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Utility of Cartridge-Based Nucleic Acid Amplification Test (CBNAAT) in early detection of Pulmonary Tuberculosis in Sputum Negative Retroviral Positive Patients'

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Abstract

Background: HIV-TB co-infection increases the mortality of an individual. The clinical presentation of pulmonary tuberculosis depends on the immune status of an individual and an immune-suppressed individual with HIV can present with atypical features, thus posing diagnostic challenges. For the detection of TB using microscopy, the sensitivity is an issue and it is addressed partly by the implementation of CBNAAT in HIV patients for the detection of TB. ***Aims and objectives***: To assess the usefulness of CBNAAT in the early detection of pulmonary tuberculosis with smear negative HIV patients and its correlation with CD4 count. ***Materials and methods***: PLHIV patients, age more than 18 years with symptoms suggestive of PTB were considered. Total of 94 PLHIV patients with sputum microscopy negative samples who met the inclusion criteria were included in the study. Sputum sample of at least 1 ml of each patient was analysed by CBNAAT X-pert MTB/RIF. Diagnostic yield of CBNAAT was compared with CD4 counts of patients. ***Observations and results***: Among 94 PLHIV patients, 51 were females and 43 were males. Mean CD4 count was 273. Out of 94 sputum negative samples, CBNAAT detected 13(13.8%) PTB cases, which was significant. One rifampicin resistance case was detected among 13 CBNAAT positive cases. One PTB cases detected in CD4 count up to 100cells/ml. 5 cases between CD4 count 100-200, 2 cases between CD4 count 201-300, 3 cases between CD4 count 301-400 and 2 cases detected in CD4 count more than 500. ***Conclusion***: CBNAAT detects pulmonary TB in PLHIV with greater efficacy than sputum microscopy, also helping in early diagnosis in less than 2 hours. It also detects rifampicin resistance with high specificity and can be used for screening for MDR-TB so that early therapy can be started, thus decreasing the incidence of MDRTB.

Keywords: HIV-TB co-infection, sputum microscopy, CBNAAT, CD4 count.

INTRODUCTION

According to WHO at least one third of 35.3 million people living with HIV worldwide are infected with latent TB. Globally about 14.8% of patients with TB are co infected with HIV. Persons co-infected with HIV-TB are 29.6 times (27.1 - 32.1) more likely to develop active TB disease than persons without HIV [1]. Tuberculosis is one of the most common opportunistic Infection amongst PLHIV [2]. The clinical presentation of pulmonary tuberculosis depends on the immune status of an individual and an immune-suppressed individual with HIV can present with atypical features, thus posing diagnostic challenges [3].

Detection of pulmonary tuberculosis by sputum-based techniques includes microscopy and culture. However, in people living with HIV, sputum production is scanty and the also the sputum contains a smaller number of bacilli due to fewer cavitation's, thereby decreasing the sensitivity and specificity of sputum microscopy as a diagnostic tool [3].

To overcome these shortcomings, mycobacterial culture is an alternative. It is a time- consuming technique which can take 4-8 weeks for the result thereby causing a delay in early initiation of anti-tubercular drugs, increasing the risk of transmission to close contacts and also the spread to extra-pulmonary regions within the same individual [4]. Other opportunistic infections which have a selective range of CD4 counts in which the disease occurs, TB occurs throughout the course of HIV [5]. CBNAAT can detect as few as 131 CFU/ml of MTB whereas sputum microscopy has a limit of detection of ~10,000 CFU/ml of MTB. X-pert MTB/RIF is the initial diagnostic test to detect pulmonary TB and rifampicin resistance in patients with signs and symptoms of tuberculosis as recommended by WHO [6].

MATERIALS AND METHODS

All retroviral positive patients with clinical suspicion of pulmonary tuberculosis including symptoms of cough with or without expectoration for more than two weeks, weight loss, fatigue, hemoptysis, and loss of appetite attending out-patient and in-patient department of in Shri B M Patil hospital, Vijayapura, from November 2019 to April 2021 was considered for sputum analysis. Two sputum samples (one spot sample and other one early morning sample) was sent for NTEP laboratory for detection of AFB (acid fast bacilli) by method of ZN staining.

The patients whose both sputum samples negative for AFB were considered as sputum negative retroviral positive patients and was considered for the present study. Those patient's sputum samples were sent for CBNAAT (Cartridge Based Nucleic Acid Amplification) analysis. Usefulness of CBNAAT testing in sputum smear negative samples was assessed.
Study type: cross- sectional study.

INCLUSION CRITERIA:

1. All retroviral positive patients with clinical suspicion of pulmonary tuberculosis
2. Patients whose sputum sample is negative for AFB.

EXCLUSION CRITERIA:

Smear positive tuberculosis with HIV infection.

RESULTS

All 94 patients included in the study were retroviral positive and sputum negative. These 94- smear negative retroviral positive patients' sputum samples were subjected to CBNAAT analysis. Out of 94 smear negative samples, 13 samples were positive by CBNAAT analysis. Among those 13 samples, which were positive by CBNAAT analysis, one sample was rifampicin resistant. A total of 13 cases were detected by CBNAAT analysis, among them 7 were females and 6 were males.

The mean age group of patients was 36.22 years with range from 18 to 64 years. Most of the patients were between age group 30 and 39 years with standard deviation of 10.1. Among 94 cases included in the study, 51 were females and 43 were males. The mean CD4 count of patients included in the study was 273.3 cells per cubic millimetre of blood with range 67 to 560 cells/mm3. Most of the patients had CD4 count between 101 and 200. The mean BMI of patients was 18.5 with SD of 1.35and range from 15 to 22. In total of 94 patients, 60 patients had BMI less than or equal to 19, 34 patients had BMI more than 19. Majority of the patients had low BMI, which was less than 19.

There was statistical significance found between age and CD4 count with p value of 0.001 by chi-square testing. There was statistical significance between rifampicin resistance and CBNAAT with p value of 0.00. There was statistical significance between BMI and CD4 count with p value of 0.001. Most of the patients had low CD4 count between 101 and 200, also had BMI less than19.0. There was statistical significance between BMI and CBNAAT with p value of 0.001. Most of the CBNAAT positive case (12 cases) had BMI less than 19. There was no statistical significance between CD4 count and CBNAAT results. Lower CD4 count was observed in most of the CBNAAT positive cases. There was no statistical significance between CD4 count and gender. There was no statistical significance between CD4 count and rifampicin resistance. One sample which was rifampicin resistant had low CD4 count of 179 cells/mm3.

There was no statistical significance between age and CBNAAT results. There was no statistical significance between gender and CBNAAT results.

DISCUSSION

Concomitant Human Immunodeficiency Virus (HIV) infection and Tuberculosis (TB) is a lamentable medical phenomenon with dreadful social and economic impact across the globe, aptly described as a cursed duet. TB is the leading cause of death among people living with HIV, accounting for one in five HIV-related deaths. In India, it is estimated that 62% of HIV positive patients are affected with Tuberculosis (TB) so it is the most common Opportunistic Infection2.

In our study, the mean age group of patients was 36.22 years and most of the patients were between 30 and 39 age group: with range and SD. In a study by Kavya et al [1], most of the patients were of age group 31 to 50 years. In another study by Deewan et al [7], the mean age group was 35 years.

In our study, total 94 patients were included in the study, among them 51 were females and 43 were males; female preponderance was observed in our study. The gender ration observed in our study was like the study conducted by V Rajkumar et al [8], in which, a total of 150 were included in the study; among them 58% were female and 42% were males.

In our study, the mean CD4 count was 273. Maximum number of the patients in the study had CD4 count between 101 and 200. In a study by Deewan et al [7], their mean CD4 count was 230. HIV causes immunosuppression by direct depletion of host CD4+ T lymphocytes, which results in lymphocytopenia and down regulation of these immune cells. Vulnerability to TB diseases is increased in HIV positive patients. HIV infected patients with decreased CD4+ T cell count is associated with increased risk of TB, especially CD4+ T lymphocyte count less than 200 cells/mm3 is much more accompanied with higher TB incidence, which is observed in our study. Therefore, CD4+ T lymphocyte count remains the best predictor of a patient's immunological and clinical status, the risk of opportunistic infections like TB, and helps in diagnostic decision making, particularly for patients with advanced HIV disease. This could be partly due to impaired restoration of TB specific immunity when patients are severely immune compromised at ART initiation and it might be because of primary infection or re-infection with the bacilli or re-activation of the existing latent TB because of severe immunosuppression [9].

The mean BMI of the patients in our study was 18.5. Low BMI is a risk factor for development of TB. In a study conducted by I Maro et al [10], low BMI and falling BMI were independently and significantly associated with increased risk of developing TB. These observations suggest that malnutrition contributes to HIV-associated TB. HIV-infected adults should be screened for TB disease. Risk of TB is even higher among PLHIV with low or falling BMI. While patients with low or falling BMI constitute the minority of subjects at risk for developing HIV-associated TB, recognizing the falling BMI may be a particularly useful predictor of TB risk among patients with a negative TST, in part because malnutrition can lead to TST anergy and thus thwart the identification of individuals who would benefit from INH preventive therapy. Low BMI is related to a greater bacillary burden during HIV-TB co- infection.

In our study, a total of 94 sputum negative samples with HIV positive status were subjected to CBNAAT analysis. CBNAAT detected 13 samples as positive. The detection rate of CBNAAT was higher than sputum microscopy testing. In a similar study done by V Rajkumar et al [8], sensitivity of CBNAAT (82.3%) was more than sputum microscopy (63.7%). In another study conducted by Deewan et al [7],

CBNAAT positivity (40%) was more than sputum microscopy (11%). The incidence of TB in underdeveloped countries is increasing, and this is thought to be because of associated poor hygiene conditions and the greater prevalence of AIDS. The global priorities for TB care and control are to improve case-detection and to detect cases earlier, including cases of smear- negative disease which are often associated with co-infection with the human immunodeficiency virus (HIV) and to enhance the capacity to diagnose multidrug-resistant tuberculosis [11]. These cases are often misdiagnosed due to the limitations of conventional diagnostic techniques.Due to low sensitivity and increased number of smear negative tuberculosis in HIV positive patients, it results in missing out many positive cases. In our study too, we observed that CBNAAT positivity rates were higher compared to sputum studies [12].

Culture, although extremely sensitive and specific system for TB diagnosis, needs two to eight -weeks to yield results and therefore alone does not assist in early diagnosis. CBNAAT is a molecular method of culture of Mycobacterium tuberculosis which also gives Rifampicin drug resistance in same sitting. It gives result within two hours. Unlike conventional nucleic acid amplification tests (NAATs), CBNAAT MTB/RIF is unique because sample processing and PCR amplification and detection are integrated into a single self-enclosed test unit, the CBNAAT Cartridge [12].

In the present study, among 13 CBNAAT positive cases, one case was detected as rifampicin resistant. The X-pert MTB/RIF (X-pert) assay is an automated nucleic acid amplification test that can detect both Mycobacterium tuberculosis and mutations associated with rifampicin resistance in the same sitting. CBNAAT can be a useful test for screening for MDR- TB. This is of reference to TB endemic areas like India where there is high prevalence of MDR- TB. . Failure of drug resistance leads to treatment failure and increases the spread of drug resistant strains in the community.[9]

CONCLUSION

CBNAAT plays vital role in early detection of mycobacterium tuberculosis which is important in reducing the infectivity and droplet spread and decreases the incidence of TB burden. CBNAAT reduces the false negative rates of sputum microscopy. CBNAAT detects only mycobacterium species whereas sputum microscopy detects both mycobacterium and non - mycobacterium species, hence, reduces the false positive rates. Emphasis should be made on nutrition of the patient as it impacts greatly on the treatment outcomes and malnourished patients are prone for tuberculosis infection. CBNAAT should be made primary testing modality for all presumptive TB cases even without HIV infection. It greatly reduces the incidence of MDR-TB and improves detection of drug resistance .

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