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DIAGNOSTIC YIELD OF BRONCHOALVEOLAR LAVAGE GENE XPERT IN SPUTUM NON-PRODUCERS AND SMEAR NEGATIVE, PULMONARY TUBERCULOSIS CASES AT IRD, SMS MEDICAL COLLEGE, JAIPUR.

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Conflicts of Interest: Nil

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Abstract:

Background: Tuberculosis (TB) has been and remains a major global health problem. India accounts for one fourth of the global TB burden.

Methods: This was a tertiary hospital based, descriptive type of observational study conducted on fifty consecutive patients with clinicoradiologically consistent pulmonary tuberculosis who were either sputum smear negative for AFB or sputum non-producers at the Department of Tuberculosis and Chest Diseases, Institute of Respiratory Diseases, Jaipur from October 2017 to October 2018.

Results: The positivity of BAL AFB smear & Gene Xpert were 15 (30%) & 32 (64%) respectively. With BAL MTB culture as the gold standard, BAL AFB smear showed a sensitivity of 35%, specificity of 90%, positive predictive value (PPV) of 93.3%, negative predictive value (NPV) of 25.7%. BAL Gene Xpert showed a sensitivity of 72.5%, specificity of 70% and PPV of 90.60% and NPV of 38.9%.

Conclusion- GeneXpert and AFB smear microscopy share almost same specificity but sensitivity of GeneXpert is much higher than AFB smear microscopy in respiratory samples as shown in our study.

Keywords: GeneXpert, AFB smear microscopy, Specificity, Sensitivity.

Introduction

Tuberculosis (TB) has been and remains a major global health problem. India accounts for one fourth of the global TB burden[1]. Based on sputum microscopy, patients are classified as either smear positive or smear negative tuberculosis. A substantive number of patients remain undiagnosed by conventional sputum microscopy. In such situations, Gene Xpert/ Cartridge Based Nuclear Acid Amplification Test (CBNAAT), with a turnaround time of 2 hours, serves as a good diagnostic tool[2].By making an early diagnosis, morbidity, progression, spread of the disease & lung damage by fibrosis can be prevented.

Fiberoptic bronchoscope (FOB), has been adopted in smear negative patients in an attempt to diagnose tuberculosis[3]. Among the bronchoscopic materials, bronchoalveolar lavage (BAL) is the best diagnostic material for the diagnosis of PTB[,4,5,6]. This study was undertaken to assess the role of Gene Xpert in BAL specimen for the diagnosis of PTB among patients who have clinical features and chest X-ray suggestive of PTB, but sputum smear negative for AFB.

Materials and methods

This was a tertiary hospital based, descriptive type of observational study conducted on fifty consecutive patients with clinicoradiologically consistent pulmonary tuberculosis who were either sputum smear negative for AFB or sputum non-producers at the Department of Tuberculosis and Chest Diseases, Institute of Respiratory Diseases, Jaipur from October 2017 to October

2018. This study was approved by the Institutional Review Board, SMS medical College, Jaipur.

Inclusion Criteria

Patients with clinical suspicion of PTB based on clinical symptoms and signs or radiological features, who either had sputum smear (two samples) negative for Tuberculosis or not producing adequate sputum.

Exclusion Criteria

Extrapulmonary tuberculosis, HIV positive patients and those who had contraindications for fibreoptic bronchoscopy were excluded.

The patients were subjected to detailed history and clinical examination, relevant blood investigations and chest x-ray. Two samples of sputum were sent for AFB smear- one at the spot and another next day morning sample. Patients with both samples negative were included in study.In case if patients were not producing sputum spontaneously, they were subjected to a procedure of sputum induction.

Sputum induction (SI)

After asking the patient to gargle his/her mouth with clean water, nebulization with 20 ml of 3% NaCl via the Ultrasonic nebulizer '420AI' was done. Patients who produced adequate (10 ml) of sputum were termed SI success and the rest as SI failures. AFB smear(SI) negatives and sputum induction failures were included for further study.

Bronchoscopic procedure

After written informed consent, bronchoscopy was performed via transnasal route under local anesthesia. Gross observations on examining bronchial mucosa were noted. BAL was taken by instilling normal saline at room temperature through the internal channel of fibreoptic bronchoscope and aspirated into a trap connected to suction tubing, maintaining a suction pressure of <100mmHg.15 to 30 ml of saline was instilled each time and about one fourth to half of this was retrieved in the suction trap. BAL was taken till around 100 ml of fluid was collected. BAL was preferably taken from abnormally visible areas. If no abnormality was visualized, BAL was taken from radiologically localized lobe or lobes.

BAL was subjected to the following:

AFB smear- ZN technique was used for staining.

Mycobacterial culture- BACT/ALERT 3D. All positive culture samples were subjected to either 'NAP test' or 'TB Ag MPT4 Rapid' immunochromatographic assay to differentiate between Mycobacterium tuberculosis complex (MTBC) and Mycobacteria Other Than Tuberculosis (MOTT).

Gene Xpert/CBNAAT - The results from measured fluorescent signals, with embedded calculation algorithms, were: invalid, if PCR inhibitors are detected with amplification failure; negative or positive. If positive, the strain was categorized as susceptible or resistant to rifampicin.

Statistical analysis - Statistical analysis was performed with the Epi info version 7.2.1.0 statistical software package. Qualitative / categorical data was presented as proportion and was analysed using Chi square test. Quantitative data was presented as mean and standard deviation and the difference in mean was analysed using t test.

Results

50 patients were included in our study, 33(66%) males and 17(34%) females. The mean age was 41.4±15.2 years. Common presenting complaints were cough (100%), expectoration (88%) and fever (78%). Radiologically,48% (24/50) patients had cavitatory disease. Also,13(26%), 17(34%),20(40%) had mild, moderate and far advanced diseases respectively, with the proportion of patients diagnosed as PTB in each category were 15%, 47.5% and 37.5% in mild, moderate and far advanced disease respectively. Predominant findings on bronchoscopy were secretions,24(48%), followed by hyperemia 21(42%) & hemorrhagic 3 (6%).

Table No 1: Gender wise distribution of the cases

	Tuberculosis		Non-Tuberculosis		Total	
Gender	No	%	No	%	No	%
Male	28	70	5	50	33	66
Female	12	30	5	50	17	34
Total	40	100	10	100	50	100

Chi-square = 0.031 with 2 degrees of freedom; P = 0.985 NS

Table 2: Comparison of BAL AFB smear with BAL culture (Gold Standard)

	BAL Culture		
BAL AFB	Tuberculosis	Non-TB	Grand Total
Positive	14	1	15
Negative	26	9	35
Grand Total	40	10	50

Table 3: Comparison of BAL Gene Xpert with BAL culture (Gold Standard)

	BAL Culture		
BAL Gene Xpert	Tuberculosis	Non-TB	Grand Total
Positive	29	3	32
Negative	11	7	18
Grand Total	40	10	50

The positivity of BAL AFB smear & Gene Xpert were 15 (30%) & 32 (64%) respectively. With BAL MTB culture as the gold standard, BAL AFB smear showed a sensitivity of 35%, specificity of 90%, positive predictive value (PPV) of 93.3%, negative predictive value (NPV) of 25.7%. BAL Gene Xpert showed a sensitivity of 72.5%, specificity of 70% and PPV of 90.60% and NPV of 38.9%.

Table 4: Comparison of BAL AFB smear with BAL Gene Xpert

	Gene Xpert		
BAL AFB	Positive	Negative	Grand Total
Positive	15	0	15
Negative	17	18	35
Grand Total	32	18	50

A Kappa statistical analysis between BAL AFB smear and Gene Xpert, showed an agreement of 0.388 (0.202 – 0.575), indicating a fair agreement.

Discussion

Conventional methods of diagnosis are less sensitive and time consuming, in the diagnosis of smear negative PTB. Gene Xpert aims at rapid identification of mycobacteria. A 2013 Cochrane systematic review showed that this test is highly accurate when compared to culture, Xpert has about 88% sensitivity and 98% specificity for PTB. In smear-negative patients with TB, Xpert had a sensitivity of 67%[7].

Our study had a male: female ratio of 2.33:1, which was in concordance with Rao et al [8] which had a ratio of 2:1. This male predominance might be due to the fact, females in our country do not report their symptoms and have relatively lower priority and access for medical facilities.

Radiologically, 13 patients (26%) had mild disease ,17(34%) had moderately advanced and 20 (40%) had far advanced disease. Similar method of classification was used by Rawat et al[9]. Also, the proportion of patients diagnosed as PTB in each category in our study were 15%, 47.5% and 37.5% in mild, moderate and far advanced disease respectively. This observation was due to increased bacterial load in more severe disease leading to increased yield in these groups. Out of the 21 patients with hyperemia on bronchoscopy, 17 (80.95%) turned out tubercular, whereas 20 out of 24 patients (83.3%) with secretions turned out tubercular, making secretions a more sensitive predictor of tubercular yield. These findings correspond to the ones by Kulpati et al[10], in which yellowish white secretions were noted in PTB cases. Diagnostic yield of bronchoscopy for tuberculosis was 80% (40/50) in our study. Diagnostic yield for tuberculosis in various published studies ranged from as low as 10% to as high as 100%[11,12,3,14,15,16,17]

BAL AFB smear showed a sensitivity of 35%, specificity of 90%, positive predictive value (PPV) of 93.3%, negative predictive value (NPV) of 25.7% and accuracy of 46% in diagnosis of PTB, similar to other studies [18,19,20]. BAL Gene Xpert had a higher sensitivity compared to AFB smear (29/40; 72.5% vs 14/40; 35%). The sensitivity, specificity, positive predictive value and negative predictive values of BAL gene Xpert in this study were 72.5%, 70%,90.6%,38.9% respectively, which correlated with similar studies[18,20,21,22,23]

However, the sensitivity and positive predictive value of Xpert MTB/RIF assay to detect MTB was very high (72.5% and 90.6% respectively), while the specificity and negative predictive value in this study was low (70% and 38.9%) as compared to the international studies (100 % and 92.1% respectively) [24,25] . Possible explanations include false positive tests in the presence of a negative culture, or laboratory error.

Limitation

The limitation of this study was that only ZN staining, Mycobacterial culture and Gene Xpert of sputum and BAL sample were performed and no other investigative method for diagnosis of PTB. Therefore, no comparison with other methods was possible.

Conclusion

GeneXpert and AFB smear microscopy share almost same specificity but sensitivity of GeneXpert is much higher than AFB smear microscopy in respiratory samples as shown in our study. In a resource limited setting with high case burden, a positive Gene Xpert, owing to its simplicity, sensitivity and automation, can serve as a useful adjunct for the diagnosis of PTB in BAL specimens of smear negative PTB suspects.

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