ROLE OF FIBEROPTIC BRONCHOSCOPY AND GENEXPERT IN EVALUATING SPUTUM SMEAR NEGATIVE PULMONARY TUBERCULOSIS SUSPECTS

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ABSTRACT

BACKGROUND

The objective of this study was to assess the efficacy of GeneXpert (CBNAAT) and Fiber Optic Bronchoscopy as diagnostic tools in sputum negative pulmonary tuberculosis suspects.

MATERIALS AND METHODS

A prospective study was conducted on 55 patients who were pulmonary tuberculosis suspects with sputum smear negative for acid fast bacilli. In all these patients, sputum was sent for GeneXpert test. Fiber optic bronchoscopy was done in all those whose sputum test for GeneXpert was negative, Broncho alveolar lavage (BAL) was collected and sent for Acid fast staining and GeneXpert test.

RESULTS

A total of 55 patients who were pulmonary tuberculosis suspects with sputum smear negative for AFB staining were evaluated in this study. Out of 55 patients, sputum for GeneXpert test was positive in 14 patients (25.45%), BAL for Acid fast bacilli staining was positive in 3 patients (5.45%) and BAL for GeneXpert was positive in 12 patients (21.81%). All BAL for AFB positives (3) were CBNAAT positives. Rifampicin resistance was detected in 1 patient out of 29 GeneXpert positive patients (3.44%).

CONCLUSION

Using both Fiber optic Bronchoscopy and GeneXpert MTB/RIF assay (CBNAAT) in sputum AFB negative pulmonary tuberculosis suspects increases the diagnostic confirmation of tuberculosis and also helps in early detection of rifampicin resistance.

KEYWORDS

Sputum Smear, Bronchoscopy, Bal, GeneXpert.

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BACKGROUND

Tuberculosis is caused by Mycobacterium Tuberculosis. This bacterium is aerobic, multiplies slowly and has characteristic acid fast staining. This disease effects any part of our body except hair and nails. Pulmonary Tuberculosis is the most common type of Tuberculosis followed by lymph node Tuberculosis. Tuberculosis is the most common cause of death due to single infectious agent. It accounts for over a quarter of avoidable deaths worldwide. Globally the incidence of Tuberculosis accounts for 10.4 million out of which India accounts for an incidence of 2.79 million (27%). Mortality due to Tuberculosis globally accounts for 13 lakhs of which India accounts for 4.23 lakhs (33%). India accounts for 24% of global burden of Multi drug resistant Tuberculosis.[1]

A sputum positive Pulmonary Tuberculosis patient can infect 10-15 patients in a year. By detecting active pulmonary Tuberculosis early, an appropriate treatment can be initiated, and disease transmission can then be controlled. Some patients presenting with active pulmonary TB may, however, exhibit negative sputum Acid fast smears. Fibreoptic Bronchoscopy is considered a good option for these cases that pose a diagnostic challenge.[2] Using Bronchoscopy we can get different type of materials like bronchoalveolar lavage (BAL), bronchial washings, transbronchial needle aspirations and biopsy. All these materials will help in diagnosing Tuberculosis when they are subjected to microbiological investigations.

The GeneXpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) is a cartridge based nucleic acid amplification test (CBNAAT). It employs five distinct molecular beacons (nucleic acid

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probes), each labelled with a differentially coloured fluorophore and responding to a specific nucleic acid sequence within the rpoB gene of M. tuberculosis[3] It can detect TB along with rifampicin resistance in less than two hours, directly from untreated sputum samples[3] Revised National TB Control Programme (RNTCP) is also currently using Xpert MTB/RIF to diagnose pulmonary TB, paediatric TB, extrapulmonary TB and rifampicin resistance and Multi Drug Resistance Tuberculosis in high risk populations like HIV positive as recommended by WHO under 2013 policy recommendations.[4]

A substantive number of pulmonary tuberculosis patients remain undiagnosed by conventional sputum microscopy. These cases also play an important role in the disease transmission. Moreover, on the basis of Chest radiography only as the diagnostic tool, many patients are wrongly started on

Anti-Tubercular Treatment (ATT). In the above two situations, Cartridge Based Nuclear Acid Amplification Test (CBNAAT) of sputum or BAL samples (Bronchoalveolar Lavage) looks convincing as a good diagnostic method for the purpose of diagnosing or ruling out pulmonary tuberculosis.

Aim of the Study

The aim of this study was to assess the efficacy of GeneXpert (CBNAAT) and Fiber Optic Bronchoscopy as diagnostic tools in sputum negative pulmonary tuberculosis suspects.

MATERIALS AND METHODS

A prospective study conducted on 55 patients with clinical suspicion of Tuberculosis based on symptoms (cough >2 weeks, haemoptysis, low grade fever,, loss of weight, loss of appetite, night sweats) or chest radiograph (cavitation, consolidation, nodule and alveolar opacities) who have a negative sputum smear for Acid fast bacilli (spot and morning samples) attending to the Santhiram Medical College and General Hospital, Nandyal from January 2018 to October 2018.

Inclusion Criteria

All patients who are pulmonary tuberculosis suspects by clinical symptoms and radiological examination with sputum smear samples for AFB negative.

Exclusion Criteria

Patients with sputum smear positive for Pulmonary Tuberculosis, all extra pulmonary Tuberculosis patients, patients not willing to give consent.

Investigations

Chest X-ray PA view, CT scan chest (if necessary) Sputum for AFB (Spot and morning samples). Sputum for Culture and sensitivity, Gram staining

Sputum for KOH mount, Sputum for Malignant cytology. Complete hemogram, Serum creatinine, Blood urea, Blood glucose (fasting and post prandial), viral screening.

ECG, 2D ECHO.

GeneXpert MTB/RIF- In my study for all 55 patients Sputum for GeneXpert was done.

Fiber Optic Bronchoscopy

Bronchoalveolar Lavage (BAL) collected and sent for AFB Staining, BAL for CBNAAT, BAL for culture and sensitivity, BAL for KOH mount, BAL for malignant cytology.

In my study for all 55 patients, sputum was sent for GeneXpert test. Out of 55 patients 14 patients (25.45%) sample came to be positive for sputum GeneXpert. Fiber optic bronchoscopy was done in remaining 41 patients.

Pre-Requisites: Fiberoptic Bronchoscopy

1) Informed written consent from the patient
2) The procedure is carried out electively with patient nil orally for four to six hours before.
3) Lignocaine sensitivity test.
4) Pre-medication 30 to 45 minutes prior to bronchoscopy with atropine intra muscularly and nebulization with 4% xylocaine.
5) Oro pharyngeal local 10% lignocaine spray, intra nasal application of lignocaine jelly.
6) Bronchoscopy is carried out under short acting midazolam.

Data Analysis

The following soft wares were used for analysis 1) Microsoft Excel-2013 for data entering 2) SPSS version 10 for cross tabulation and analysis.

RESULTS

In our study, 55 patients were included. 30 patients were males (54%) and 25 patients were females (46%). Male to female ratio is 1.2:1. Majority of patients 27/55 (49.09%) were in the age group of 41 to 60 yrs.

The most common presentation was cough (90.9%) followed by dyspnoea (72.7%), loss of appetite (72.7%), loss of weight (70.9%), night sweats (10.9%) and haemoptysis (7.2%). Radiological presentations: – Pneumonia 20/55 (36.36%), fibrocavitating lesions 12/55 (21.8%), bronchiectasis changes 4/55 (7.2%), normal chest X-ray with clinical symptoms 1/55 (1.8%), infiltrating lesions 13/55 (23.6%), mass lesions 3/55 (5.45%) and nodularity 2/55 (3.63%). Out of 55 patients, 20 patients (36.36%) presented radiologically as consolidation Out of these patients with consolidation, 11 patients presented with right upper zone consolidation, 4 patients with right lower zone consolidation, 5 patients with bilateral upper zone consolidation and 1 patient with right upper zone and mid zone consolidation. 12 patients presented with fibro cavitary lesions (right upper zone-7, left upper zone-3, left midzone-1, bilateral upper zone-1).

For all 55 patients sputum for GeneXpert test was done and Mycobacterium was detected in 14 patients (25.45%). Fiber optic bronchoscopy was done in rest of 41 patients, Bronchoalveolar lavage (BAL) was collected and sent for acid fast staining and GeneXpert test. In 3 patients (5.45%) BAL was positive in smear for acid fast staining and in 12 patients

(21.81%) BAL for GeneXpert test detected Mycobacterium. Thus in 29 patients (52.7%) out of 55 sputum smear negative patients, active Tuberculosis was diagnosed using bronchoscopy and GeneXpert test.

Out of 55 patients, 18 patients were previously treated for Pulmonary tuberculosis (32.72%), remaining patients 37/55 (67.27%) were new cases. Out of 18 previously treated cases, 11 patients were diagnosed as having pulmonary tuberculosis relapse (61.11%). Out of these 11 patients, 6 (54.54%) patients were sputum positive for GeneXpert, with Rifampicin resistance detected in 1/18 (1.81%) by CBNAAT MTB/RIF. Remaining 5 (45.45%) patients were BAL positive for GeneXpert test.

Out of 55 patients, 15/55 (27.27%) patients were Diabetic. Out of 15 diabetic patients in our study, Sputum for GeneXpert was positive in 5 patients and Bronchoalveolar lavage for GeneXpert was positive in 3 patients. Out of 55 patients 3/55 (5.45%) patients were HIV positive, in this 1/3 (33.33%) patient was sputum positive for GeneXpert.

Out of 20 patients with consolidation, active Tuberculosis was detected in 9 patients (45%) by sputum GeneXpert test and in 8 (40%) patients by Bronchoscopy. Out of these 8 patients, BAL was positive for AFB staining in 2 patients and in 6 patients BAL was positive by GeneXpert test. In remaining 3 patients, sputum and BAL for Mycobacterial culture were negative (Mycobacterial culture samples were sent to TB unit Govt. hospital Nandyala under RNTCP programme). In 12 patients with fibrocavitary lesions, active Tuberculosis was detected in 2 patients by sputum GeneXpert test and in 3 patients by Bronchoscopy (BAL for GeneXpert), In 13 patients with infiltrative lesions radiologically, active Tuberculosis was detected in 3 patients by sputum GeneXpert test, in 1 patient by BAL for acid fast staining and in 1 patient by BAL for GeneXpert test. Out of 4 patients presented with radiologically with bronchiectasis, active Tuberculosis was diagnosed in 1 patient by BAL for GeneXpert test. Out of 2 patients with nodular lesions, active Tuberculosis was detected in 1 patient by BAL for GeneXpert test.

In our study, out of 55 cases fiber optic bronchoscopy was done in 41 patients, out of these 41 patients, in 16 patients no abnormality detected. Blood clots in 2 patients (both in right lower lobe), thick mucopurulent secretions observed in 18 cases, erythematous mucosa is observed in 2 patients, cicatrized and distorted bronchial openings with mucoid secretions observed in 3 patients.

Age Group	No. of Patients
20-40	14
41-60	27
>61	14
Table 1	

Presenting Complaints	Patients (%)
Cough	50 (90.9%)
Fever	35 (63.6%)
Loss of Appetite	40 (72.7%)
Loss of Weight	39 (70.9%)
Night Sweats	6 (10.9%)
Haemoptysis	4 (7.2%)
Dyspnoea	40 (72.7%)
Table 2	

Radiological Findings	Patients (%)
Consolidation	20/55 (36.36%)
Fibro Cavitating Lesions	12/55 (21.8%)
Bronchiectasis Changes	4/55 (7.2%)
Infiltrates	13/55 (23.6%)
Normal Chest X-Ray	1/55 (1.8%)
Mass Lesions	3/55 (5.45%)
Nodularity	2/55 (3.63%)
Table 3	

Radiological Presentations	Sputum for GeneXpert	BAL for AFB	BAL for GeneXpert
Consolidation (20)	9 (45%)	2 (10%)	6 (30%)
Fibrocavitary Lesions (12)	2 (16.6%)	0	3 (25%)
Infiltrative Lesions (13)	3 (23.07%)	1 (7.69%)	1 (7.69%)
Bronchiectasis (4)	0	0	1 (25%)
Nodularity (2)	0	0	1 (50%)
Table 4			

Bronchoscopy Findings in 41 Patients	Number of Patients	BAL for AFB Staining	BAL for GeneXpert Test
Thick Mucopurulent Secretions	18/41 (43.09%)	03 (16.66%)	09 (50%)
Blood Clots	2/41 (4.87%)	0	0
Normal (No Abnormality)	16/41 (39.02%)	0	0
Cicatrised and Distorted Bronchial Openings with Mucoid Secretions	3/41 (7.31%)	0	2 (66.66%)
Erythematous Mucosa	2/41 (4.87%)	0	1 (50%)
Table 5			

In our study out of 55 patients, 29 (52.72%) patients were diagnosed as having active Tuberculosis by sputum for GeneXpert test, BAL for AFB staining and BAL for GeneXpert test. In rest of the 26 (47.27%) patients we advised to consult at TB unit, Nandyal government hospital for sputum Mycobacterial culture and sensitivity.

DISCUSSION

In this prospective study Fiber optic Bronchoscopy & GeneXpert showed high sensitivity and specificity in patients with sputum smear negative pulmonary tuberculosis.

Despite being less infectious than sputum positive pulmonary tuberculosis, smear negative pulmonary tuberculosis serves as an important cause of transmission in communities by delaying diagnosis[5] A 2013 Cochrane systematic review showed that GeneXpert test is highly accurate.[6] In smear-negative patients with Tuberculosis suspects, GeneXpert had a sensitivity of 67%. For rapid detection of Rifampicin resistance, the sensitivity is 94% and specificity is 98%. In our study, no complications occurred among patients undergoing bronchoscopy which is similar to a study by Anderson and coworkers[7]. Fiber optic bronchoscopic studies provide various types of specimens (aspirates, brushes, lavage fluids and biopsies) which may be useful for early diagnosis of sputum smear negative pulmonary tuberculosis.[8]

In my study, 55 cases were included. 30 (54.54%) males and 25 (45.45) females. Male to female ratio is 1.2:1. Majority of patients 27/55 (49.09%) were in the age group of 41 to 60 yrs. In a study conducted by Pierre Le Palud et al[9] on 162 patients, median age was 54 years and male to female ratio was 1.7. In another study by Sanjay Avashia et al,[10] total no of patients was 72 (male 41, female 31. male to female ratio 1.32). In another study by Dr. S. Subbarao, K. Siva Prasad et al,[11] mean age of PTB patients was 45 Yrs. with male preponderance. Mean age in males is 46 yrs. mean age in females was 42 yrs. In my study cough (90.9%) being most common symptom followed by breathlessness (72.7%) and loss of appetite (72.7%). In my study majority of patients were having more than two symptoms. In another study by Sanjay Avashiaetal[10] most common symptom was cough (72.2%) followed by fever (69.4%). In a study by Pierra Le Palud et al,[9] most common symptom was cough (51.9%) followed by general symptoms (45.1%). In my study, most common radiological presentation was Consolidation 36.36% followed by infiltrate lesions and ill-defined opacities 23.6%. In study by Le Palud et al,[9] nodules 53.7% were most common finding followed by pneumonia 27.1%. In another study by Sanjay Avashia et al[10] most common lesions in chest imaging were consolidation followed by fibro cavitary lesions. In my study, Diabetic patients were 15 out of 55 with sputum smear negative for Acid fast staining. Out of these 15 Diabetic patients, 8 patients (53.33%) were detected as having Pulmonary tuberculosis. In these 8 patients, 5 patients were detected by sputum GeneXpert 5 and 3 patients were detected by BAL for GeneXpert. In study Dr. S. Subbarao, K. Siva Prasad et al,[11] Diabetes mellitus was Comorbidity in 20 cases. Out of these 20 patients, 10 smear negative cases become positive by GeneXpert. In my study, 18/55 (32.72%) patients were previously treated for Pulmonary Tuberculosis. In these 18 patients, 11/18 (61.1%) were detected positive by combined sputum GeneXpert and BAL for GeneXpert. In our study on 55 patients who were sputum smear negative Pulmonary Tuberculosis suspects, 26 patients (47.27%) were diagnosed as having active Pulmonary Tuberculosis through GeneXpert and Fiber Optic Bronchoscopy. 1 patient was rifampicin resistant which is detected by sputum for GeneXpert and this patient had already taken ATT in the past. In my study 3/55 patients were diagnosed as HIV positive. In these 3 patients, 1/3 (33.3%) patient was detected as having active Pulmonary Tuberculosis by sputum for GeneXpert. In a study conducted on HIV patients by R Dewan, S. Anuradha et al[12] CBNAAT diagnosed 10 (25%) cases of rifampicin resistance among the 40 Mycobacterium tuberculosis positive cases. History of previous ATT intake was found in 7 out of 10 (70%) rifampicin resistant patients. Line Probe Assay further revealed that 9 of 10 patients who were detected rifampicin resistant by GeneXpert also had isoniazid resistance. In a study by D. Pragati Rao, K. Lakshmi Sowjanya,[13] Tuberculosis was positive in 59 cases out of 231 HIV positive patients (25.54%). GeneXpert positive and sputum smear for AFB negative cases were 45 (76.27%).

In a study conducted by Subhasis Mukherjee et al[14], out of 228 patients of Pulmonary Tuberculosis 190 patients were sputum smear negative and 38 patients were sputum smear positive. GeneXpert was positive in 111 patients. Overall, sensitivity of GeneXpert was 48.68%. Baughman et al,[15] reported 87% of bronchoscopy sample positivity in sputum smear negative cases. Kennedy et al,[16] observed that early diagnosis of sputum smear negative Pulmonary Tuberculosis was possible in 38% of patients if different bronchoscopy procedures such as transbronchial biopsy and post bronchoscopy sputum, in addition to bronchoalveolar lavage were studied. Pandeetal,[17] reported that immediate diagnosis was possible in 35% of patients using Bronchoscopy. Charoenratanakul et al,[18] found that the diagnostic yield of overall bronchoscopic procedures was 32.5% in smear negative Pulmonary Tuberculosis suspected patients. Fujii et al,[19] found Acid fast Bacilli in 40% of their bronchoscopy specimens. Bronchoalveolar lavage had significant sensitivity and specificity in a study by Conde et al,[20] and was useful in diagnosing Pulmonary Tuberculosis in 72% of cases.

CONCLUSION

In my study both Bronchoscopy and GeneXpert MTB/RIF assay (CBNAAT) together were found to be very useful in the early diagnosis of active pulmonary tuberculosis in sputum smear negative patients. This helps us to start appropriate treatment and to prevent disease transmission from sputum smear negative patients. Early diagnosis and initiation of anti-tuberculosis treatment helps to prevent further lung damage in sputum negative pulmonary patients. GeneXpert MTB/RIF has high sensitivity and specificity for diagnosis of both smear positive and smear negative pulmonary tuberculosis cases with high rates of detection of rifampicin resistance and greater concordance with gene sequencing for RIF resistance when compared with culture. Widespread application of this assay can increase the case detection rates of both drug sensitive and MDRTB, thereby facilitating early treatment decisions and curbing transmission.

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