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CASE SERIES

A Breakthrough in the Challenges of Tuberculosis Diagnosis: Lateral Flow Urine Lipoarabinomannan (LAM) Assay for the Diagnosis of Active Tuberculosis in a Subset of Human Immuno Deficiency Virus (HIV) Patients at Hawassa University Comprehensive Specialized Hospital, Hawassa, Ethiopia

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Background: Tuberculosis is commonly detected late or not at all in HIV-positive people. Rapid and sensitive molecular tests like Gene X-pert have recently become available to replace or supplement existing conventional tests for detecting tuberculosis, and the World Health Organization (WHO) recommends that these rapid techniques be used as the initial diagnostic test for tuberculosis to avoid delays in starting appropriate treatment. The lipoarabinomannan was approved by the national ministry of health in August 2021 for the detection of active tuberculosis in specified groups.

Case Summary: It is not uncommon for tuberculosis to be difficult to diagnose in this population, and we believe that our experiences with urine lipoarabinomannan for the detection of active tuberculosis will benefit other clinicians and, ultimately, patients. We discussed the experiences of two human immunodeficiency virus (HIV) patients with putative active tuberculosis, whose tuberculosis workups were negative by conventional methods, including gene expert but found to be positive by urine lipoarabinomannan and who were started on anti-tuberculosis medicines and improved. They are now in a good condition and are taking their medications regularly without any problems.

Conclusion: Ending the suffering of HIV patients necessitates lobbying for more accurate tuberculosis diagnosis. The urine Lipoarabinomannan (LAM) assay will address the shortcomings of traditional sputum-based diagnostic tests including sputum Acid Fast Bacilli (AFB) and Gene X-pert, making it a credible alternative for diagnosing tuberculosis in people with HIV. The results of this case series demonstrated that TB LAM is a milestone for the difficulties in TB diagnosis in HIV patients. As of now, the national guideline only suggests urine LAM for HIV patients who fulfill the set criteria. We recommend the stakeholders to increase the availability, and extrapolate the recommendation to other populations including non-HIV patients.

Keywords: urine lipoarabinomannan, diagnosis of tuberculosis, human immuno deficiency virus

Introduction

Tuberculosis (TB) continues to be a leading cause of morbidity and mortality around the world.[1,2] Owing to an increase in TB notifications in recent decades and a significant rise in the use of WHO-recommended molecular diagnostics (WRDs), national TB programs miss 2.9 million of the estimated 10 million people who get TB each year.[2,3]

Ethiopia is still one of the world's 30 countries with the highest TB burden, with an estimated TB incidence rate of 140/100,000 people (157,000 people per year) and 21,000 TB fatalities (19/100,000 people) in 2018. From 421 per

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100,000 in 2000 to 140 per 100,000 in 2019, the incidence of tuberculosis has decreased by an annual average of 8–9%. In the previous few decades, Ethiopia has also seen a decrease in tuberculosis mortality, though at a slower rate than incidence.[1,4]

The prevalence of TB/HIV co-infection in Ethiopia is 22%, according to a recently published systematic review and meta-analysis study. Additionally, there is a correlation between the high incidence of TB-HIV co-infection and the high prevalence of HIV/AIDS in the general population[5].

Rapid and sensitive molecular tests have recently become available to replace or supplement existing conventional tests for detecting tuberculosis and drug resistance, and the World Health Organization (WHO) recommends that these rapid techniques be used as the initial diagnostic test for tuberculosis detection and rifampicin (RIF) resistance to avoid delays in starting appropriate treatment.[6,7] These recommendations have been implemented recently by the national tuberculosis control program.[8] Some tuberculosis patients have urine excretion of lipoarabinomannan, a key cell wall component of M. tuberculosis that is heat stable.[9] Many mycobacteria rely on the virulence factor lipoarabinomannan (LAM), a significant mycobacterial cell wall lipoglycan that regulates the host immunological response.[10]

The urine LF-LAM assay is an immunocapture assay that detects the mycobacterial LAM antigen in urine and could be used as a point-of-care diagnostic for a subset of people with HIV who are presumed to be infected with active tuberculosis. Despite its low sensitivity, the assay can be utilized as a quick, bedside rule-in test for HIV-positive people, especially in emergency situations where a timely TB diagnosis is vital to the patient's survival. The Alere Determine TB LAM Ag is the only commercially available urine LAM test that has been approved by the World Health Organization. The presence of mycobacterial LAM antigen in the urine does not indicate treatment resistance.

The urine LF-LAM test can be used in the following circumstances:[4,7]

1. LF-LAM is recommended in inpatient settings to aid in the diagnosis of active tuberculosis in HIV-positive adults, adolescents, and children with TB signs and symptoms (pulmonary or extrapulmonary), who have advanced HIV disease or are seriously ill, or who have a CD4 cell count of less than 200 cells/mm3, regardless of TB signs and symptoms.
2. The World Health Organization recommends using LF-LAM in outpatient settings to help diagnose active tuberculosis in HIV-positive adults, adolescents, and children who have TB signs and symptoms (pulmonary or extrapulmonary); are seriously ill; or have a CD4 cell count of less than 100 cells/mm3 regardless of TB signs and symptoms.

All patients with signs and symptoms of pulmonary TB who are able to produce sputum should have at least one sputum specimen submitted for a molecular assay as part of their initial diagnostic test. This includes HIV-positive children and adolescents who are able to submit a sputum sample. Because lateral flow-LAM (LF-LAM) results are likely to be available before molecular test results, treatment decisions should be made based on the LF-LAM result while additional diagnostic tests are awaited. LF-LAM should be used in conjunction with other tests to supplement clinical judgment. It should not be used as a substitute or as a screening tool.[4–7]

In general, the World Health Organization recommends using urine LAM testing in addition to routine diagnostic tests for HIV-infected patients with signs and symptoms of pulmonary and/or extrapulmonary tuberculosis and CD4 >100 cells/microL, as well as for HIV-infected patients who are seriously ill (defined as respiratory rate >30/minute, temperature >39°C, heart rate >120/minute, and unable to walk unassisted) in regions with high rates of HIV and TB. The lipoarabinomannan was approved by the national ministry of health in August 2021 for the detection of active tuberculosis in specified groups.[4,7]

Ethical Approval

The patients granted informed consent for the publication of these case reports after we received approval from the Hawassa University Institutional Review Board (IRB).

Case Presentation

Case A

Patient A; This is a 40-year-old male patient who came with a non-productive cough for one month and a three-month history of unquantified but significant weight loss. He also had a history of losing his appetite. On initial presentation, he appeared to be chronically ill, and all of his vital signs were within normal limits. The man weighed 52 kilograms and stood 1.74 meters tall, with a BMI of 17.2 kilograms per square meter, indicating that he was underweight. The lymphoglandular system revealed 3 by 4 cm enlarged masses that were mobile, had no overlying skin color change, and were tender in the cervical areas bilaterally, as well as 2 by 3 cm enlarged masses that were soft in consistency, mobile, had no overlying skin color change, and were non-tender on the submental areas. Other findings in the abdomen were a palpable mass in the right upper quadrant, about 5 cm below the right costal border, indicating hepatomegaly, and a soft mass along the line of spleen expansion, suggesting splenomegaly. He was then probed for a possible TB diagnosis, despite the fact that all of the standard TB diagnostic tests were negative. However, as shown below, the abdominal ultrasonography and FNAC (fine needle aspiration cytology) both supported the tuberculosis diagnosis. Abdominal ultrasonography revealed calcified and hypoechoic micronodules in the liver and spleen, as well as numerous enlarged centrally necrotic intra-abdominal lymphadenopathies, indicating disseminated tuberculosis (likely resolving). A FNAC biopsy revealed bilateral cervical and submental lymphadenopathies, with a tuberculous abscess as the most likely diagnosis. He was then tested for retrovirus infection and was found to be positive. The CD4 cell count was 14 cells per millimeter squared. He was offered urine LAM for tuberculosis diagnosis, and the result was positive for TB LAM. He began antiTB treatment, and on the tenth day of treatment, he was started on highly active antiretroviral therapy (HAART) with Tenofovir+Lamivudine+Dolutegravir (TLD) as per the recommendation.[8,9] He is now on his 7th month and is apparently healthy, and taking his medication regularly. His weight also increased to 63 kilograms, with a BMI of 20.8, which is normal. The viral load was done 2 weeks back, and it was 800 copies, which is below the threshold for viral transmission (greater than 1000 copies).[8,11]

Case B

Patient B: The patient, a 27-year-old man, was just diagnosed with HIV/AIDS (3 months ago) after being tested for HIV serostatus following notification that his wife had tested positive for the virus at a nearby clinic. He has no complaints about anything else. All of the physical evidences were unremarkable. Except for the CD4 count, which was determined to be 77cells/mm3, all baseline examinations, including tuberculosis investigations using a sputum gene expert, were non-revealing, and he subsequently tested for TB LAM, which yielded a positive result. He was subsequently started on anti-TB as recommended, and after a month, he was started on HAART withTenofovir+Lamivudine+Dolutegravir (TLD).[11,12] He is using his medications without any problems so far, and the viral load will be sent on his six month of HAART initiation.[11]

Discussion

Despite recent advances in rapid diagnostics, obtaining a microbiological diagnosis of tuberculosis in HIV patients remains difficult. These patients may have problems producing sputum and may have paucibacillary illnesses, making current tuberculosis detection laboratory testing less effective and reliable. Negative laboratory test results cannot reliably rule out tuberculosis in these populations.[5–7,13–17] There is a need for tuberculosis (TB) diagnostics that are simple to use, can screen non-sputum samples, and can offer quick results for the treatment of immunocompromised patients.[18]

The urine LAM assay (urine-based detection of mycobacterial cell wall lipoglycan lipoarabinomannan) is a TB diagnostic test.[10,19–24] The test is available in numerous commercial variants, and the assays are low-cost test strips that may be used at the point of care and provide results in 25 minutes. The tests have moderate to high specificity (88 to 99%) in the populations on which they have been tested[3,25] and are particularly sensitive in HIV patients with low CD4 cell levels (56% in one meta-analysis).[19,25]

A heat-stable component of the bacilli's outer cell wall, LAM is generated by metabolically active or degenerating Mycobacterium bacteria. LAM is filtered by the kidney and can be identified in the urine, with test prototypes dating back to the 1930s.[2,10,18,26]

We described the case of two HIV patients who presented with signs and symptoms of tuberculosis and were found to be positive for urine LAM despite negative results from routine tuberculosis workups. Urine is a non-invasive sample that is readily available in patients who are unable to expectorate, such as children, the elderly, and

adults without a productive cough, as well as those with disseminated, extrapulmonary, and non-cavitary disease. LAM is easy to use, requires no sputum samples, which reduces the risk of aerosols, requires no additional instrumentation, and may be utilized in decentralized laboratories. As a result, LAM is a potential test for the early diagnosis and treatment of tuberculosis in persons who have signs and symptoms that are suggestive of the disease, with particular importance for low-resource health institutions in low- and middle-income countries with the greatest TB burden.[2,8,26]

The TB LAM (lipoarabinomannan) Ag (antigen) assay should be used to rule-in TB diagnosis in children with signs and symptoms of pulmonary or extrapulmonary TB, advanced HIV disease, serious illness, a CD4 cell count of less than 200 cells/mm3 in inpatient settings (irrespective of signs and symptoms) or a CD4 cell count of less than 100 cells/mm3 in outpatient settings (irrespective of signs and symptoms).[4,5,7,8]

Conclusion

Ending the suffering of HIV patients necessitates lobbying for more accurate tuberculosis diagnosis. The urine Lipoarabinomannan (LAM) assay will address the shortcomings of traditional sputum-based diagnostic tests including sputum Acid Fast Bacilli (AFB) and Gene X-pert, making it a credible alternative for diagnosing tuberculosis in people with HIV. The results of this case series demonstrated that TB LAM is a milestone for the difficulties in TB diagnosis in HIV patients. As of now, the national guideline only suggests urine LAM for HIV patients who fulfill the set criteria. We recommend the stakeholders to increase the availability, and extrapolate the recommendation to other populations including non-HIV patients.

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Author Contributions

All authors contributed significantly to the work reported, whether in the conception, study design, execution, data acquisition, analysis, and interpretation, or in all of these areas; participated in the drafting, revising, or critical review of the article; gave final approval of the version to be published; agreed on the journal to which the article was submitted; and agreed to be responsible for all aspects of the work.

Disclosure

The authors have indicated that they have no conflicts of interest in this case report.

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