflora in the oral cavity. However, it can turn into a pathogen in immunocompromised patients, and it is worsened by the presence of local or systemic factors. Some of these local factors are poor oral hygiene, long-term use of antiseptics, smoking, and alcohol consumption. The systemic factors include salivary gland dysfunction, hormonal disorders, xerostomia, long-term broad-spectrum antibiotic therapy, age, dietary factors, cancer, HIV infection, and malnutrition. Malnutrition causes a deficiency in cellular immune response that leads to susceptibility against opportunistic infections such as candidiasis. Local and systemic factors can trigger the transformation of dimorphic candida from the commensal phase in the form of blastoconidia into the hyphae phase, resulting in adhesion, colonization, and invasion. The symptoms of oral candidiasis infection may vary from asymptomatic to symptomatic, such as burning sensation, dysphagia, and decreased sensation. The predilection of the anatomical location is the tongue, palate, and buccal mucosa.

Oral candidiasis acts as an initial symptom and can be a progressive sign of HIV disease. Malnutrition is a systemic factor that can be a confounding variable and associated with the increased number of candida. Oral herpes is one of the oral manifestations that can occur and aggravate the clinical condition of HIV patients. Another opportunistic infection is tuberculosis (TB). A poor nutritional status increases the risk of TB. Tuberculosis infection causes a decrease in nutrition intake, malabsorption, and changes in body metabolism, which result in decreased body mass and fat (wasting) as a manifestation of protein energy malnutrition. HIV and malnutrition lead to susceptibility against infections, such as candidiasis, oral herpes, and TB. Oral manifestations can also be a progressive sign of HIV/AIDS stage and also a risk for oral complications. This oral manifestation can cause discomfort and difficulty in eating and swallowing, thus leading to malnutrition. The CD4+ cell count is in accordance with the oral cavity examination: a low CD4+ count causes several clinical manifestations. The purpose of this case report is to explain oral opportunistic infections in a patient with HIV wasting syndrome.

Case Report

A 20-year-old woman with HIV wasting syndrome, pleura pneumonia, pulmonary TB and oral lesions was referred to the Hasan Sadikin Hospital Internal Medicine Department. The patient was hospitalized 2 days ago with a phlegm cough, fever, weight loss, and night sweats and had felt shortness of breath since then. Based on the anthropometric method (MUAC), malnutrition status was reported, estimated body weight of 33.75 kg, height of 165 cm. Patient show a weak body with inflammation anemia, and hemolytic anemia aggravated by anti-tuberculosis drugs rifampicin and isoniazid. The patient's family (patient's mother) had a history of tuberculosis since 5 years ago. The Patient has had HIV since 1 year ago...
(without any treatment. Anti-retroviral (ARV) was given to the patient for 23 days and anti-tuberculosis drug was also given after 9 days of hospital admission.

The patient was referred to the department of oral medicine for consultation to manage the oral lesions. She complained of pain, decreased sensation, swallowing difficulty, and white membranes in almost all parts of her oral cavity. Extraoral examination showed an anemic conjunctiva and non-icteric sclera. Bilateral cervical lymph nodes were palpable but not painful. Brownish crusts were also seen on the patient’s lips. Intraoral examination showed several ulcerative lesions covered by a yellowish membrane with an irregular shape on the upper and lower labial mucosa. White plaques were observed on the dorsum of the tongue, buccal mucosa, and palate (Fig. 1). Laboratory tests showed a decrease in hemoglobin, hematocrit, leukocytes, erythrocytes, mean corpuscular hemoglobin concentration (MCHC), basophils, neutrophils, lymphocytes, albumin, anti herpes simplex virus (HSV)-1 IgG (54.3), and CD4 (Table 1).

Based on patient’s history, clinical features, and laboratory examination, a diagnosis of oral candidiasis, herpetic stomatitis and coated tongue was determined in HIV patients with wasting syndrome. The patient was treated for a month and prescription of systemic anti-tuberculosis therapy, ciprofloxacin, cotrimoxazole, paracetamol, N-acetyl cysteine, and albumin 25% was given to her by the department of internal medicine. On the first visit, the department of oral medicine gave the patient nystatin oral suspension 2 mL 4 times a day, chlorhexidine gluconate 0.2% mouth rinse 10 mL 3 times a day, vitamin B₁₂ 3 times a day, folic acid once a day, and Vaseline album to thinly coated the lips 3 times a day as a therapy for her condition.

After one week of therapy, extraoral examination showed the improvement of the lip lesions and the healing of the crusting. Intraoral examination showed that the white plaque on the dorsum and lateral of the tongue was reduced. Other painful ulcers with a yellowish base, an uneven base, and irregular edges on the right lateral tongue and thinning erythema-based lesions on the upper and lower labial mucosa were observed. Mouthwash therapy of 0.025% hyaluronic acid exhaust gargle three times a day, 50 mg of vitamin B₁₂ three times a day, and 1 mg of folic acid once a day were then prescribed (Fig. 2).

After three weeks of therapy, the white plaque on the dorsum, lateral right and left of the tongue has been reduced. Prescription of 0.1% chlorhexidine gluconate mouth rinses three times a day and nystatin oral suspension 2 mL four times a day was given to the patient (Fig. 3). On the last visit, the white plaque on the dorsum of the tongue has been reduced but there was depapillation of the tongue and there was a thinned white plaque on the lateral right of the tongue. The white plaque on the lateral left of the tongue has disappeared. Nystatin oral suspension 2 mL 4 times a day, vitamin B₁₂ 50 mcg 2 times a day and folic acid 1 mg were then continue to be administered (Fig. 4).

**Figure 1.** (a) Lips; brownish yellowish crusts (b)(c)(d) dorsum, lateral tongue; white pseudomembranes (e)(f) upper, lower labial mucosa; ulcerative lesions covered by membranes.
**Figure 2.** (a) Lips; crusts has disappeared (b) tongue dorsum; thinning white plaque (c)(d) lateral tongue; thinning white plaque and regional ulcer (e)(f) upper and lower labial mucosa-like mucosae with; thinning erythematous based.

**Table 1.** Complete laboratory examination

<table>
<thead>
<tr>
<th>Examination</th>
<th>1&lt;sup&gt;st&lt;/sup&gt;</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt;</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt;</th>
<th>4&lt;sup&gt;th&lt;/sup&gt;</th>
<th>5&lt;sup&gt;th&lt;/sup&gt;</th>
<th>Normal value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>7.6(L)</td>
<td>5.8(LL)</td>
<td>5.6(LL)</td>
<td>5.8(LL)</td>
<td>10.2(L)</td>
<td>12.3-15.3 g/dL</td>
</tr>
<tr>
<td>Hematocrite</td>
<td>23.4(L)</td>
<td>18.9(LL)</td>
<td>18.2(LL)</td>
<td>18.7(LL)</td>
<td>31.5(L)</td>
<td>36.0-45.0%</td>
</tr>
<tr>
<td>Erythrocytes</td>
<td>3.03(L)</td>
<td>2.10(L)</td>
<td>2.03(L)</td>
<td>2.07(L)</td>
<td>3.66(L)</td>
<td>4.2-5.5 million/μL</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>3.69(L)</td>
<td>7.80</td>
<td>5.39</td>
<td>2.84(L)</td>
<td>2.44(L)</td>
<td>4.50-11.0 ×10&lt;sup&gt;3&lt;/sup&gt;/μL</td>
</tr>
<tr>
<td>Trombocytes</td>
<td>137(L)</td>
<td>407</td>
<td>450</td>
<td>403</td>
<td>344</td>
<td>150-450 thousand/μL</td>
</tr>
<tr>
<td>MCV</td>
<td>77.2(L)</td>
<td>90.0</td>
<td>89.7</td>
<td>90.3</td>
<td>86.1</td>
<td>80-96 fl</td>
</tr>
<tr>
<td>MCH</td>
<td>25.1(L)</td>
<td>27.6</td>
<td>27.6</td>
<td>28.0</td>
<td>27.9</td>
<td>27.5-33.2 pg</td>
</tr>
<tr>
<td>MCHC</td>
<td>32.5(L)</td>
<td>30.7(L)</td>
<td>30.8(L)</td>
<td>31.0</td>
<td>32.4(L)</td>
<td>33.4-35.5%</td>
</tr>
<tr>
<td>Basophil</td>
<td>0(L)</td>
<td>0(L)</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>0.2-1.2 %</td>
</tr>
<tr>
<td>Eosinophil</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>0-4%</td>
</tr>
<tr>
<td>Rod Neutrophils</td>
<td>0(L)</td>
<td>0(L)</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>3.0-5.0 %</td>
</tr>
<tr>
<td>Neutrophils segment</td>
<td>90(H)</td>
<td>92(H)</td>
<td>91(H)</td>
<td>-</td>
<td>81(H)</td>
<td>40-70%</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>8(L)</td>
<td>3(L)</td>
<td>4(L)</td>
<td>-</td>
<td>11(L)</td>
<td>22.0-44.0 %</td>
</tr>
<tr>
<td>Albumin</td>
<td>-</td>
<td>1.90(L)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3.4-5.0 g/dL</td>
</tr>
<tr>
<td>Ig E</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>107.3</td>
<td></td>
<td>0-387.0 IU/mL</td>
</tr>
<tr>
<td>Anti HSV IgG</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>54.30</td>
<td></td>
<td>non-reactive&lt; 9,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>reactive &gt;11</td>
</tr>
<tr>
<td>CD4</td>
<td>16 (L)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>410-1590 cell/μL</td>
</tr>
<tr>
<td>Yeast (culture)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3+</td>
<td>-</td>
<td>-</td>
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</table>
HIV Wasting Syndrome causes progressive damage to cells in immune system, particularly CD4+ T-lymphocytes, and hematological abnormalities. Normal counts of CD4+ cells in healthy people is 500-1500 cells/mm$^3$ while HIV-infected people will experience a slow decline in their CD4+ cell counts and generally opportunistic infections will begin when the CD4+ cell count is 350 cells/mm$^3$ or lower. In this patient, there’s a decrease in her CD4+ cell counts down to 16 cells/µL, hence this patient was susceptible to infection.$^{12,13,14}$ Hematologic abnormalities in HIV-patients like low blood cell counts, or cytopenia including anemia, leukopenia, and thrombocytopenia were caused by mutiple factors and associated with advanced stage of HIV.$^{15}$ Anemia of inflammation and chronic disease or known as AI/ACD occurs in patients with chronic or inflammatory infections.

**Figure 3.** (a) Lips; no crusts (b)(c)(d) dorsum, lateral of the tongue; thinning white plaque (e)(f) upper and lower labial mucosa improving.

**Figure 4.** (a) Lips have improved (b)(c)(d) white plaque on the dorsum, the lateral tongue has improved (e)(f) upper and lower labial mucosa has healed.

**Discussion**

HIV Wasting Syndrome causes progressive damage to cells in immune system, particularly CD4+ T-lymphocytes, and hematological abnormalities. Normal counts of CD4+ cells in healthy people is 500-1500 cells/mm$^3$ while HIV-infected people will experience a slow decline in their CD4+ cell counts and generally opportunistic infections will begin when the CD4+ cell count is 350 cells/mm$^3$ or lower. In this patient, there’s a decrease in her CD4+ cell counts down to 16 cells/µL, hence this patient was susceptible to infection.$^{12,13,14}$ Hematologic abnormalities in HIV-patients like low blood cell counts, or cytopenia including anemia, leukopenia, and thrombocytopenia were caused by mutiple factors and associated with advanced stage of HIV.$^{15}$ Anemia of inflammation and chronic disease or known as AI/ACD occurs in patients with chronic or inflammatory infections.
This disease could be caused by rheumatoid arthritis, ulcerative colitis, Crohn’s disease and Hodgkin's lymphoma. This chronic anemia is characterized by iron deficiency for erythropoiesis but showed normal or increased iron reserves. This occurs because the synthesis of inflammatory agents such as cytokine IL-6 by macrophages that stimulates the synthesis of hepcidin by the liver. Increased levels of hepcidin cause iron retention in macrophages instead of being released to transferrin to be delivered to erythroblasts. Hepcidin also decreases iron delivery from erythrocytes to plasma, which also reduces iron availability. This patient has inflammatory anemia caused by tuberculosis and aggravated by hemolytic anemia. The decreases in hematologic stats increases the risk for developing candidiasis, and susceptibility to other infections such as HSV.

In this case, oral manifestations was found and diagnosed as herpetic stomatitis (Fig. 1e, 1f) and oral candidiasis. We diagnosed stomatitis herpetica based on clinical examination showed in the form of irregular shape ulcers collection coated with a yellowish membrane on the upper and lower labial mucosa. The anti-HSV IgG examination also showed reactive signaling positive for HSV-1. This occurs because in HIV/AIDS patients, the body's defenses declines and caused opportunistic agents such as Candida and HSV-1 to be pathogens. The interaction between HIV and HSV-1 is synergistic and can influence each other. In HIV patients, impaired immunity can cause reactivation of HSV-1, arise severe clinical symptoms and in some cases can be life threatening. On the other hand, HSV-1 infection in a person can increase susceptibility to HIV infection. HSV-1 also has the potential to interact with HIV and trigger HIV reactivation and accelerate the development of HIV disease itself. In HIV patients there’s pathological change, mainly the malfunction of CD8+ T-cells and CD4+ dysfunction, causing HSV-1 reactivation. T-cells could act as a portal of entry for HIV and could facilitate acquisition of HIV. HSV-1 and HIV could also infect the same cell, and this co-infection can produce a pseudo type particle (HSV enveloped virion) containing the HIV genome. Replication of the herpes virus in HIV-infected patients gave clinical features such as recurrent HSV-1 lesions but can be treated with antiretroviral drugs which induced recovery of the patient's immune system.

Oral candidiasis occur in about more than 90% of patients with HIV/AIDS and the infection is an early manifestation and important marker of disease’s progression towards AIDS. Clinical manifestation of oral candidiasis in HIV/AIDS patients is white pseudomembranes that can be removed, leaving erythematous areas, and painful. Generally they are found in the cheek, tongue, and soft palate. Pseudomembranous candidiasis is the most common form of candidiasis in AIDS patients. In this case’s patient, there are white pseudomembranes in almost the whole oral cavities, such as buccal mucosa, dorsal surface of the tongue, and palate.

The mechanism between oral candidiasis and HIV begins with morphological changes in the form of blastoconidia and hyphae through tissue invasion, and it is influenced by environmental factors. HIV damages the immune system, particularly CD4+. Oral candidiasis triggers the receptors in CD4+ cells, macrophages, monocytes, and dendritic cells can induce AIDS. Th-17 cells, which act as mucosal immune protection against C. albicans, are impaired in people with HIV. Dendritic cells display immature phenotypes and damaged antigen images. Naive CD4+ T-cells and differentiated CD4+ T-cells, including Th-17 cells, fail to regulate the mucosal expression of IL-17, IL-22, and S100a8 (antimicrobial agent) as a defense against oral C. albicans infection. IL-17 activation induces antimicrobial production, such as β-defensins, cathelicidins, and S100 proteins by keratinocytes. Neutrophils have the ability to control and eliminate fungal infections by both intracellular and extracellular mechanisms. Intracellularly, phagocytosis kills fungus with reactive oxidative metabolites and granule products, such as lactoferrin, defensin myeloperoxidase, and azurophil. Extracellularly, fungus is eliminated either by neutrophil degranulation with the release of antimicrobial proteins or by neutrophil extracellular traps, which consist of chromatin fiber tissues that contain antimicrobial proteins.

In this report, the patient’s diagnosis is Stage IV HIV/AIDS with Wasting Syndrome. Laboratory tests showed decrease of hemoglobin, hematocrit, erythrocytes and it showed hypochromic anemia from MCHC examination results. The anemia is also characterized by
malnutrition with low albumin, body mass index and decreased CD4+ count which develops the risk of AIDS-related anemia. In this patient the inflammatory anemia is aggravated by hemolytic anemia. Inflammatory anemia began with normocytic-normochromic anemia, and when the disease got heavier it became hypochromic anemia. These leucocytes, lymphocytes, and basophils play a role in regulating the immune system and in this patient, all values are below normal which causing the patient susceptible to opportunistic infections. Albumin levels are associated with nutritional status, with normal albumin levels being 3.4-5.0 g/dL. However, the albumin value in this patient is low at 1.9 g/dL, thus, the patient can be said to be malnourished. The levels of albumin was used as a nutritional status standard because of their ease of measurement, but in the study conducted by Jean Claude et al., the sensitivity and specificity of albumin levels for malnutrition in HIV patients have not been established yet because albumin levels were also connected to other many clinical manifestations. In HIV-patients with low albumin levels, it shows a catabolic state of end-stage disease. Catabolism causes weight loss despite adequate energy and protein intake.

Nutrition and HIV/AIDS are interconnected. HIV causes immune damage that triggered malnutrition which caused rapid development of HIV infection towards the AIDS phase. One of the factor causing malnutrition is the lack of appetite, due to swallowing food difficulty caused by infections such as oral and oropharyngeal candidiasis. Prolonged malnutrition could be accompanied by deficiencies and immunological abnormalities resulting in a decreases in the number of macrophages, erythrocytes, natural killer (NK) cells and suppressed the total lymphocyte counts. In addition, drugs or any substances such as cigarettes, chemotherapy agents, zidovudine (AZT), heavy metal ions (mercury ions) produced free radicals in the body causing oxidative stress. The malnutrition and oxidative stress caused disruption in the immune system so that the patient became susceptible to infection. The main challenge of HIV became even more problematic since HIV was accompanied by oral candidiasis which could aggravate and accelerate the development of HIV infection, therefore it is important to treat oral candidiasis in order to gain better nutrition, which in turn can improve quality of life and better survival rate in HIV-infected patients. Clinically, candidiasis in this patient has improved despite experiencing a recovery slowdown in her nutrition status.

Malnutrition will increase the risk of tuberculosis. In tuberculosis patients, often found malaise symptom, they are anorexia, decreased appetite, weight loss, and night sweats. Decreased appetite occur from infection with mycobacterium tuberculosis which activates macrophages by IFN-γ and the production of endogenous pyrogens IL-1, IL-4, IL-6, TNF-α. Endogenous pyrogens circulate systemically and reaction to the hypothalamus. The effects of endogenous pyrogen cytokines on the hypothalamus cause prostaglandin production. Prostaglandin restores the brain cortex which causes increased leptin production to cause appetite suppression. This patient is undergoing anti-tuberculosis treatment which is slowly improving. Patient in this study has signed the informed consent documents which agree this case to be published.

Conclusion

HIV wasting syndrome in immunocompromised patients stimulate opportunistic infections such as oral candidiasis, herpetic stomatitis and tuberculosis. The proper management of oral lesions along with adequate nutrition is closely related to the improvement of oral conditions which in turn improves systemic conditions.

Conflict of Interest

The authors declare that there are no conflict of interest.

References


