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Original Research Article

Efficacy of cartridge based nucleic acid amplification test to diagnose tubercular pleural effusion

Prem P. Gupta[1]*, Adarsh B. Mynalli[1], Aparna Yadav[2]

[1]Department of Respiratory Medicine, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India
[2]Department of Microbiology, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India

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***Correspondence:**
Dr. Prem P. Gupta,
E-mail: gparkas@yahoo.co.in

ABSTRACT

Background: Tuberculosis (TB) remains a major health concern worldwide. Extra pulmonary tuberculosis (EPTB) in India accounts up to 20% of all tuberculosis cases. EPTB often remains undetected and untreated due to variable clinical presentation and lack of diagnostic means. Early detection of TB and drug resistance is important in the management of TB. The aim of present study was to assess the role of cartridge based nucleic acid amplification test in rapid diagnosis of tubercular pleural effusion.
Methods: The study screened 211 symptomatic patients. The patients with clinical and radiological presentations suggestive of pleural effusion were analyzed using light's criteria to make a diagnosis of tubercular pleural effusion; these patients submitted pleural fluid sample for smear microscopy after concentration for presence of acid fast bacilli under light emitting diode based fluorescent microscopy (LED-FM), and for cartridge based nucleic acid amplification test (CBNAAT) using GX4 GeneXpert MTB/Rif test system. The results were statistically analyzed.
Results: Out of patients who had pleural effusion without any pulmonary tuberculosis, pleural fluid biochemistry analyses using light's criteria detected 20 tubercular pleural effusions (11 male and 9 female). Seven patients had history of extrapulmonary tuberculosis in past, all of them received treatment with effective treatment compliance in past. Pleural fluid microscopic examination for detection of acid-fast bacilli was not able to detect acid-fast bacilli in any of these 20 patients diagnosed with tubercular pleural effusion. CBNAAT could authentically detect *M. tuberculosis* in 5/20 patients diagnosed with tubercular pleural effusion. There was no impact of gender, previous history of tuberculosis, history of anti-tuberculosis treatment (ATT) intake, or compliance to ATT on CBNAAT status in this study.
Conclusions: CBNAAT has the potential to significantly authenticate tubercular etiology in some of smear-negative pleural fluid specimens with rapid test results. It has an added advantage to assess the rifampicin drug sensitivity. All this contribute hugely in diagnosis and management of tubercular pleural effusion.

Keywords: Cartridge based nucleic acid amplification test, GeneXpert MTB/Rif test, Extrapulmonary tuberculosis, Pleural effusion, Rifampicin resistance

INTRODUCTION

Tuberculosis (TB) is, presently, a leading cause of death worldwide alongside HIV. Despite being isolated by Robert Koch in 1882, as well as the availability of effective treatment and the use of a live attenuated vaccine, TB remains one of the deadliest communicable diseases. According to WHO estimates 1.5 million of TB

deaths occurred globally in 2014. India is presently one of the nine high burden countries for TB and accounts for 23% of the global TB burden with 2.2 million patients with tuberculosis, and additionally for a third of the 'missing cases' that do not get diagnosed or notified.[1]

Tuberculosis may involve pulmonary as well as extra pulmonary sites (EPTB); former constituting the bulk of burden. Diagnosis of pulmonary tuberculosis poses lesser difficulties when compared to extrapulmonary tuberculosis since direct smear microscopy and cartridge based nucleic acid amplification test (CBNAAT) provide rapid and authentic diagnosis in majority of patients with pulmonary tuberculosis. It is estimated that 15% to 20% of all TB cases have extra pulmonary site involvement including lymph nodes, meninges, kidney, spine and growing ends of the bones.[2]

The major hindrances to the diagnosis of EPTB are often atypical clinical presentation and lack of standardized laboratory methods. The diagnosis is compromised due to paucibacillary nature of the disease with low bacterial load in extrapulmonary specimens.

Histocytological examination has its limitations as it cannot differentiate between TB and other related diseases like sarcoidosis or non-tubercular mycobacterial. Serological assays including antigen and antibody detection which were used very frequently in past had a reputation of creating more diagnostic confusion than solving the problem and lead to wide spread misleading results; these tests were very rightly banned by the government of India. Other tests that are also being employed for the diagnosis of EPTB include tuberculin test and polymerase chain reaction (PCR) assays; however, the specificities and sensitivities of these tests are variable. Also, these tests require many technical steps, and some have a relatively long turnaround time.[3]

Rapid identification is essential for initial treatment initiation, improved patient outcome as well as for more effective public health intervention and it relies mainly on Nucleic acid amplification techniques (NAAT).[4] Cartridge based nucleic acid amplification test (CBNAAT), specific for *Mycobacterium tuberculosis*, has been recently introduced for detection of TB. It has an added advantage of detecting rifampicin resistance as it targets the rpoB gene of mycobacteria, which is the critical gene associated with rifampicin resistance. In a study including pulmonary tuberculosis patients, the overall sensitivity, specificity, positive predictive value and negative predictive value of CBNAAT test (GeneXpert MTB/RIF assay) were found to be 98.6%, 100%, 100% and 93.8%, respectively.[5]

Pleural TB is the second most frequent form of extrapulmonary TB and the most frequent cause of exudative pleural effusions in areas with a high prevalence of HIV infection. The diagnostic workup includes pleural fluid aspiration; however, pleural fluid smear and culture are often negative due to the paucibacillary nature of pleural TB.[6,7]

CBNAAT, which is a recommended tool to diagnose pulmonary tuberculosis, its efficacy in the diagnosis of tubercular pleural effusion has not been widely studied. We planned this study to evaluate the role of CBNAAT in early diagnosis of tubercular pleural effusion using CBNAAT compared to conventional sputum microscopy and early detection of mycobacterial susceptibility to rifampicin.

METHODS

The present study was undertaken at the departments of respiratory medicine and microbiology at institute. All eligible patients attending the respiratory medicine department during study period with symptoms suggestive of tuberculosis and who were diagnosed to have pleural effusion using digital chest radiographs including standard Posterio-anterior and lateral views (Table 1) and who consented for present study, were further investigated for diagnosis of tuberculosis. All these patients underwent chest ultrasonography to assess the characteristic of pleural effusion and to mark most readily approachable thoracic site for thoracentesis.

Table 1: Diagnostic evaluation of patients following clinical presentation.

Diagnostic evolution
Clinical symptoms
Cough more than two weeks
Fever more than two weeks
Haemoptysis
Significant weight loss
Significant decrease in appetite
History of any tuberculosis treatment in past
Chest radiograph suggestive of pleural effusion

Table 2: Light's criteria.[8]

Pleural fluid	Pleural fluid /serum protein ratio	Pleural fluid /serum lactate dehydrogenase ratio	Pleural fluid lactate dehydrogenase (U/L)
Transudative	< 0.5	< 0.6	< 2/3 URL**
Exudative*	≥ 0.5	≥ 0.6	≥ 2/3 URL**

Pleural fluid was collected after informed consent from each patient from point of aspiration marked by chest ultrasonography taking all aseptic precautions. The pleural fluid samples were submitted for biochemical analyses using light's criteria (Table 2).[8] All patients fulfilling the light's criteria were considered as having tubercular pleural effusion. Pleural fluid earlier collected from each patient was also analyzed by microbiological tests: pleural fluid smear microscopy after concentration for presence of acid fast bacilli under light emitting diode based fluorescent microscopy (LED-FM) and pleural fluid CBNAAT. Pleural fluid microscopic examination after concentration of pleural fluid was done at the department of microbiology at institute.

Cartridge based nucleic acid amplification test

The Xpert MTB/Rif test is a cartridge-based fully automated NAAT (nucleic acid amplification test) currently recommended by WHO 9 and adopted by revised national tuberculosis control programme run by government of India for detection of tuberculosis case and rifampicin resistance. The underlying principle of Xpert assay being detection MTB and rifampicin resistance by polymerase chain reaction based amplification of the 81-bp rpoB gene segment and probing for the mutations that are related to rifampicin resistance. The assay is automated and completes within 2 hours, with minimal hands-on technical time.[10,11]

The test is highly specific and does not give cross reactions with any other bacterial species including a comprehensive panel of mycobacteria thereby excluding non-tubercular mycobacteria. Although molecular amplification is already a proven technology in TB diagnosis, other existing tests are too complex for routine and widespread use in field conditions at peripheral level. GeneXpert, the test device platform, was launched by Cepheid in 2004 and simplifies molecular testing by fully integrating and automating the three processes (sample preparation, amplification and detection) required for real-time PCR-based molecular testing.

The Xpert MTB/RIF test uses a cartridge containing all elements necessary for the reaction, including lyophilized reagents, liquid buffers and wash solutions. With observing aseptic technique, pleural fluid sample was collected in a falcon tube. The sample was loaded into cartridge and analyzed for presence of mycobacteria and rifampicin resistance in GX4 System (with 4 modules). CBNAAT was also carried out at the department of microbiology using GeneXpert MTB/Rif test module.

Statistical analysis

Statistical analyses were done using SPSS 24 software. The tests used were Pearson chi-square, Continuity correction, Fisher's exact test, Likelihood ratio, Linear-by-linear association.

RESULTS

The present study screened 211 patients with clinical symptoms suggestive of pulmonary tuberculosis. Out of patients who had pleural effusion without any pulmonary tuberculosis over chest radiographs and chest ultrasonography, the pleural fluid biochemistry analyses using light's criteria (Table 2) detected 20 pleural effusions with etiology of tuberculosis. The detailed characteristics of these 20 patients are shown in Table 1. There were 11 male and 9 female patients. Seven patients had history of extrapulmonary tuberculosis in past, all of them received treatment: six patients received anti-tuberculosis treatment (ATT) once and one patient received ATT two times on two separate occasions. All of them had good compliance to anti-tuberculosis treatment adherence. Three patients had a family member with diagnosed pleural effusion.

Table 3: Characteristics of patients with pleural effusion.

Parameters	Frequency	Percent
Subjects with all study parameters completed	20	100
Male study subjects	11	55
Female study subjects	9	45
History of extrapulmonary tuberculosis	7	35
History of ATT intake-once only	6	30
History of ATT intake-two times	1	05
Positive sputum AFB status in these cases in past	3	15
compliance to ATT in past	7	35
Past treatment completion in extrapulmonary tuberculosis cases	7	35
Family history with tubercular pleural fluid	3	15

Table 4: CBNAAT status in patients with pleural effusion.

Detection of *M. tuberculosis* by CBNAAT					
		Frequency	Percent	Valid Percent	Cumulative percent
Valid	Not detected	15	75.0	75.0	75.0
	Detected	5	25.0	25.0	100.0
	Total	20	100.0	100.0	

Pleural fluid concentration smear examination for acid fast bacilli under light emitting diode based fluorescent microscopy (LED-FM) could not detect acid fast bacilli in any patient diagnosed to have tubercular pleural effusion based on light's criteria. Table 4 provides details of CBNAAT outcome; five out of 20 patients had a positive CBNAAT confirming the presence of *M. tuberculosis* in specimen of these patients. There was no rifampicin resistance in any of these patients screened by CBNAAT.

Table 5: Impact of gender over pleural fluid CBNAAT status.

	Value	df	Asymp. sig. (2-sided)	Exact sig. (2-sided)	Exact sig. (1-sided)
Pearson chi-square	0.067[a]	1	0.795		
Continuity correction[b]	0.000	1	1.000		
Likelihood ratio	0.068	1	0.795		
Fisher's exact test				1.000	0.604
Linear-by-linear association	0.064	1	0.800		
N of valid cases	20				

a) 2 cells (50.0%) have expected count less than 5. The minimum expected count is 2.25. b) P value is 0.795 which is >0.05. Hence, there is no strong association between these two parameters.

Table 6: Impact of history of tuberculosis over pleural fluid CBNAAT status.

	Value	df	Asymp. sig. (2-sided)	Exact sig. (2-sided)	Exact sig. (1-sided)
Pearson chi-square	1.832[a]	1	0.176		
Continuity correction[b]	0.659	1	0.417		
Likelihood ratio	1.770	1	0.183		
Fisher's exact test				0.290	0.207
Linear-by-linear association	1.740	1	0.187		
N of valid cases	20				

a) 2 cells (50.0%) have expected count less than 5. The minimum expected count is 1.75. b) P value is 0.176 which is >0.05 which is insignificant. Hence, there is no strong association between these two parameters.

Table 7: Previous episodes of ATT and pleural fluid CBNAAT status.

	Value	df	Asymp. sig. (2-sided)
Pearson chi-square	3.863[a]	2	0.145
Likelihood ratio	3.693	2	0.158
Linear-by-linear association	2.980	1	0.084
N of valid cases	20		

a) 5 cells (83.3%) have expected count less than 5. The minimum expected count is .25 b) P value is 0.145 which is >0.05 which is insignificant. Hence, there is no strong association between these two parameters.

There was no impact of gender on CBNAAT status as shown in Table 5. A previous history of tuberculosis had no influence over CBNAAT outcome results (Table 6). Moreover, history of ATT intake (Table 7) and compliance to ATT taken during previous episode of tuberculosis (Table 8), both had no influence over CBNAAT results in tubercular patients. A summary of study outcomes showing comparative efficacy of CBNAAT versus Smear microscopic examination in detection of *M. tuberculosis* in pleural fluid with an added advantage of showing mycobacterial susceptibility to rifampicin is shown as a flowchart in Figure 1.

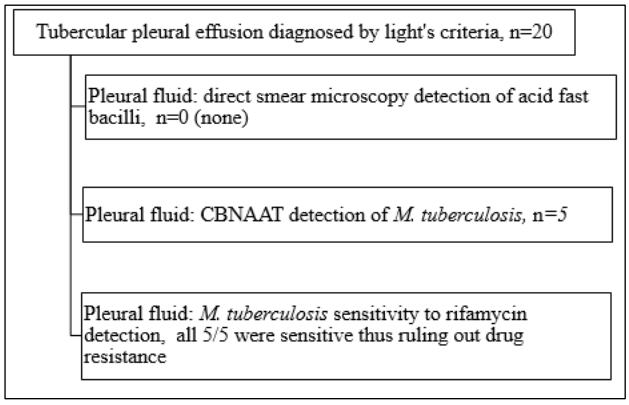

Figure 1: Summary of study outcomes showing efficacy of CBNAAT in detection of *M. Tuberculosis* in pleural fluid with an added advantage of showing rifampicin sensitivity.

Table 8: Compliance to previous episodes of ATT and pleural fluid CBNAAT status.

	Value	df	Asymp. sig. (2-sided)	Exact sig. (2-sided)	Exact sig. (1-sided)
Pearson chi-square	1.832[a]	1	0.176		
Continuity correction[b]	0.659	1	0.417		
Likelihood ratio	1.770	1	0.183		
Fisher's exact test				0.290	0.207
Linear-by-linear association	1.740	1	0.187		
N of valid cases	20				

DISCUSSION

Tuberculosis has been a major challenge in countries suffering with a high load of HIV co-infection along with a resource-limited socio-economic scenario.[12] These risks are further increased manifold due to increased probability of presence of multi-drug resistant tuberculosis. To address these challenges, there is a critical need for rapid and authentic screening for TB and detection of drug resistance for early initiation of appropriate treatment.

Although TB affects the lungs in many patients, extrapulmonary TB serves as the initial presentation in about 25% of adults, and primarily involves the lymph nodes and pleura.[13] Earlier, TB pleural effusions were considered to occur largely due to delayed hypersensitivity reaction. The animal modal of guinea pigs sensitized with heat killed *M. tuberculosis* were injected with tuberculin into the pleural cavity that lead to large protein-rich pleural effusion over a 24-hour period.[14] Moreover, in past researchers were unable to culture *M. tuberculosis* from pleural fluids. As a result, the pathogenesis was presumed to be due to delayed hypersensitivity rather than a direct infection of the pleural space.

The pleural effusion is usually a manifestation of paucibacillary mycobacterial infection within the pleural space, which is acquired from initial parenchymal lesions and results in an immunological response that increases pleural fluid formation and decreases pleural fluid removal.[15]

Initially, there is a neutrophilic inflammatory response within the pleura followed by a protracted lymphocyte driven immune reaction which is characterized by pleural granuloma formation and release of adenosine deaminase (ADA). Polymorphonuclear leukocytes are the first cells to respond, remaining the predominant cells for the first 24 hours, and are then followed by macrophages, which peak at 96 hours, and then by lymphocytes. It seems the polymorphonuclear leukocyte influx is a specific response to pleural injury and, either through itself or its interaction with the macrophage, plays a role in host defence mechanisms against the tubercle bacilli.[16,17]

The cellular mechanisms hypothesis in pleural TB suggests that a potent T-helper type 1 (Th1)-like immunity is accountable for the containment of *M. tuberculosis* and these protective effects are antagonized by T-helper type 2 cytokines, mainly interleukin (IL)-4.[18] Activated Th1 cells, mediate release of interferon gamma (IFN-γ) and other Th1 cytokines, activate macrophages to kill *M. tuberculosis*, whereas Th2 cytokines block this effect.[19]

The predominance of Th1 immunity in TB pleural effusions is characterized by the high levels of IFN-γ, and other inflammatory cytokines; the proportion of helper T-cells in pleural fluid are also elevated compared with peripheral blood thus, creating a compartmentalized pleural space.[16,18] The frequency of IL-4 producing T-cells representing Th2 immunity, is significantly lower in pleural fluid compared to peripheral blood[18]. With the advent of improved culture media, it is now possible to culture *M. tuberculosis* from both pleural fluid and pleural tissue in as many as 70% of cases.[20] It is plausible that the likelihood of a positive pleural fluid culture decreases with time, as the effusion becomes lymphocyte predominant along with containment of viable mycobacteria.

Conventional smear microscopy, often used as a first line of diagnostic tool for diagnosis of pulmonary tuberculosis being a simple, economical, and easy-to-do test, could not provide diagnosis in any subjects in present study. Apart from being an operator dependent test, it needs over 10,000 bacilli per ml to give a positive result. In present study, cartridge based nucleic acid amplification test (CBNAAT) detected *M. tuberculosis* in pleural fluid samples of 5/20 patients with suggested tubercular effusion diagnosed based on Light's criteria.

Additionally, mycobacterial susceptibility to rifampicin was ascertained in all these five patients. The Xpert MTB/RIF test exhibits high sensitivity and specificity for detecting pulmonary TB disease. An in- vitro study demonstrated a limit of detection of as few as 131 colony-forming units/mL of MTB, compared with approximately 10,000 colony-forming units/mL with conventional smear microscopy. CBNAAT is a useful surrogate test for screening for MDR-TB as past studies on drug resistance have shown that rifampicin resistance

seldom occurs alone and around 90 % of rifampicin resistant patients are diagnosed to have MDR-TB.[21] CBNAAT is having unmatched significance in TB endemic areas like India where there is high prevalence of MDR-TB, around 3% in new cases and 12 to 18% in previously treated cases.[21]

One study from India observed the positivity rate for detection of mycobacteria with CBNAAT assay was 32% in pleural fluid specimen.[22] Another study reported 15.8% of tubercular pleural fluid specimen to be positive for mycobacteria over CBNAAT.[23] Hillemann et al found 3 positive GeneXpert results out of 113 pleural fluid samples (2.9%) all of which were negative on mycobacterial culture.[24] Although GeneXpert assay is considered a breakthrough in the diagnosis of TB and EPTB, one of the major limitations of this technique is that it cannot distinguish between viable and non-viable microorganisms while detecting mycobacterial DNA. Hence it should not be used to monitor patients or efficacy of the treatment.

This molecular technique of GeneXpert assay is relatively more expensive than traditional culture methods; however, it makes an important contribution to the modern-day detection of TB with higher sensitivity and provides a more rapid diagnosis than culture and histology. Study findings support the routine use of GeneXpert assay for the diagnosis of EPTB in pleural fluids as time factor has a very crucial role in its laboratory diagnosis.

CONCLUSION

GeneXpert assay has the potential to significantly improve and escalate the diagnosis of smear-negative pleural fluid specimens. Also, detection of rifampicin resistance aids in prompt initiation of appropriate therapy and thus improving the overall quality of TB care.

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