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BRONCHOALVEOLAR LAVAGE IN THE DIAGNOSIS OF SPUTUM SCARCE AND SPUTUM SMEAR AND GENEXPERT NEGATIVE PULMONARY TUBERCULOSIS

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ABSTRACT **Background:** The menace of tuberculosis can be curtailed by halting the chain of onward transmission by early detection of Mycobacterium Tuberculosis (M. TB). Broncho alveolar lavage sampling (BAL) in sputum scarce or smear negative Pulmonary TB (PTB), can help achieve early diagnosis.

Methods: In this retrospective study, BAL samples of sputum smear negative or sputum scarce suspected PTB were analysed to assess its role in early diagnosis of PTB.

Results: BAL Gene Xpert detected M. TB in 47.06% sputum smear and GeneXpert negative / sputum scarce patients, with one third of these having Rifampicin resistance. Growth of M. TB by liquid culture (MGIT) of BAL was seen in 31.37%. GeneXpert had a sensitivity and specificity of 75%, and 65.7% respectively.

Conclusion: BAL analysis by GeneXpert and MGIT Culture is an important diagnostic tool and should be mandatory in suspected smear negative / sputum scarce PTB patients.

KEYWORDS : BAL in PTB, Sputum negative Tuberculosis

INTRODUCTION:

Tuberculosis continues to be a menace worldwide with more than 10 million new cases and 1.5 million deaths annually and with an estimated 3 million cases remaining undiagnosed each year[1]. India is the highest contributor to the world TB load, adding 26.9 lakh TB cases in 2019 or 27% of the global cases[2]. Additionally, an estimated 1.7 billion people worldwide are infected with M. tuberculosis and are thus at risk of developing the disease[1]. To effectively lessen the impact of this disease, patients must be diagnosed early and treated effectively so that the chain of onward transmission can be curtailed and this infective contagious disease can be decimated. Microbiological and/or molecular diagnosis is the foundation on which treatment of tuberculosis should be based, especially with the rise in drug resistant tuberculosis (DR-TB) across the world. One of the challenges faced in diagnosis is obtaining an adequate relevant sample, especially in extra pulmonary tuberculosis (EPTB); and in pulmonary tuberculosis (PTB) when patient is not producing sputum or the sputum sample is negative for Mycobacterium Tuberculosis (M. TB). In fact, up to 50% of clinically and radiologically suspected cases of PTB are negative for acid-fast bacilli (AFB) on direct sputum smear microscopy[3] and if left untreated, around 70% of these patients would require anti TB chemotherapy within 30 months, and importantly nearly half of these cases would develop active disease within the first three months[4]. Moreover, the risk of infectivity of sputum smear negative PTB has been estimated to be around 17%[5] which is high enough to perpetuate the cycle of transmission of M. TB.

Giving empirical anti tuberculous treatment to such patients should be the last resort after all endeavours to arrive at a confirmatory diagnosis heave failed, because if treatment is inappropriate we may create drug resistant TB or alternatively we might miss out or delay the correct diagnosis as it may not be tuberculosis at all. Broncho alveolar lavage (BAL) samples obtained by Fiberoptic bronchoscopy are the key to early diagnosis in sputum smear negative or sputum scarce suspected PTB patients. BAL sampling must be considered an essential step and incorporated in national TB control programmes if we are to diagnose PTB early and break the chain of transmission. Hence this retrospective study analysed the proportion of sputum smear and GeneXpert negative / sputum scarce suspected cases of PTB whose diagnosis of TB including drug resistant TB could be confirmed by molecular and/or microbiological testing of BAL samples. The sensitivity, specificity , positive predictive value and negative predictive value of BAL GeneXpert compared to BALMGIT liquid culture was also ascertained.

MATERIALS AND METHODS:

Data of patients at a tertiary care hospital, suspected clinically or radiologically or both to have PTB and who underwent Fiberoptic bronchoscopy for diagnosis as they were not producing adequate sputum or were sputum smear negative in 2 consecutive samples and in whom M. TB was not detected in sputum GeneXpert samples, was analysed retrospectively to evaluate the importance of sampling BAL fluid for early diagnosis of PTB. Patients referred to our centre who had received less than 14 days of empirical anti TB chemotherapy were included in the study. As per the protocol in our department for diagnosing patients suspected to have PTB clinically or on X-ray Chest, patients were subjected to investigations like CBC, liver and renal function tests, blood sugar evaluation, HIV screening, urine microscopy, ECG and HRCT Scan of chest, and Sputum smear for AFB and sputum GeneXpert. In patients not producing sputum, an attempt was made to induce the same using hypertonic saline nebulization. If M. TB was not detected in the sputum smear or GeneXpert tests, then patients who had no contraindications to Fiberoptic bronchoscopy and who gave written, informed consent for the procedure were subjected to Broncho alveolar lavage (BAL) sampling by Fiberoptic bronchoscopy. Patients were kept nil orally for at least six hours before the procedure. Pre medication was done with 0.5mg glcoypyronium I.M. and nebulization with short acting bronchodilator half an hour before the procedure. Topical anaesthesia with 2% lignocaine was used for upper respiratory tract and trans tracheal instillation. Patients were sedated with IV short acting benzodiazepine midazolam during the procedure. Broncho alveolar lavage was done by wedging the Fiberoptic bronchoscope into the most distal segment suspected on HRCT Scan, injecting aliquots of 30 ml three times and collecting the return each time by suctioning into a closed system trap device. The lavage was acceptable when the return collected was around 50% of inserted fluid each time This BAL fluid was sent for Ziehl Neelsen smear microscopy for cytology, gram stain and bacterial culture, AFB smear, GeneXpert molecular assay and liquid culture using mycobacteria growth indicator tube (MGIT). Post bronchoscopy sputum was also sent for AFB smear examination.

RESULTS:

Data of 51 patients satisfying the above inclusion criteria and undergoing bronchoscopy in a period of around one year, was analysed. Of the 51 patients, 16 (31.37%) were male and 35(68.63%) female, age group ranging from 18 to 85 years, mean age around 36.5 years. Most patients presented with the cardinal symptoms of cough lasting for more than a week, fever, fatigue, loss of appetite and weight loss. The Chest X-ray revealed consolidation in 49.02% cases, infiltrates or soft opacities in 33.33%, consolidation with cavitation in 11.76%, consolidation with effusion in 3.92% (2 patients), collapse consolidation in 1.96% (1 patient). The predominant HRCT findings in 37 patients (72.55%) were consolidation and tree in bud appearance. Cavitatory consolidation was seen in 11 patients (21.57%), consolidation with effusion in 2 and 1 patient had collapse consolidation. Fiberoptic bronchoscopy was normal in 39 patients (76.47%), 11 (21.56%) had unhealthy mucosa and 1 patient (1.96%) had mucus plugging. There were no complications in any patient during the procedure. Table 1 indicates that in the BAL samples sent for analysis, Mycobacterium Tuberculosis (M. TB) was detected by Gene Xpert in 24 of the 51 patients (47.06%), with 8 of the 24 (33.33%) patients having Rifampicin resistance while in 16 of the 24 Rifampicin resistance was not detected. Growth of M. TB at end of 6 weeks by liquid culture (MGIT) of BAL was seen in 16 of the 51 samples (31.37%). Overall, in the 51 patients in whom two samples of sputum smear were negative for acid fast bacilli and sputum Gene Xpert also did not detect M.TB; diagnosis of TB was confirmed by BAL sampling in 56.86% (29 out of 51) cases . Using liquid culture MGIT as the gold standard, GeneXpert had a sensitivity of 75% (47.4% - 91.7%) and specificity of 65.7% (47.7%-80.3%), positive predictive value of 50% and negative predictive value of 85.2% (Table 2). However, culture is an imperfect reference standard, especially in patients with a lower bacterial load or those who have received anti tuberculous drugs[6].

Table 1: Bal Yield By Genexpert And Mgit In Suspected Ptb Patients (sputum Smear And Sputum Genexpert Negative Or Sputum Scarce)

BAL SAMPLE	GENEXPERT	MGIT
M.TB DETECTED / GROWTH	47.06 %	31.37 %
M.TB NOT DETECTED / NO GROWTH	52.94 %	68.63 %

Table 2: Sensitivity And Specificity Of Genexpert With Mgit Culture As Gold Standard

	Estimated	95% Confidence Interval	
	Value	Lower Limit	Upper Limit
Prevalence	0.314	0.195	0.46
MGIT GeneXpert Sensitivity	0.75	0.474	0.917
MGIT GeneXpert Specificity	0.657	0.477	0.803
For any particular positive test result, the probability that it is:			
True Positive	0.5	0.296	0.704
False Positive	0.5	0.296	0.704
For any particular negative test result, the probability that it is:			
True Negative	0.852	0.654	0.951
False Negative	0.148	0.049	0.346

DISCUSSION:

WHO's global End TB Strategy prioritizes early diagnosis of TB, which should include the universal availability of DST, and systematic screening of contacts and high-risk groups. However, not much emphasis has been placed on obtaining high quality samples like BAL for diagnosis of sputum smear negative or sputum scarce suspected PTB patients, which is the key to reducing the diagnostic delay and cutting off the chain of transmission. More than one third of patients with pulmonary TB cannot produce sufficient sputum or are sputum smear negative and are at an increased risk of having a poor outcome themselves as well as of spreading the disease due to a delay in diagnosis and treatment[7]. Using molecular diagnostic tests like Gene Xpert and microbiological tests like liquid culture on BAL specimens not only increases diagnostic sensitivity but also aids in rapid and early diagnosis of drug resistant TB.

BAL done by Fiberoptic bronchoscopy is an uncomplicated and safe diagnostic interventional tool yielding good results. Compared to bronchial washing the detection rate of M. TB by culture or CBNAAT has been reported to be significantly higher in BAL specimens[8], probably due to lower concentration of aspirated local anaesthetic which can inhibit growth of M. TB and also because lavage is usually done from targeted bronchial sub segments as assessed by HRCT Scan. Studies have reported sensitivity of BAL CBNAAT ranging from 31.3-83.8% and specificity ranging from 92.4-98.2%[9,10]. In our study BAL GeneXpert had a sensitivity of 75% and specificity of 65.7%. The lower specificity compared to other studies could be due to inclusion of referred cases which had received less than 14 days of empirical anti TB chemotherapy resulting in negative cultures. Studies have reported BAL CBNAAT positive yields between 48 to 75% [8,10] and BAL MGIT positive culture yields ranging from 32% to 76 %[6, 10] in sputum smear negative TB. In our study the BAL Gene Xpert samples detected M. TB in 47.06% cases and BAL MGIT culture grew M. TB in 31.37%. One third (33.33%) of the samples in which M. TB was detected by GeneXpert showed resistance to Rifampicin. There were no complications during the procedure in any patient.

Fiberoptic bronchoscopy has become a common, easily available, simple procedure and BAL sampling itself is a safe, relatively non-invasive compared to brush or trans bronchial biopsies and an effective diagnostic modality which should be incorporated as a necessary step in diagnosis of sputum scarce or sputum smear and GeneXpert negative suspected PTB cases for early, rapid diagnosis of TB and detection of Drug Resistant TB.

CONCLUSION:

In our study group of 51 patients where sputum smear and Gene Xpert could not detect M.TB , BAL sampling detected M.TB by BAL CBNAAT GeneXpert in 24 patients (47.06%) with Rifampicin resistance detected in 8 patients and M.TB growth was seen in BAL MGIT in 16 patients (31.37%).. Thus in sputum smear and Gene Xpert negative for M.TB and in sputum scarce suspected PTB patients, a definitive diagnosis of PTB and rapid and early detection of drug resistant TB can be achieved by subjecting them to Fiberoptic bronchoscopy and sampling BAL fluid for Gene Xpert. Hence BAL sampling should be incorporated as a necessary step in the diagnostic algorithm in suspected PTB patients for early detection and for controlling the spread of PTB.

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