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Role of GeneXpert in the diagnosis of extrapulmonary tuberculosis

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Abstract

The World Health Organization endorsed the cartridge-based nucleic acid amplification test Xpert MTB/RIF (GXP) for the diagnosis of tuberculosis (TB). Studies about GXP efficiency in extrapulmonary TB (EPTB) are scarce. Hence, we decided to study the role of GXP in EPTB.

This prospective observational study, conducted in the pulmonary medicine department of a tertiary care hospital after ethics committee permission, recruited 200 EPTB patients. The diagnosis of TB was achieved with the help of clinico-radiological correlation with microbiological test positivity. Acid-fast bacilli (AFB) culture was treated as the comparative gold standard. Patients who had no or incomplete data were excluded from the study. Data was analyzed to calculate the sensitivity, specificity, positive predictive value, and negative predictive value for the diagnosis of TB and the detection of rifampicin resistance.

The majority of cases were women (126 patients: 63%). The mean age was 23.71 years. On GXP, 130 (65%) had detected mycobacterium tuberculosis (MTB), and 70 (35%) did not. Adding AFB culture data, 168 (81.5%) showed microbiological evidence of TB, and 32 (18.5%) were negative. On the drug susceptibility test, 131 cases were rifampicin-sensitive, 32 were rifampicin-resistant TB, and in 5 cases, data was unavailable. The most common extrapulmonary site of involvement was the lymph node, with 94 patients (47%). The most common lymph node involved was the cervical lymph node, with 70 patients (74.5%). The sensitivity, specificity, positive predictive value, and negative predictive value of GXP in EPTB collectively were 76.68%, 86.48%, 96%, and 45.7%, respectively.

GXP is useful for the rapid detection of EPTB and the identification of rifampicin resistance, especially in a high-prevalence country like India.

Key words: CBNAAT, EPTB, tuberculosis.

Introduction

Tuberculosis (TB) remains a major health problem accounting for millions of new cases and deaths every year worldwide. India is the highest burden country in the world having an estimated incidence of 24.2 lakh cases in 2022 [1]. In 2022, with an increase in notification of over 13% as compared to 2021, the case notification rate was approximately 172 per lakh population [2]. Extra pulmonary tuberculosis (EPTB) is frequently a diagnostic and therapeutic challenge. It is a common opportunistic infection in people living with HIV/AIDS and other immunocompromised states such as diabetes mellitus and malnutrition [3]. EPTB encompasses the various conditions caused by Mycobacterium tuberculosis infection of organs or tissues

outside the lungs. For example: pleura, lymph nodes, abdomen, genitourinary tract, skin, joints, bones or meninges. Symptoms and signs are specifically related to the affected organ system. There is a paucity of data from clinical trials in EPTB and most of the information regarding diagnosis and management is extrapolated from pulmonary TB. Acid Fast Bacilli (AFB) liquid culture is considered as the gold standard test for determination of TB but the turnaround time is 2–8 weeks, and it requires trained personnel and expensive lab equipment [4]. Smear microscopy for acid fast bacilli (AFB) is one of the rapid and inexpensive tests available, but it has poor sensitivity and poor predictive value in the diagnosis of both pulmonary and extra pulmonary tuberculosis. Xpert MTB/RIF (rifampicin) assay (GXP) is a novel, integrated, cartridge-based, nucleic acid amplification test (CBNAAT) for rapid diagnosis of MTB. It can be used for quick detection of rifampicin resistant tuberculosis (RRTB), in both pulmonary and EPTB cases [5,6]. GXP test has been developed and launched by a foundation for innovative new diagnostics (FIND) and Cepheid Corporation in 2004. However, the development of the GXP was completed in 2008. The World Health Organisation (WHO) endorsed the GXP for the use in TB endemic countries in December 2010 declaring it a major milestone for global diagnosis of tuberculosis [7]. GXP has a relatively high specificity in EPTB while sensitivity is generally lower and highly variable among sample types and test method [8]. Hence, we decided to study the role of GXP in the detection of EPTB in a tertiary care hospital. The objective was to evaluate diagnostic accuracy of GXP for the detection of mycobacterium tuberculosis in extra pulmonary samples by calculating sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and compare with conventional techniques like acid fast bacilli smear microscopy and culture.

Materials and Methods

A prospective observational study was conducted in pulmonary medicine department of a tertiary care hospital after institutional ethics committee permission (PG Academic Committe/Ecarp/2021/07). Sample size was calculated taking into consideration 15% [3,8], as the proportion of EPTB using the sample size calculator which yielded 196 which was rounded off to 200. Diagnosed EPTB patients, referred to our pulmonary medicine outpatient and in-patient department whose GXP, AFB culture and line probe assay (LPA) reports were available were enrolled in the study. These EPTB cases majorly consisted of lymph node TB and TB pleural effusion and some CNS TB, TB spine, other bone TB, Abdominal TB, TB pericardial effusion, and others referred for opinion to our department. Demographic data, clinical history, examination findings and radiological tests of these patients were noted. Diagnosis of TB were achieved with the help of clinico-radiological correlation with microbiological test positivity. AFB culture (liquid culture method) was treated as the comparative gold standard. Patients who

had no or incomplete data were excluded from the study. Invalid and erroneous GXP reports were repeated and confirmed MTB detected or not detected reports were only included in the study.

Ultrasound guided lymph node biopsy and fine needle aspiration cytology samples in lymph node TB, pleural fluid and pleural biopsy samples in TB pleural effusion, cerebrospinal fluid studies in TB meningitis, CT guided biopsy sample of vertebrae and paravertebral collections in TB spine, colonoscopy guided biopsy samples in abdominal TB cases; whose GXP, AFB smear and culture, LPA reports were recorded.

Qualitative data was represented in percentages and mean. Data was analysed to determine the performance (sensitivity, specificity, PPV, NPV) of GXP and compare it with conventional technique like AFB Smear and Culture. The sensitivity, specificity, PPV and NPV were calculated for diagnosis of TB and detection of rifampicin resistance using formulas. Chi-square test was used to study significance.

Results

Two hundred patients were included in the study. The mean age was 23.71 years. Majority of the patients were of age group 11-20 years with 92 (46%) patients and second most common age group was 21-40 years with 91 (45.5%) patients. The age group of 0-10 years, 41-60 years, 61-80 years; consisted of 1(0.5%), 14 (7%) and 2(1%) patients respectively. Out of the 200 patients, 74(37%) were men and 126 (63%) were women. The most common site of EPTB in this study was lymph nodes with 94 patients (47%) and the second commonest was pleural effusion with 69 patients (34.5%). Table 1 summarises the different sites of involvement in EPTB. Few patients had disseminated EPTB wherein they had more than one site involvement. Hence the sum total of no of patient's belonging to individual subtypes exceeds 200 due to the overlap. Cervical lymphadenopathy was the most common site of lymphadenopathy with a total of 70 out of 94 patients (70%) and the second commonest site was mediastinum with 22 patients (23.4%).

Out of the total 200 patients, 130 (65%) patients had GXP report suggesting MTB detected and in 70(35%) patients MTB was not detected. Table 2 enlists the comparison of GXP at different EPTB sites. Out of the total; 60/94 (63.8%) lymphadenopathy, 29/69 (42%) of pleural effusion, 22/33(66.6%) Bone TB, 12/20 (60%) abdominal TB and 3/5 (60%) pericardial effusion, had detected MTB on GXP. In the small numbers of CNS, skin, breast and retropharyngeal TB all (100%) were GXP MTB detected.

Of the 200 patients, 168 detected MTB by GXP and/or AFB culture methods and 32 were negative microbiologically. Of the 168; 5 had only GXP evidence of TB, 38 were only AFB culture positive and 125 had both GXP and AFB culture evidence of TB. Table 3 enumerated

the GXP and AFB culture reports. On DST; 131 were rifampicin sensitive, 32 were RRTB and in 5 data was unavailable. Of the 32 RRTB; 23 were multi-drug resistant (MDR) TB, 7 were pre-extensively drug resistant with additional fluoroquinolone resistance (PRE XDR FQ) TB, 1 was pre-extensively drug resistant with additional second-line injectable resistance (PRE XDR SLI) TB, 1 was extensively drug resistant (XDR) TB.

Out of the 200 patients; 145 were Mantoux positive, 15 were Mantoux negative and in 40 patients, the test was not done. Out of the 200 patients; 125 were true positive (both GXP MTB detected and AFB culture positive), 32 were true negative (both GXP MTB not detected and AFB culture negative), 5 were false positive (only GXP MTB detected) and 38 were false negative (GXP MTB not detected and AFB culture positive). Sensitivity, specificity, positive predictive value and negative predictive value of GXP in EPTB were 76.68%, 86.48%, 96% and 45.71% respectively. The sensitivity, specificity, PPV, NPV negative of GXP for diagnosis of TB at each extrapulmonary sites is given in Table 4 and Figure 1.

Discussion and Conclusions

Rapid identification of TB is essential for early treatment and to improve patient outcomes. GXP is helps to achieve the same. We discuss results from our study in relation with our study objectives and other similar studies.

In the study by Chander et al, the mean age of patients was 26.67 ± 11.72 years and most of the patients were in the age group of 15-34 years [9], which was almost similar to our study. In the study by Sankar et al [10], most common forms were lymph node TB (35%) followed by pleural (20), bone (10) and genitourinary (9%). Cerebrospinal, abdominal, skin sites etc. accounted for remaining 26% cases. Similar distribution was observed in our study with most common site been lymph node followed by pleura. Cervical lymph nodes were the most common site of involvement and reported in 60% to 90% patients with or without involvement of other lymphoid tissue as reported by Mohapatra et al. [11], which concurred with our study results.

The GXP is believed to be a "game-changer" in the field of TB diagnostics. In the most of the studies it has been documented that less than 50% compared were diagnostic on GXP where as our study documented a higher diagnostic yield of 65% on GXP test. Ahmed et al in 2014 did a similar study with a total of 100 extra pulmonary samples were processed, (60 pus, 19 pleural fluids, 16 ascitic fluids and 5 CSF). Out of these 37% had MTB detected on GXP test, 17% were AFB culture positive and 12 % were AFB smear positive [12]. Avashia et el in 2016 in their study on comparison of conventional methods with GXP in extra pulmonary tuberculosis, found a diagnostic yield of 37% [13]. The study by Uppe et al, a comparison study of GXP versus AFB Culture in Extra pulmonary tuberculosis in 2019, showed that 39.33%

of all extra pulmonary sample detected MTB [14]. The most probable reason for this increase in the positivity in our study may be because of increase in the availability of GXP as an upfront test for diagnosis in the current era. In our study sensitivity of GXP was 76.68%, specificity was 86.48%, PPV was 96% and NPV was 45.71%, with respect to culture as reference standard in EPTB. The results are similar to other studies. Mechal et al in 2019 showed the sensitivity and specificity of GXP 79.3% and 90.3% respectively in EPTB [15]. In the study conducted by Sasikumar et al, the PPV and NPV were 96% and 47% [16]. In a study by Habous et al, of 168 non respiratory samples, 52 samples were positive by both culture and GXP, 9 samples were detected positive only by culture [17]. In our study, GXP was false positive in 5 cases. False positivity of GXP results has been reported previously and occurs because of the presence of dead MTB in the test samples, particularly among previously treated patients. There are highly likely chances for such patients to receive avoidable anti-TB therapy. Hence, careful history taking with emphasis on previous treatment with anti-TB drugs is essential to prevent unnecessary treatment of such false positive cases.

Worldwide, tuberculosis resistance to anti-bacillary treatments was estimated by WHO in 2017 at 18% in treated cases and 3.5% in new cases. The national anti-tuberculosis drug resistance survey (NDRS) from India 2014-16 showed that RR-TB was estimated in 6.19% among all TB patients with 2.84% among new and 11.60% among previously treated TB patients [18]. The WHO recommended GXP in 2010 for the diagnosis of pulmonary tuberculosis and subsequently in 2013 for the diagnosis of extra-pulmonary tuberculosis [1]. WHO recommendations for the integration of GXP in the process of TB diagnosis are linked to its short time to results and demonstrated performance (sensitivity and specificity) for both pulmonary and extra-pulmonary tuberculosis diagnosis. In our study out of 200 patients; 32 (16%) patients were rifampicin resistant. This increased estimate could be due to referral bias to a tertiary care centre of majorly difficult to treat TB cases. In Sasikumar study, the sensitivity, specificity, PPV, NPV of GXP in diagnosis and detection of rifampicin resistance in extra pulmonary TB cases was 97%, 95%, 97%, 95%, respectively [16]. Our study, the sensitivity, specificity, PPV, NPV of GXP in diagnosis and detection of rifampicin resistance in extra pulmonary TB cases was 90.32%,99.24%,96.55%,98.49% respectively, which is similar to the above study. In our study out of 32 Drug resistant cases, 23 were Multidrug resistant (MDR),7 were Pre-XDR with fluoroquinolone resistance (FLQ), 1 was Pre-XDR with second line injectable resistant (SLI) (as per old PMDT guidelines) and 1 was XDR TB.

In our study, 60/94 (63.8%) lymphadenopathy, 29/69 (42%) of pleural effusion, 22/33(66.6%) Bone TB, 12/20 (60%) abdominal TB and 3/5 (60%) pericardial effusion had MTB detected. But the sites of CNS, cutaneous, breast, retropharyngeal abscess were less in numbers as compared to lymph node and pleural TB cases. CNS, cutaneous, various site abscess TB cases

need supportive medical and surgical management beyond the conventional therapy for TB and are usually referred cases. All three cases of CNS TB were GXP MTB detected (100%). This data is not possible to be analysed due to bias of confirmed CNS TB cases only being referred to the pulmonary medicine department usually for suggestions on the TB treatment regimens. Similar is the scenario with skin, breast, and retropharyngeal space TB cases, hence analysis of these small number of system wise cases was not done.

The comparison and discussion as related to statistics for GXP diagnosis at various other sites is as follows. The study conducted by Sasikumar had sensitivity, specificity, PPV, NPV of GXP in diagnosis of lymph node TB cases as 77%, 80%, 95%, 42%, respectively [16]. As per studies by Boehme et al., Armand et al., Causse et al., Tortoli et al.; GeneXpert sensitivity in lymph node samples using AFB culture as a reference standard, ranged from 50% to 100% [19-22]. In our study sensitivity, specificity, positive predictive value, negative predictive value of GeneXpert in diagnosis of lymph node TB cases was 70.42%, 70.52%, 90.9%, 36.36%which is similar to above study. In the study by Meldau et al, GXP in pleural TB showed sensitivity from 58-100% and specificity ranges from 87-100% [23]. However, in our study sensitivity, specificity, and positive predictive value, negative predictive value of GXP in diagnosis of pleural TB cases was 63.8%, 73.3%, 88.2%, 39.2%. In Massi et al study[24], for Bone TB and GXP, the sensitivity value of 100%, specificity value of 16.6%, PPV of 35.48%, and NPV of 100%. In the study conducted by Held et al, the sensitivity of the GXP was 95.6%, the specificity 96.2%, the PPV 97.7% and NPV 92.6% in Spinal TB [25]. However, sensitivity, specificity, PPV, NPV of GXP in diagnosis of bone TB cases in our study was 95.4%, 33.3%, 91.30%, 50%. In a metanalysis of 12 studies (699 samples) that tested GXP in abdominal TB, and compared the results against culture as a reference standard (10 studies had more than 10 samples). The estimates of sensitivity varied widely and ranged from 42% to 100%. The pooled estimate of sensitivity was calculated as 81.2% (95% CI, 67.7–89.9%). The pooled specificity was 98.1% (95% CI, 87.0–99.8%) [26]. In our study sensitivity, specificity, PPV, NPV of GXP in diagnosis of Abdominal TB cases was 85.7%, 100%, 100%, 33.3%. In a study by Saeed et al, pericardial fluid GXP showed high sensitivity (84.3%), specificity (100%), with PPV (100%), and NPV (96.7%) [27]. However, sensitivity, specificity, positive predictive value, negative predictive value of GeneXpert in diagnosis of pericardial TB cases in our study was 100%, 0.00%, 75%, 0.00%. Studies regarding the above extra pulmonary sites are less and the specificity and negative predictive value was not able to calculate due to the less sample size for above cases, as there were only true positives.

Our study is an addition to the available literature and call for data by the WHO on TB. GXP has always been useful for rapid detection of TB and identification of rifampicin resistance, especially in a high prevalence country like India. Our study reiterates the same. GXP should

be used in routine TB diagnosis due to the rapid turnaround time, early diagnosis and the management of patients with presumptive TB. The test results must always be confirmed by AFB culture and further drug susceptibility tests in clinically discordant and drug resistant TB cases.

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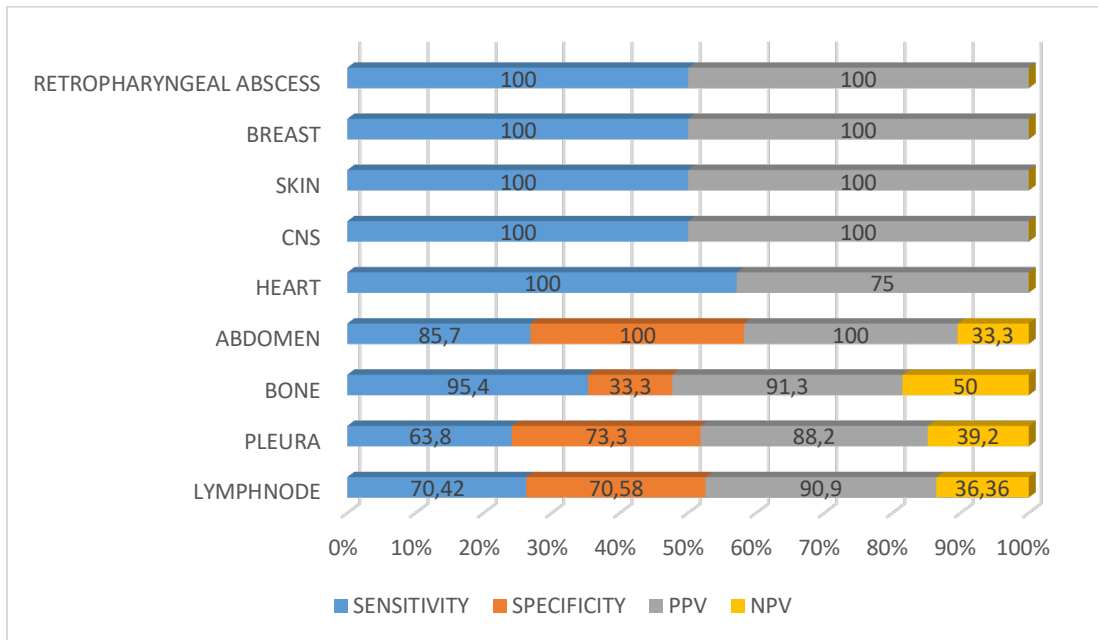
Figure 1. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) of GeneXpert for diagnosis of TB at each extrapulmonary sites.

Table 1. Different sites of extrapulmonary tuberculosis.

Sites	No. of cases (%)
Lymph nodes	94 (47)
Pleural effusion	69 (34.5)
Bone	33 (16.5)
Abdominal	20 (10)
Pericardium(heart)	5 (2.5)
Cns	3 (1.5)
Skin	1 (0.5)
Breast	1 (0.5)
Retropharyngeal abscess	1 (0.5)

Table 2. Comparing GeneXpert in different sites.

Sites	Total no. of cases	GeneXpert MTB detected
Lymph nodes	94	60(63.8%)
Pleura	69	29(42%)
Bone	33	22(66.6%)
Abdomen	20	12(60%)
Heart	5	3(60%)
CNS	3	3(100%)
Skin	1	1(100%)
Breast	1	1(100%)
Retropharyngeal space	1	1(100%)

MTB, mycobacterium tuberculosis; CNS, central nervous system.

Table 3. Comparing GeneXpert and AFB smear and culture.

No. of cases	GeneXpert Only	AFB smear and culture Only	Both GeneXpert and AFB culture
POSITIVE	5	38	125
NEGATIVE	38	5	32

AFB, acid-fast bacilli; Chi-square test; p-value is <0.00001; the result is significant at p<0.05.

Table 4. Sensitivity, specificity, positive predictive value, negative predictive value of GeneXpert for diagnosis of tuberculosis at each extrapulmonary sites.

Site	Sensitivity	Specificity	PPV	NPV
Abdomen	85.7	100	100	33.3
Bone	95.4	33.3	91.30	50
Breast	100	Could not be calculate	100	Could not be calculated
CNS	100	Could not be calculate	100	Could not be calculated
Heart	100	Could not be calculated	75	Could not be calculated
Lymphnode	70.42	70.58	90.9	36.36
Pleura	63.8	73.3	88.2	39.2
Retropharyngeal space	100	Could not be calculate	100	Could not be calculated
Skin	100	Could not be calculated	100	Could not be calculated

PPV, positive predictive value; NPV, negative predictive value; CNS, central nervous system.