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The use of urine lipoarabinomannan for establishing pulmonary TB in HIV patient: case report and systematic review

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ABSTRACT

Introduction: Indonesia is still the country that provides the second-largest estimated number of TB cases worldwide. Several patients had TB with HIV-positive. HIV-positive patients with symptoms suggestive of pulmonary tuberculosis often difficult to produce sputum of sufficient quality. Lateral flow lipoarabinomannan examination with urine specimens is expected to be easy, inexpensive, fast, and accurate point-of-care testing. The aim of this research was to assess the sensitivity and specificity of the lateral flow method in detecting lipoarabinomannan (LAM) from urine specimens in HIV-positive patients with suspected pulmonary tuberculosis. Sputum cultures were utilised as a reference standard.

Case Description: A 21-year-old male patient came to the clinic complaining of a cough that had not subsided since the previous month. Cough felt throughout the day with a little white phlegm. The patient admitted to having high-risk sexual behavior and had been tested positive for HIV but had not started antiretroviral therapy. The laboratory examination results showed that the leukocyte count was 3600/mm³ and the radiological examination revealed a chest X-ray within normal limits. The patient had been tested for sputum smears with negative results but was still advised to start TB treatment. The patient has not started treatment because he feels that his sputum smear test results are negative. Currently, the patient is not willing to have his sputum checked again. The polyclinic doctor knows the lipoarabinomannan (LAM) examination that uses urine specimens to diagnose TB but does not yet know its effectiveness for this patient.

Conclusion: In this case report, the patient was unwilling to do a diagnostic test related to the TB. The systematic review was that the Alere Determine™ TB LAM Ag may not be clinically applicable for diagnosing tuberculosis infection in patients living with HIV at this time. However, Fujifilm SILVAMP TB LAM® could be regarded as a supplementary tool to the established diagnostic protocol for tuberculosis in HIV-positive patients.

Keywords: HIV positive, lipoarabinomannan, tuberculosis diagnosis.

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INTRODUCTION

Indonesia is currently still the country that provides the second-largest estimated TB cases worldwide. Several patient had TB with HIV-positive. In 2019, the estimated TB incidence in Indonesia was 845.000 people with 19.000 of them in HIV positive patients. The number of deaths from HIV TB coinfectd patients is estimated at 4.700 people every year.¹

A study in Thailand about HIV-infected patients with tuberculosis revealed that positive HAART patients had a 96.1%, 94.0%, and 87.7% probability of survival at one, two, and three years after the diagnosis of TB infection. The lower survival rate was established in several

patients who did not receive HAART (44.4%, 19.2%, and 9.3%, respectively).² Approximately 84 (20.9%) of the 402 adult patients who were followed for 96 months and were co-infected with tuberculosis and HIV perished, according to the other systematic review; 318 (79.1%) were censored. A total of 29 fatalities (34.5% or 29 out of 84) occurred among co-infected patients during the first five months following the initial dose of anti-TB therapy. The duration of follow-up for the study participants was 6920 person-months. Additionally, the data indicates that the combined incidence rate for adult patients co-infected with tuberculosis and HIV was 12.1 per 1000 person-months, with a 95% confidence interval ranging

from 9.77 to 14.98. 85%, 88%, and 91% were the respective survival rates at 5, 15, and 25 months after treatment initiation for tuberculosis.³

The approach to diagnosing TB in patients with HIV infection is not different from that in patients without HIV infection. The symptoms, chest X-ray, and AFB sputum are still the main modalities. However, in patients with HIV infection, AFB sputum is often negative.⁴ Seventy-six to eighty-five percent of pulmonary tuberculosis cases involving sputum devoid of smears occur in HIV-positive patients across multiple institutions in Indonesia.⁵ Individuals who test positive for HIV but have negative sputum smears have a higher mortality risk during or

prior to the diagnostic procedure than those who test negative for HIV. The timely identification of smear-negative pulmonary tuberculosis in individuals living with HIV and AIDS (PLWHA) has a positive effect on mortality rates. Lipoarabinomannan antigen (LAM), an intracellular lipopolysaccharide presents in the cell wall of mycobacteria, functions as a potent virulence factor, inciting an immune response from the host and contributing to the development of tuberculosis (TB) infection. According to research, LAM antigen has been identified in sputum, serum, and urine samples. Urine is superior to sputum for examination purposes due to the simplicity of procuring and storing specimens, as well as the reduced risk of infection associated with specimen collection.¹ This study aims to determine the sensitivity and specificity of lipoarabinomannan urine examination for the diagnosis of pulmonary tuberculosis infection in HIV-positive patients.

CASE DESCRIPTION

A 21-year-old male patient came to the clinic complaining of cough that had not subsided since the previous month. Cough felt throughout the day with a little white phlegm. The patient admitted to having high-risk sexual behavior and had been tested positive for HIV but had not started antiretroviral therapy. The laboratory examination results showed that the leukocyte count was 3600/mm3 and the radiological examination revealed a chest X-ray within normal limits. The patient had been tested for sputum smears with negative results, but was still advised to start TB treatment. The patient has not started treatment because he feels that his sputum smear test results are negative.

Currently the patient is not willing to have his sputum checked again. The polyclinic doctor is aware of the lipoarabinomannan (LAM) examination that uses urine specimens to diagnose TB but does not yet know its effectiveness for this patient.

DISCUSSION

The detection of lipoarabinomannan (LAM) in urine specimens using the lateral flow method provides hope for addressing challenges in the diagnostic process of tuberculosis infection, both pulmonary and extrapulmonary, in people with HIV and AIDS, especially those who find it difficult or even unable to produce sputum. The World Health Organization has driven efforts to create point-of-care testing for tuberculosis that is easy, low cost, quick to get results, and has high accuracy.^{6,7}

To assist in the diagnosis of active tuberculosis in the following circumstances, including inpatient settings: the urine LF-LAM test is applicable under the following conditions: TB-symptomatic adults, adolescents, and children who are HIV-positive and have advanced HIV disease, are seriously weak, or have a CD4 cell count below 200 cells/mm3 regardless of TB symptoms. The World Health Organization recommends that outpatient settings utilize LF-LAM to diagnose active tuberculosis in HIV-positive adults, adolescents, and children who exhibit TB signs and symptoms (pulmonary or extrapulmonary), are gravely ill, or have a CD4 cell count of less than 100 cells/mm3 despite TB symptoms.⁷

This investigation uncovered two manuscripts containing sensitivity and specificity analyses that were pertinent to the subject matter (Table 1). Following a comprehensive review of the literature,

Bjerrum et al. performed a systematic analysis of 15 primary research articles with the objective of evaluating the precision of Alere Determine™ TB LAM Ag. Patients over the age of 15 who were HIV-positive and exhibited symptoms suggestive of tuberculosis (cough, fever, weight loss, and night sweating) or who disregarded such symptoms were the subjects of the third study. 15 studies involving 6,814 participants were examined in this article; of these, 1,761 (or 26%) were diagnosed with tuberculosis.⁸ The accuracy of the LF LAM in diagnosing tuberculosis in subjects exhibiting symptoms and signs suggestive of tuberculosis was evaluated in eight patients across these fifteen studies, which involved a total of 3449 subjects, of which 1277 (37%) had tuberculosis. The pooled sensitivity and specificity values for the LF LAM were 42% (31% to 55%) and 91% (85% to 95%), respectively.⁷ Four studies assessed patient subjects outpatient treatment involving 1196 subjects, 409 (34%) with tuberculosis, with pooled sensitivity and specificity (95% Credible Interval) values of 29% (17% to 47%) and 96% (91% to 99%). five studies that assessed the accuracy of LF LAM based on CD4 count levels, it was seen that pooled sensitivity increased with increasing immunodeficiency, from 16% (8% to 31%) in subjects with CD4 counts >200 cells/μL; to 24% (14% to 38%) in subjects with CD4 counts between 101 to. 199 cells/μL; and 54% (38% to 69%) in subjects with a CD4 count ≤100 cells/μL.⁸ All studies used Alere Determine™ TB LAM Ag. The patient in this case report is an HIV positive patient in an outpatient polyclinic with a weakened immune system, which can be assumed to be not severe. The LF-LAM is a simple diagnostic modality, making it suitable for point-of-care testing in the outpatient setting. However, with

Table 1. Basic characteristic of the studies

Author	Study Design	Total Population	Specimen	Index Test	Reference Test	Key Results
Bjerrum S et al ⁸	Systematic Review	6814 subjects from 15 studies	Fresh urine	Alere Determine™ TB LAM Ag	Culture and/or nucleic acid amplification test (NAAT)	Pooled sensitivity and specificity
Broger T et al ⁹	Primary Cross-Sectional Study	1595 subjects	Frozen urine	Fujifilm SILVAMP-LAM Alere Determine™ TB LAM Ag	Culture and NAAT	Sensitivity and specificity

the overall pooled sensitivity and pooled sensitivity values in the outpatient setting being unsatisfactory (still below the standard sensitivity value set by WHO for active tuberculosis diagnostics of 65%), it is possible that the LF-LAM has not been able to change the management of these patients. However, LF-LAM can be recommended as a diagnostic add-on in HIV positive patients with more severe symptoms and immune suppression

Regarding to the Broger at al., the researchers used frozen urine specimens stored in Biobanks from five separate independent studies. According to the five studies testing the accuracy of the Fujifilm SILVAMP TB LAM conducted between 2012 and 2012. 2017. Researchers tested Fujifilm SILVAMP TB LAM and Alere Determine™ TB LAM Ag using urine specimens stored in Biobanks. Based on exclusion criteria, 1595 subjects were obtained from the five studies. In detecting active tuberculosis, SILVAMP-LAM sensitivity was 70.7% (95% CI: 59.0%-80.8%) and LF-LAM sensitivity 34.9% (95% CI: 19.5%-50.9%).⁸ In outpatients, SILVAMP-LAM sensitivity was 70.6% (95% CI: 45.3%-89.6%) and LF-LAM sensitivity of 27.9% (95% CI: 5.4%-62.7%). Sensitivity was increased in the group with a low CD4 count and decreased in the group with a higher CD4 count. 8 In subjects with a CD4 count ≤ 100 cells / μL , SILVAMP-LAM sensitivity was 87.1% (95% CI: 79.3%-93.6%) and LF-LAM sensitivity was 56.0% (95% CI: 43.9%-64.9%). Specificity of SILVAMP-LAM and LF-LAM were 90.9% (95% CI: 87.2%-93.7%) and 95.3% (95% CI: 92.2%-97.7%), respectively. The specificity of SILVAMP-LAM was lower in the group with a CD4 count ≤ 100 cells/ μL , 80.5% (95% CI: 69.8%-89.7%), compared to the group with the higher CD4 count.⁹

The patient in this case report is an HIV positive patient in an outpatient polyclinic with a weakened immune system which can be assumed to be not severe. SILVAMP-LAM and LF-LAM are simple diagnostic modalities, making them suitable for point-of-care testing in the outpatient setting. Currently SILVAMP-LAM and LF-LAM

are available in Indonesia with relatively lower costs but are not widely used and are still limited, making it more difficult to reach. Data on the prevalence of TB in HIV positive is quite good in Indonesia. Because the sensitivity value of LF-LAM in the outpatient setting is unsatisfactory (still below the standard sensitivity value set by WHO for active tuberculosis diagnostics of 65%), it is possible that the LF-LAM cannot change the management of these patients. However, LF-LAM can be recommended as a diagnostic add-on in HIV-positive patients with more severe symptoms and immune suppression. Different things can be seen in SILVAMP-LAM, with a sensitivity value in the outpatient setting that has exceeded the standards set by WHO, causing SILVAMP-LAM to possibly change the diagnostic management of HIV positive outpatients who do not produce sputum, even though currently in Indonesia could not be done due to limited availability of tools.

CONCLUSION

In this case report, the patient was a 21-year-old HIV-positive male in an outpatient clinical situation who presented symptoms suggestive of tuberculosis but had difficulty producing sufficient quality sputum specimens. Examination with urine specimens is expected to help diagnostic management in this patient. Based on the results of the critical review, we concluded that for the clinical situation appropriate to the patient in this case report, Alere Determine™ TB LAM Ag had a sensitivity of 29% (95% CI: 17% to 47%) and 27.9% (95% CI: 5.4% to 62.7%) cannot be used in the diagnostic management of pulmonary tuberculosis infection. On the other hand, With a sensitivity of 70.6% (95% CI: 45.3% to 89.6%), the Fujifilm SILVAMP TB LAM® may be suggested as an adjunctive diagnostic protocol in ambulatory clinical settings for tuberculosis infection in patients who are HIV-positive. Additionally, we acknowledge the necessity for additional investigation to evaluate the precision of Fujifilm SILVAMP TB LAM® and Alere Determine™ TB LAM Ag in clinical scenarios specific to Indonesia.

DISCLOSURES

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This study did not receive any funding/grant.

Conflict of Interest

The authors disclose that there is no potential conflict of interest.

Author Contribution

Djiwa Margono (DM) and Pranudiah Yulianti Ningtias (PYN) were writing the original draft, visualization, project, and investigation, Ardiana Kusumaningrum (AK) as a supervision, and formal analysis Dimas Seto Prasetyo (DSP) as a supervision, and editing.

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