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Research Article

Study of Role of CBNAAT in Bronchial Washings of Patients with Presumptive Pulmonary Tuberculosis with Negative Sputum Smear

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Abstract

Background: According to WHO Global Tuberculosis Report 2017, approximately 1.3 million deaths occurred due to TB in HIV negative people and 300000 additional deaths in HIV positive people. Although Culture is gold standard, it takes very long time for positivity whereas Conventional microscopy has low sensitivity. The aim of this study is to determine diagnostic accuracy of Cartridge Based Nucleic Acid Amplification Test (CBNAAT) bronchial washings of patients with presumptive pulmonary tuberculosis with negative sputum smear and sputum non producers.

Materials and Methods: Patients with clinical and radiological suspicion of PTB who have undergone bronchoscopy in the period of October 2017 to July 2019 were included in this study. Sensitivity, Specificity, Positive Predicted value and Negative Predicted Value of CBNAAT bronchial washings were calculated using culture as the gold standard.

Results: Among 102 patients who have undergone bronchoscopy, 60 were culture positive, 59 were CBNAAT positive, 23 were AFB smear positive and Rifampicin resistance was detected in 5. CBNAAT Bronchial washings had 85% Sensitivity, 80.9% Specificity, PPV and NPV are 86.4% and 79.1%.

Conclusion: CBNAAT has higher sensitivity in immediate confirmation of pulmonary tuberculosis when compared to AFB smear and can also be used in detection of Rifampicin resistance. Patients who were culture negative but CBNAAT positive and started on ATT should be carefully followed up for clinical and radiological improvement.

Keywords: *Bronchial Washings; Xpert MTB Rif; Rifampicin Resistance*

Introduction

Tuberculosis is one of the oldest and deadliest diseases in the world and also a major health problem. Even though effective chemotherapy for tuberculosis has been available for decades, TB still remains a public health challenge all over the world.

In 2017, approximately 1.3 million deaths occurred due to TB in HIV negative people and 300000 additional deaths in HIV positive people. Globally, approximately 10.0 million people developed TB diseases in which two thirds were in developing countries and among

them India was leading with 27% of TB cases [1]. Deaths due to TB are intolerable as anti-tubercular drugs are commonly and easily available having more than 90% of cure rates.

Notifications on TB cases has stabilized in recent years. About 64% of the estimated 10.0 million people who developed TB were notified as newly diagnosed cases. In 1993, the World Health Organization (WHO) declared Tuberculosis as a global emergency because of the scale of the tuberculous epidemic and the HIV pandemic.

National tuberculosis programme (NTCP) started in 1962 and when reviewed in 1992 resulted in the genesis of Revised National Tuberculosis Control Programme (RNTCP). The programme tested as a pilot project in 1993 was found to be effective. The expansion of the programme was started in 1998. To help and address the situation, a Global strategy called DOTS (Directly Observed Treatment Short course) was introduced [2].

Drug resistant Tuberculosis has become a major problem. Primary resistance is the presence of resistant strains of tuberculosis bacilli in patients who have never received anti tubercular drugs or received them for less than 1 month. Acquired drug resistance implies that patient initially had a drug susceptible organism which developed resistance in the course of treatment which may occur when a patient is exposed to single drug through failure of the programme to ensure adherence to treatment, or because of irregular supply of drugs, poor quality of drugs, inappropriate prescription, or, rarely due to improper absorption of medications.

Early diagnosis of pulmonary tuberculosis helps in prevention of progression and spread of disease, morbidity and permanent damage by fibrosis. Major task is getting precise and faster diagnosis to initiate treatment at a very early stage. 40 - 60% of pulmonary TB cases are sputum negative for acid fast bacilli [3]. Since major portion are smear negative patients but are still infectious, bronchoscopy is routinely performed for these subset of patients of pulmonary tuberculosis [4]. Bronchoalveolar lavage is sent for ZN staining and mycobacterial cultures. ZN staining has very low sensitivity of 41% whereas culture which is considered as gold standard has sensitivity of 86% but the results takes 6 - 8 weeks [5].

Overcoming most of these shortcomings a new diagnostic assay known as Xpert MTB/RIF assay has been developed recently. CBNAAT is a hemi nested real-time PCR test which simultaneously identifies MTB/RIF resistance. Diagnostic efficacy of CBNAAT is comparable to culture in sputum samples and provides results within 2 hours [6]. There are limited studies on utilization of CBNAAT BAL fluid for PTB diagnosis in high TB burden country like India. WHO recommended the use of CBNAAT in December 2010.

With this background this study has been taken to make a definitive diagnosis of tuberculosis by bronchial washings CBNAAT in sputum smear negative/non sputum producing patients with suspected pulmonary tuberculosis.

Materials and Methodology

This is a cross sectional study conducted in Department of Respiratory Medicine, Mamata Medical College and General Hospital and District Tuberculosis Centre, Khammam in which 102 clinicoradiologically suspected sputum smear negative PTB cases were taken in the period of October 2017 to July 2019. This study was approved by the ethics committee of institution.

Inclusion criteria: Patients above 18 years of age with clinical suspicion of pulmonary tuberculosis having symptoms of cough with or without expectoration for > 2 weeks, fever, significant weight loss, fatigue, haemoptysis and loss of appetite, abnormality in chest x ray (or) Recent History of contact with Pulmonary Tuberculosis Cases, Patients with clinical and radiological features suggestive of Pulmonary Tuberculosis but unable to produce sputum or sputum smear negative.

Exclusion criteria: Patients < 18 years of age, Patients not willing to give consent, Smear positive, extrapulmonary TB cases, with bronchoscopy contraindications like; Hypoxia (SPO_2 < 92% at room air), Associated arrhythmias, Unstable cardiac status, Bleeding diathesis,

hemodynamically unstable patient. All participants were briefed adequately in the local language, and their written informed, voluntary consent was obtained. All the enrolled subjects were subjected to a careful history, general, physical examination and had undergone basic required investigations and then underwent Fiberoptic Bronchoscopy and bronchial washings were sent for AFB smear, CBNAAT and cultures. Statistical Analysis: All data was entered into a Data Collection Proforma Sheet and the data was analysed using MS Excel. Descriptive data was represented as mean, percentages and proportions for categorical variables. Sensitivity, specificity, PPV, NPV were calculated.

Results

After completion of the study, result of 102 patients has been analyzed. The clinical data as per proforma was reviewed for all patients and following were documented.

Age and gender distribution of patients

Most common age group involved in this study was 40-60 years (50.98%) with male to female ratio of 2.28:1.

Common symptoms

Cough was the most common presenting symptom, noted in 96 patients (94.1%), followed by fever (73.5%) and loss of appetite (58.9%). Other symptoms include loss of weight (49.0%), haemoptysis (27.4%), chest pain (21.6%) and shortness of breath (19.6%) (Figure 1).

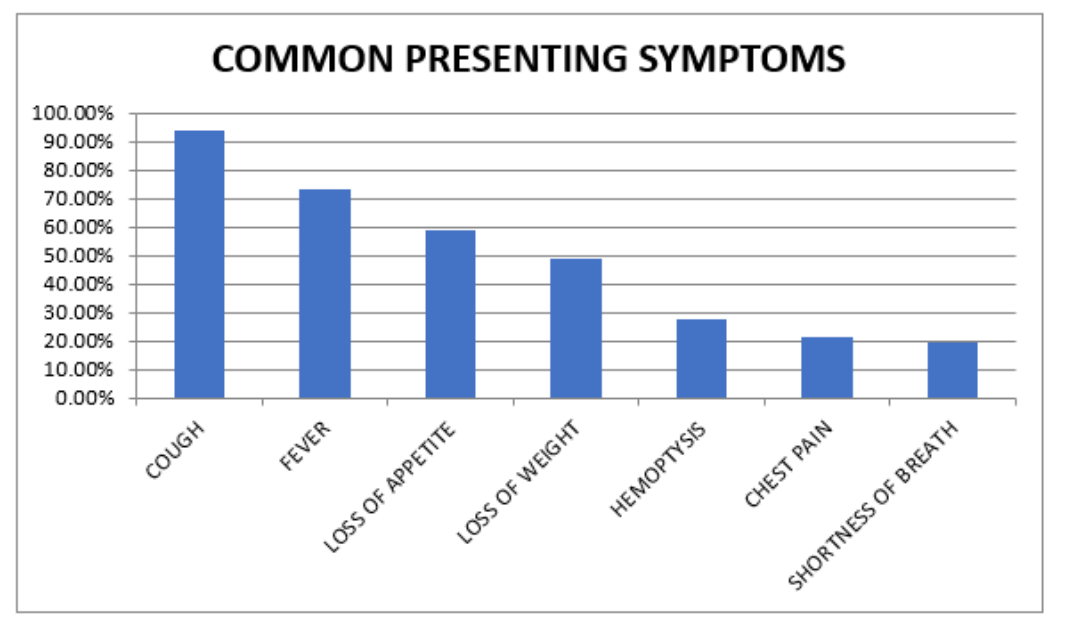

Figure 1

Radiological manifestations

On Chest X ray most common lesions seen are Consolidation (34.3%), followed by Cavitations (29.4%) and Nodular Opacities (21.6%). Others (14.7%) include Fibrobronchiectatic changes, ground glassing, miliary shadows and normal.

Bronchial washings AFB results

Bronchial washings smear for AFB was positive in 23/102 (22.55%) cases, among them predominant age group showing more positivity belongs to 40 - 60 years (30.87%) followed by 19 - 39 years (17.07%) (Figure 2).

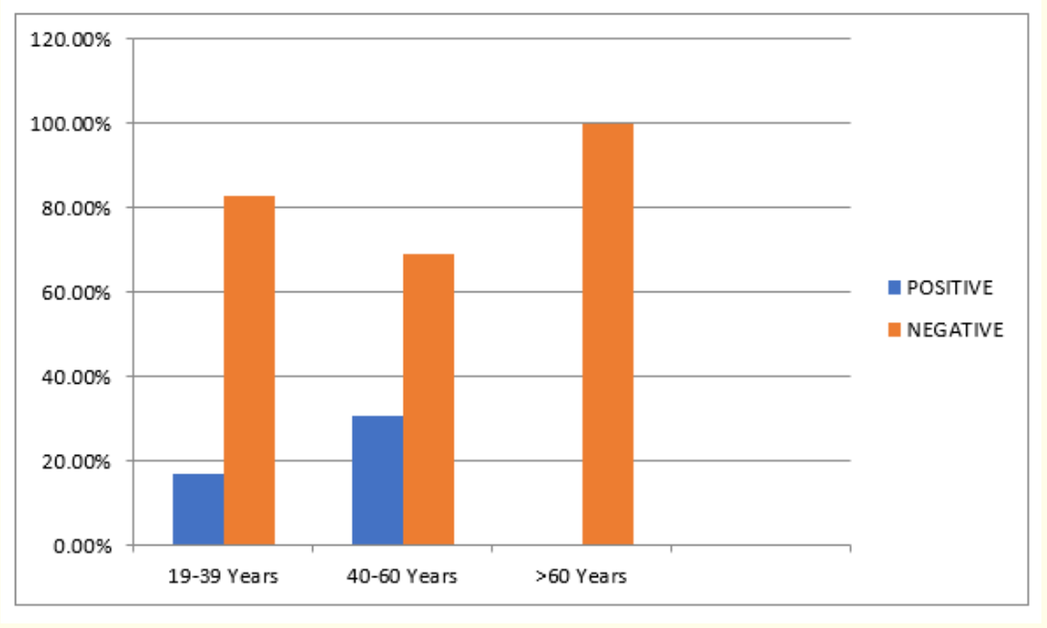

Figure 2

Bronchial washings CBNAAT

CBNAAT for Bronchial washings was detected in 59/102 (57.84%) cases and among them predominant age group showing positivity belongs to 40 - 60 years (59.61%) followed by 19-39 years (58.54%) (Figure 3).

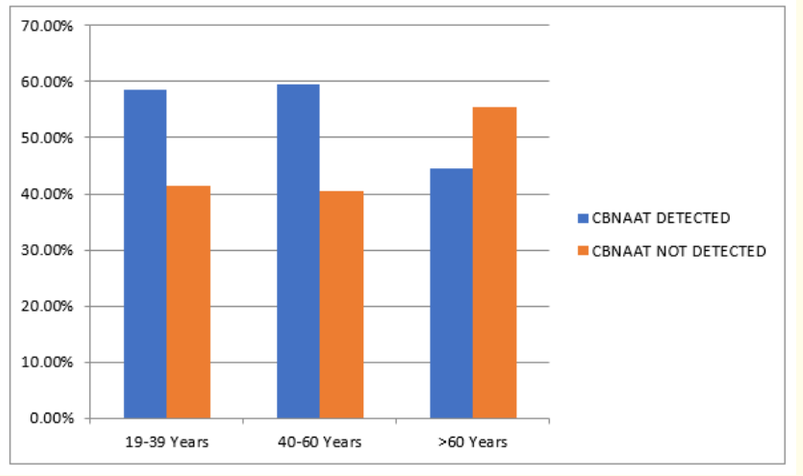

Figure 3

Bronchial washings culture results for AFB

Bronchial washings culture for AFB was positive in 60/102 (58.82%) cases, out of this predominant age group that showed culture positivity belongs to > 60 years (66.67%) followed by 40 - 60 years (61.54%) (Figure 4).

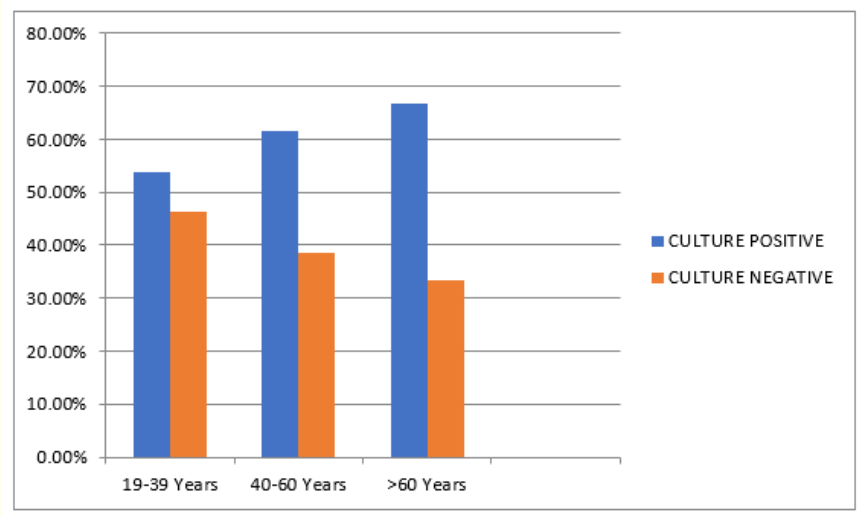

Figure 4

Sensitivity, specificity, positive predictive value and negative predictive value of bronchial washings smear microscopy and CB-NAAT

Sensitivity of bronchial washings CBNAAT (85%) is more than that of smear microscopy (36.7%) and Specificity (80.9%) was less than smear microscopy (97.6%). Positive predictive value of CBNAAT (86.4%) is less than AFB smear (95.6%) whereas negative predictive value (79.1%) is more than AFB smear (51.9%) (Figure 5).

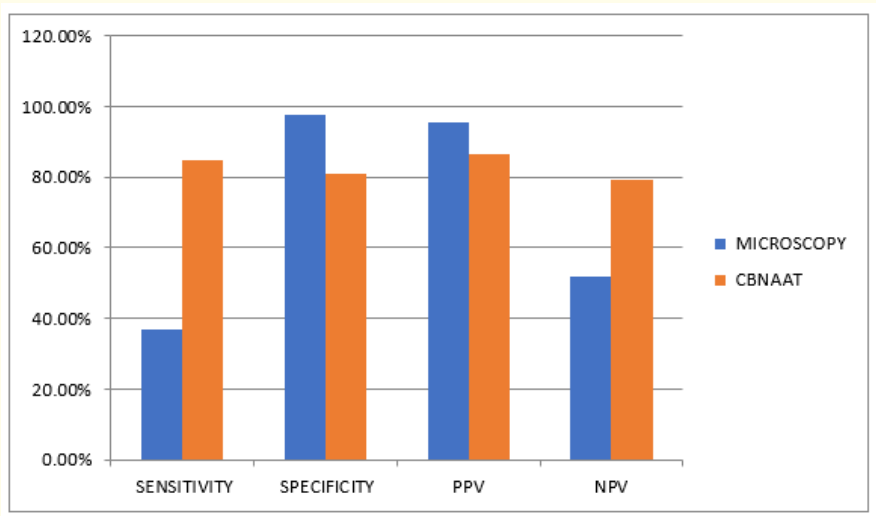

Figure 5

CBNAAT MTB detection

Out of 59 CBNAAT MTB detected cases, majority of them were Low (42.37%) detected, followed by Medium (35.59%), Very low (15.25%) and High (6.78%) with 5(8.5%) cases of Rifampicin resistance.

Of the 102 suspected cases, 60 (58.82%) cases were diagnosed as PTB at the end of the study on the basis of AFB culture of bronchial washings which was taken as the gold standard. Those cases who had no growth of mycobacteria in their BAL fluid i.e. their culture was negative for mycobacteria were considered as non-mycobacterial lung disease group. Bronchial washings for AFB smear was positive in 23 cases in the total sample population. Out of which 22 were true positive as their AFB culture was also found to be positive. One case was falsely positive for AFB smear as their culture was negative for Mycobacterium tuberculosis. Bronchial washings for CBNAAT/gene xpert was positive in 59 cases out of 102 cases; among those 51 were true positives and 8 cases were false positive, as AFB culture was negative in these 8 cases. In all these cases CBNAAT assay also detected rifampicin sensitive and resistant strains. Rifampicin was sensitive in 54 cases and resistant in 5 cases.

Discussion

Mean age was 43.12 years which was similar to the studies conducted by Amiya Kumar team [7], Barnard DA team [8]. Men outnumbered Women in the present study correlating well with studies conducted by Hiren Vadhiya team [9], Hazarika team [10], which may be due to gender differences in exposure to PTB infection and random non probable selection of the patients without any preference to gender. Common presenting complaints of cough followed by fever and loss of appetite are similar to studies conducted by Avashia S team [11]. Most common radiological features noted are Consolidation followed by Cavitations and Nodular infiltrates similar to the studies conducted by Khalil KF, Butt T [12].

Using culture as the reference standard, Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Value of Bronchial washings for AFB smear microscopy was similar to the studies conducted by Pan Yang team [13].

Our study confirmed gain in early diagnosis of sputum scarce and smear-negative PTB by Xpert MTB RIF detecting more cases when compared to smear microscopy which is explained by higher sensitivity of Xpert MTB RIF when compared with AFB smear similar to the studies conducted by Santhosh Kumar team [14]. Higher Sensitivity of CBNAAT is explained based on higher detection limit being 131 colony-forming unit/ml compared to the AFB smear detection is 10,000 cfu/ml as per the study by Dinnes J., *et al* [15].

PPV of CBNAAT is less than AFB Smear. CBNAAT amplifies any DNA either from live or dead bacilli. So solely based on this test, it cannot be assumed that positive result indicates active disease [16]. NPV of CBNAAT is more than AFB Smear suggesting that a negative result accurately excludes TB in most situations. Our study revealed rifampicin resistance subsequently confirmed by Line Probe Assay which we would have missed with ZN staining. Given high sensitivity of CBNAAT in detecting rifampicin resistance 95%, the NPV is greater than 98% in settings of low prevalence and with high prevalence of rifampicin resistance. Possibility of rifampicin resistance is excluded by the negative result [XPERT MTB/RIF implementation manual].

Conclusion

The present study concludes that the CBNAAT/gene Xpert assay on Bronchial washings specimen provides an accurate and early diagnosis and treatment of sputum smear negative cases and can prevent disease progression as well as transmission to the community.

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