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Correlation of Oral Hairy Leukoplakia, HAART and CD4+ in HIV-infected Pediatric Patients at UPIPI Soetomo Hospital Surabaya, Indonesia

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Abstract

Indonesian pediatric population infected with Human Immunodeficiency Virus (HIV) has increased drastically in recent years. The number of new infection among infants and children (< 4 years) multiplied in 2010-2016. However, since healthcare and laboratory facilities are scarce to many areas in the country, many children living with HIV are still left undiagnosed and unaware of their status. Oral Hairy Leukoplakia (OHL) as HIV-associated oral manifestation can be a useful marker in making presumptive diagnosis and prediction of the course of HIV. However, Indonesian study on OHL in pediatric HIV-infected population is still lacking, thus the study aim was to evaluate the correlation of OHL based on the use of Highly Active Antiretroviral Therapy (HAART) and immunosuppression degree among HIV-infected Indonesian pediatric patient. HIV-infected pediatric patients attending the outpatient clinic, Intermediate Care and Infectious Disease Centre (UPIPI), Dr. Soetomo Hospital between June-October 2017 were examined intraorally for the presence of OHL. Other relevant data were collected from interview to parents/guardians and patients' medical records for further analysis. Four (14.29%) patients showed to have OHL at examination and were severely immunosuppressed (mean CD4 counts= 74cells/mm³). Statistical analysis using chi-square test confirms a significant correlation between OHL and HAART ($P=0.027$ $P<0.05$). Correlation between OHL and degree of immunosuppression have very significant correlation ($P=0.003$ $P<0.01$). The presence of OHL may indicate a high probability that infected children are in declining CD4+ counts to AIDS or experiencing treatment failure. Through immediate follow up, mortality can be prevented.

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Introduction

Indonesia is among Asia-Pacific nations with the highest number of people infected with Human Immunodeficiency Virus (HIV) (620.000 people or equivalent to 12.2% Asia-Pacific Human Immunodeficiency Virus / Acquired

Immunodeficiency Syndrome (HIV/AIDS) population). Despite national efforts to lower the rate of transmission, the number of infection keeps growing at an alarming rate, let alone the number of AIDS-related deaths also showed a drastic increase of 68% between 2010-2016.¹

Considering Indonesia's geographical landscapes that are scattered across large bodies of water, access to healthcare and laboratory facilities is indeed scarce in many areas. Consequently, majority (65%) of Indonesian HIV-infected patient are still unaware of their HIV status and continue to transmit the infection to a larger population, with no exception to housewives.^{1,2} The increasing number of HIV-infected housewives brings direct impact to the

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number of infected infants and children. The number of new infected infants and children (< 4 years) born from HIV-positive mothers multiplied drastically by >230% in 2010-2016.²

This upsetting condition is worsened by the poor accessibility of Highly Active Antiretroviral Therapy (HAART) to pregnant mothers. Despite government regulation since 2004 has made the provision of HAART for free. HAART free of charge does not mean easy and free access. HAART coverage to HIV-infected pregnant mothers was still extremely low by the end of 2016 (14%).^{3,4}

The aforementioned conditions urge further studies on HIV markers on these infected children to aid in diagnosis and predict the course of the disease in case of no laboratory facilities are available to run confirmatory tests. As immunity of infants and children are very vulnerable, prompt diagnosis and prediction of the course of HIV disease can tremendously increase their life expectancy. HIV opportunistic oral manifestation such as Oral Hairy Leukoplakia (OHL) has been strongly associated with HIV infection and very low CD4+ counts (CD4+ counts <200 cells/m³). However, to date, published study of OHL on Indonesian pediatric population is still absent.⁵⁻⁹

The aim of this study was to evaluate the correlation of OHL with the use of HAART and degree of immunosuppression, particularly among HIV-infected pediatric patients admitted to Intermediate Care and Infectious Disease Centre (UPIPI), Dr. Soetomo Hospital, Surabaya.

Materials and methods

Ethical clearance

The study protocol was reviewed and approved by Ethics Committee of Dr. Soetomo Hospital (No: 326/Panke.KKE/V/2017) and Health Research Ethical Clearance Commission Universitas Airlangga (No: 137/HRECC.FODM/VIII/2017).

Patient selection and examination

This was a cross-sectional study carried out among pediatric HIV-infected patients attending outpatient clinic at Intermediate Care and Infectious Disease Center (UPIPI), Dr. Soetomo Hospital between June-October 2017.

Children younger than 18 years with confirmed serology for HIV infection were included. The age range follows the child age limit that is defined by the Indonesian legal system.¹⁰

Eligible patients, upon approval from parents/guardian by written consent, were examined by oral medicine specialist. Intraoral examination was performed for each patient using disposable dental mirrors and sterile gauze pads under adequate lighting. Identification of OHL was recorded on data collection sheet.

Studied parameters

Other relevant data including age, gender, HIV transmission routes, use of HAART, and laboratory results on CD4 values were obtained from questionnaire-guided interview to parents/guardians and patients' medical records. The latter were restricted to the most recent laboratory data; maximum within 6 months from the date of intraoral examination. This time range corresponds to the Indonesian Ministry of Health guideline on the regulation of CD4+ counts monitoring.¹¹

Age-related CD4+ counts (% CD4+ or CD4+ absolute counts) became the basis to determine patients' degree of immunosuppression. Patients were categorized into 4 stages of immunosuppression: no immunosuppression, mild immunosuppression, advanced immunosuppression, and severe immunosuppression following the World Health Organization (WHO) immunological classification.¹²

Definitions

OHL was identified based on its clinical features as fine white small linear patches or corrugated lesions on lateral borders of the tongue that do not scrape off (Figure 1). These features are in reference to the WHO and European Community Clearinghouse's (ECC) diagnostic criteria.^{12,13}

Degree of immunosuppression was assigned to each patient based on the latest CD4+ counts (within 6 months period) according to WHO criteria (Table 1).¹²

HIV-associated immunodeficiency	Age-related CD4 values			
	<11 months (CD4%)	12-35 months (CD4%)	36-59 months (CD4 %)	>5 years (absolute number per mm ³)
None	>35	>30	>25	>500
Mild	30-35	25-30	20-25	350-499
Advanced	25-29	20-24	15-19	200-349
Severe	<25	<20	<15	<200

Table 1. WHO immunological classification for established HIV infection¹²

Statistical analysis

The relationship between the occurrence of OHL and other variables (use of HAART and immunosuppression degree) were compared using chi-square test by Statistical Package for the Social Sciences (SPSS) 17.0 software for windows 8.1 by SPSS Inc, Chicago, United State. P-values ≤0.05 and ≤0.01 were considered significant and very significant respectively.

Results

Characteristics of the study population

A total of 47 pediatric HIV-infected patients were screened between June-October 2017. Nineteen patients were excluded from the study due to; parental rejections to provide consent, patients' uncooperation and physical resistant during examination, and the absence of recent CD4+ counts on patients' medical record (within 6 months from date of the oral examination). Many patients registered at UPIPI, Dr. Soetomo Hospital did not routinely visit the center for control and get tested for CD4+ counts, unless they experienced symptoms. The actual number of pediatric HIV-infected patients was much higher than the number of patients successfully screened. Therefore, a total of 28 patients were enrolled into this study.



Figure 1. Nine Years Old Male Patient with Latest CD4 Value <100 cells/mm³ (Suspected Immunological Failure).

Out of 28 patients, 4 (14.29%) patients were presented with OHL at the time of examination. Patients with OHL ranged from 6-10 years (mean age = 8.5 years), with equal number of males (n=2) and females (n=2). Two patients were on HAART, while the other two were HAART naïve. All patients were confirmed to be vertically infected from their mothers and classified into severe immunosuppression stage based on their CD4+ counts (mean CD4+ counts= 74cells/mm³).

	No. of Patients		Chi-square	P value
	OHL present	OHL absent		
Total	4	24		
HAART				
Yes	2 (7.14%)	22 (78.57%)	4.861	0.027*
No	2 (7.14%)	2 (7.14%)		
Degree of immunosuppression				
No	-	18 (64.29%)	14	0.003**
Mild	-	3 (10.71%)		
Advanced	-	-		
Severe	4 (14.29%)	3 (10.71%)		

Table 2. Statistical Analysis of Individual Parameters in 28 Pediatric HIV-Infected Patients. *statistically significant (P value ≤0.05). **very statistically significant (P value ≤0.01).

Correlation of OHL to HAART and degree of immunosuppression

Data were further analyzed to confirm the significance of HAART and degree of immunosuppression in the occurrence of OHL.

Statistical analysis was done using chi-square tests and the results are shown in Table 2. Use of HAART is shown to have significant predictive values in the occurrence of OHL ($P<0.05$). The relationship is even stronger for degree of immunosuppression ($P<0.01$). OHL in this study were confined only to patients with severe immunosuppression.

Discussion

HIV progression to AIDS in infants and children may be extremely rapid. This is mainly due to their immature immune system. Neonatal immune cells are not capable of mounting the same immune response to HIV infection as in adults, contributing to an immunologically tolerogenic and permissive environment for HIV to replicate and cause profound depletion of CD4.¹⁴ In many cases, HIV-associated oral lesions are the first clinical symptoms of the infection, highlighting the importance of these lesions to diagnose and predict the course of the disease.^{6,7} OHL is considered as oral lesion strongly associated with HIV infection, although its presentation is rare in HIV-infected pediatric patients.^{15,16}

The prevalence of OHL in present study is relatively high; much higher than other studies conducted in Brazil (1.3%) and Tanzania (3.9%).^{17,18} These disparities may be due to the different characteristics among the study populations (HAART regimen, adherence and duration of HAART use, HIV transmission routes, stage of HIV disease and degree of immunosuppression, nutritional status, etc.) as well as the respective cultural and geographical settings.^{5,15}

OHL presentations were significantly lower in patients on HAART compare to HAART-naïve. HAART can excellently suppress the replication of HIV, giving chance for the immune system to reconstitute.¹⁹ However, despite HAART being administered, HIV-associated oral lesions can still occur in some patients, as also clearly seen in two patients with OHL in this study. Immune status of both patients prior the start of HAART and their adherence to the HAART became important factors in explaining the presence of OHL. Study of Wilson and Sereti observed that although HAART successfully suppress viral replication, some patients initiating HAART may experience immunologic failure.²⁰

Immunologic failure is a condition when the immune system is not capable of doing recovery, despite low or even undetectable viral load. It is estimated that 50% of HAART treated patients may fail to reconstitute their CD4+ counts to level above 500 cells/mm³, and up to 16% may not achieve CD4+ counts above 200 cells/mm³, even after long term therapy.^{19,20} The risk of suffering immunologic failure is very high for HIV-infected individuals having CD4+ counts less than 100 cells/mm³ at the start of HAART as also seen in one patient's medical record.²¹ Furthermore, optimal adherence to HAART is critical if therapeutic effects of the drugs are to be attained. Both patients presented with OHL and undergoing HAART were reported to have fluctuate HAART adherence based on their medical records.^{22,23}

Assessment of immunosuppression degree showed a very significant correlation with the prevalence of OHL. All patients presented with OHL were in severe immunosuppression /AIDS. This finding is consistent with studies in Ghana, Lagos and India in which OHL were found with mean CD4 counts <200 cells/mm³.²⁴⁻²⁵ However, according to other studies, OHL and others oral manifestation could also be present in patients with CD4 counts 200-500 cells/mm³ (advanced to mild immunosuppression, or even >500 cells/mm³ (no immunosuppression).²⁷⁻²⁹

Therefore, although it is not absolute, OHL may show a high indication that HIV-infected children are in declining CD4 stage (entering AIDS) or experiencing treatment failure, thus immediate follow up is critical.

Conclusions

The presence of OHL may indicate a high probability that infected children are in declining CD4+ counts to AIDS or experiencing treatment failure. Through immediate follow up, mortality can be prevented. Further studies are required.

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Declaration of Interest

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