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Comparative Utility of Genexpert Assay over Fine Needle Aspiration Cytology in Early Diagnosis of Tuberculous Lymphadenitis

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Abstract:
Background*: Tuberculous lymphadenitis is the most common extrapulmonary manifestation of TB. Rapid and accurate diagnosis of extrapulmonary tuberculosis especially TB lymphadenitis is very challenging. Difficulty in sampling, paucibacillary nature of samples as well as long turnaround time are some of the limitations of conventional methods of smear microscopy, culture and cytomorphological diagnosis by FNAC. The objective of this study was establishing pivotal role of GeneXpert assay in early diagnosis of tuberculous lymphadenitis and its comparative utility over cytomorphological methods.*
Materials and Methods*: This prospective study was conducted over a period of one and half year i. e. from January 2017 to May 2018 in TB C & DST Laboratory Department Of Microbiology Government Medical College, Aurangabad, Maharashtra. During this period, 282 fine needle aspirate specimens of clinically suspected tuberculous lymphadenitis were referred to our laboratory. One portion of fine needle aspirate was subjected to Cytological examination and the residual material from the remaining aspirate was processed for RT-PCR by GeneXpert MTB/RIF testing. When sufficient sample was available, they were inoculated on the LJ media in the biosafety cabinets.*
Results*: Among 282 samples, 112 samples (39.79%) were positive for mycobacterium tuberculosis by GeneXpert MTB/RIF testing. In this study 9 samples were MDR-TB cases which are 8% of the total positive cases. Cytology diagnosed 35 cases as tubercular lymphadenitis showing typical features of tubercular granuloma, while 73 samples were reported as nonspecific granuloma. Hence cytology diagnosed 108 cases of TB lymphadenitis (tubercular lymphadenitis and nonspecific granuloma) while GeneXpert diagnosed 112 cases of tubercular lymphadenitis, with 9 MDR- TB cases confirmed by conventional Drug Sensitivity later. Cytology reported 70 reactive lymphadenitis, 19 abscess, and 1reactive thyroiditis.* For *70 samples the cytological picture was not clear, it was either hemorrhagic smear, acellular smear and so reported as inconclusive. Out of 117 samples that were put on culture, 74 were confirmed as culture positive for mycobacterium tuberculosis and 40 samples were confirmed as smear positive. Therefore, considering culture and smear microscopy as a composite bacteriological reference standard (CRS) total 114 cases were confirmed TB lymphadenitis cases. In our study, for GeneXpert sensitivity was 96.49% and specificity was 98.80% whereas for cytology sensitivity57.89% and specificity was75.2%.*
Conclusion: *Having diagnosed as tuberculosis either by fine needle aspiration cytology or clinically may lead to unnecessary blind anti-tubercular treatment in etiologies which mimic tuberculosis. In this study Xpert detected 39.70% samples as positive while cytology detected 25.90% samples positive. GeneXpert MTB/RIF for extrapulmonary tuberculosis samples should done because of its simplicity, reliability, and rapid turnaround time, less biohazard risk and minimal training required. Also it plays a pivotal role in detection of Rifampicin resistance TB.*
Key Word*: GeneXpert; TB Lymphadenitis; extrapulmonary tuberculosis; cytology;*

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I. Introduction

Tuberculosis (TB) is one of the top 10 causes of death worldwide. Globally, an estimated 10.0 million people fell ill with TB in 2019, a number that has been declining very slowly in recent years. Worldwide Drug-resistant TB continues to be a public health threat. In 2019, nearly half a million people developed rifampicin-resistant TB (RR-TB), of which 78% had multidrug-resistant TB (MDR-TB) [(1).]

Extrapulmonary Tuberculosis: most common is TB Lymphadenitis

In India, 20% of TB cases are estimated to be cases of extrapulmonary TB, which affects mainly the lymph nodes, meninges, kidney, spine, and growing ends of the bones[3].Tuberculous lymphadenitis is the most common extrapulmonary manifestation of TB. Extrapulmonary TB represented 16% of the 7.1 million incident cases that were notified in 2019 worldwide[2,3].

Early diagnosis plays a pivotal role in control of TB. India has the world's largest tuberculosis burden comprising 23% of the global burden of incident active TB patients annually and 27% of the world's "missing" patients, representing about 1 million patients each year who have not been notified to the Government of India's Revised National TB Control Programme (RNTCP) and who therefore may not have received effective TB care[4]. While development of effective disease treatment strategies is essential, there seems to be a lack of focus as far as very obvious and basic preventive measures as well as early case detection especially for Extrapulmonary Tuberculosis cases are concerned.

Increasing case detection rate by using newer TB diagnostic tests is critical for improving outcomes in India's TB cascade of care, especially for smear-negative, MDR TB patients, most of which are with extrapulmonary site involvement. Inability to choose right diagnostic tool by clinicians for rapid diagnosis of the specimens makes EPTB a diagnostic challenge.

Diagnosis of mycobacterial infections especially EPTB is a challenging task due to some reasons enlisted below

- ❖ Difficulty in sampling from the extrapulmonary sites: Many forms of extrapulmonary TB require invasive diagnostic sampling that can pose risk of harm to the patient and can be costly too.
- ❖ The paucibacillary nature of specimens : this makes the diagnosis by the conventional methods of smear microscopy and culture less sensitive. About 5000 and 10,000 bacilli/ml are needed in the sample for them to be detected by Ziehl-Nelsen and auramine stains. Culture allows the detection of between 10 and 100 bacteria/ml.
- ❖ Culture is the gold standard test. But limitations are associated with culture too: Culture takes several weeks, requires a highly equipped laboratory and has reduced sensitivity in paucibacillary disease.
- ❖ Characteristic cytomorphology of TB is shared with other diseases. Here an incorrect TB diagnosis (i. e. false-positive result) may either result in unnecessary treatment with anti-tubercular drugs or a missed untreated case.
- ❖ Moreover cytopathological diagnosis relies on highly trained operators.
- ❖ Use of cytopathological diagnosis, smear microscopy, culture methods remains limited by slow turnaround times, and or lack of drug resistance guidance.
- ❖ Moreover cytological techniques can affect treatment by either delaying it or causing inappropriate empiric therapy for TB to subjects without mycobacterial infections or with atypical mycobacterium.

The World Health Organization (WHO)-endorsed Xpert MTB/RIF (Cepheid, Sunnyvale, CA), combines sample processing and real-time PCR. It is fully automated benchtop cartridge-based nucleic acid amplification (CB-NAAT) assay and detects *Mycobacterium tuberculosis* complex and rifampin resistance in less than 2 hours. Moreover WHO recommends the use of Xpert MTB/RIF as the initial diagnostic test, or a replacement test instead of conventional microscopy, culture and histopathology for testing lymph nodes or other tissue from patients with suspected extrapulmonary TB[5].

Accordingly, this study was done to determine the diagnostic utility of the Xpert MTB/RIF in detecting TB lymphadenitis against fine needle aspiration cytology.

The Xpert MTB/RIF has rapid turnaround time (less than two hours), with less biohazard problems and only minimal training required.

II. Material and Methods

This prospective study was conducted over a period of one and half year i. e. from January 2017 to May 2018 in TB C & DST Laboratory Department of Microbiology Government Medical College, Aurangabad, Maharashtra. During this period, 282 fine needle aspirate specimens of clinically suspected tuberculous lymphadenitis were referred to our laboratory immediately with minimum delay along with completely filled requisition forms.

Patients were clinically evaluated by clinician for suspected tuberculous lymphadenitis. Clinical suspicion was raised in patients with

i. peripheral enlarged lymph nodes (more than 1 cm) in the neck, armpit or groin. Patients may also present with symptoms of fever, weight loss, night sweats and cough
ii. mediastinal lymph nodes: Patients with cough, fever, shortness of breath, weight loss or night sweats who have hilar widening on chest X-ray and/or mediastinal lymphadenopathy on chest CT

iii. abdominal LNTB: Patients with dull or colicky abdominal pain, abdominal distension, weight loss, night sweats or fever, and evidence of abdominal lymphadenopathy on abdominal ultrasound scan, CT or MRI

Inclusion criteria:
All suspected tuberculous lymphadenitis cases.
Exclusion criteria:
All only pulmonary tuberculosis cases were excluded

Procedure methodology

In this study, specimens were collected from patients clinically suspected of tuberculous lymphadenitis & were accepted at the laboratory at room temperature. A non-dependent aspiration was done by the Z-technique for manipulating overlying skin by an appropriately trained operator. Samples were collected aseptically in a sterile container (Falcon tube) preferably without fixatives or preservatives. If needed in some cases they were protected from drying by adding sterile saline .Specimens were transported to the laboratory as quickly as possible and processed as soon as possible.

One portion of fine needle aspirate from the involved lymph node we was smeared on a slide, fixed immediately with 95% alcohol, and subjected to Papanicolaou staining. Other portions were made into slide smears, air dried, and subjected to ZN staining. The left over portion whenever available was subjected to culture on Lowenstein-Jensen (LJ) medium. The criteria for diagnosis of tuberculosis will be taken as: (a) presence of epithelioid cell granuloma with or without necrosis (b) presence of AFB in necrotic smears stained positive for AFB by Ziehl Neelsen's technique. The residual material from the remaining aspirate was processed for RT-PCR by GeneXpert MTB/RIF testing as guided by WHO Implementing Tuberculosis Diagnostics Policy framework[6].The Xpert MTB/RIF assay was used directly on FNAC since they are not contaminated by normal flora and do need decontamination[7]. It is an automated in vitro diagnostic test using nested real-time PCR for the qualitative detection of MTB-complex and RIF resistance. The primers in this test amplify a portion of the rpoB gene containing the 81 base pair core region. The probes are designed to differentiate between the conserved wild-type sequence and mutations in the core region that are associated with RIF resistance. The results were available in approximately 2 hrs. Samples positive by GeneXpert were reported on same day.

The specific sequence of the *rpoB* gene is amplified, which is probed with five molecular beacons (Probes A – E) for detection of mutations within the rifampin resistance determining region (RRDR). Each molecular beacon is labeled with a different fluorophore. The valid maximum cycle threshold (Ct) of 39.0 for Probes A, B and C and 36.0 for Probes D and E are set for MTB/RIF data analysis.

• **MTB DETECTED:** is reported when at least two probes result in Ct values within the valid range and a delta Ct min (the smallest Ct difference between any pair of probes) of less than 2.0.
• **Rif Resistance NOT DETECTED:** is reported if the delta Ct max (the Ct difference between the earliest and latest probe) is ≤4.0.
• **Rif Resistance DETECTED:** is reported if the delta Ct max is >4.0.
• **Rif Resistance INDETERMINATE** is reported when the following two conditions are met:
1. The Ct value of any probe exceeds the valid maximum Ct (or is zero, i.e. no threshold crossing); and
2. The earliest *rpoB* Ct value is greater than:
[(Valid maximum Ct of probe in condition 1) - (delta Ct max cut-off of 4.0)].
• **MTB NOT DETECTED** is reported when there is only one or no positive probe(25)

Statistical analysis

For statistical analysis Statistical Package of Social Science (SPSS) version 21 (SPSS Inc., Chicago, IL) was used. Chi-square test for proportion was used to compare the Xpert test and cytology. The p value is 0.00012. The $p< 0.05$ is considered significant.

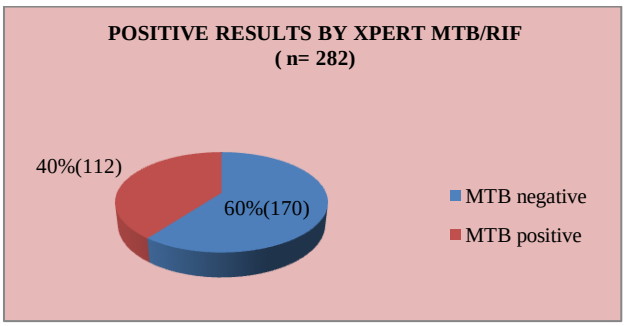
III. Result

GeneXpert MTB/RIF assay results

The present study was done to compare the utility of GeneXpert MTB/RIF assay with cytological observations. The study was carried over a period of one and a half years from January 2017 to June 2018 after the approval from institutional ethical committee. All the specimens were subjected for processing for identification of *Mycobacterium tuberculosis* as stated above in materials and methods. Total 282 samples of fine needle aspirates were received for detection of mycobacterium tuberculosis and rifampicin resistance from the clinically suspected cases of tuberculous lymphadenitis. In our laboratory all samples were tested by GeneXpert MTB/RIF assay (CBNAAT) and all tests were valid. Among 282 samples, 112 samples (39.79%) were positive and 170 samples (60%) were negative as stated in table no 1 below by GeneXpert MTB/RIF assay.

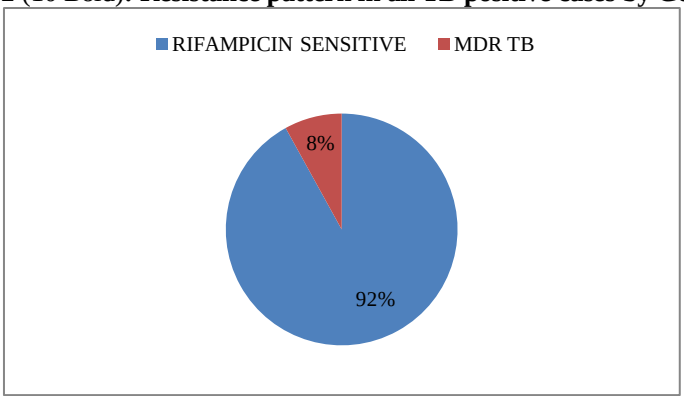
Table no 1: Shows Total MTB positive cases in all lymphadenopathy patients by XPERT MTB/RIF

TOTAL NO OF SAMPLES	MTB POSITIVE	MTB NEGATIVE
282	112	170



We received samples from a wide range of ages from 1 year to 74 years. As depicted in the table no 2, out of 112 positive samples 9 samples showed resistance to Rifampicin. Rifampicin resistance is a predictor of MDR TB because resistance to RIF, in most instances, co-exists with resistance to INH. So those resistant to Rifampicin are considered as MDR-TB. So, in this study 9 samples were MDR-TB cases which are 8% of the total positive cases.

Table no2 (10 Bold)**: Resistance pattern in all TB positive cases by GeneXpert**



Cytology results

Table no 3 depicts the various cytology reports of all 282 cases. Cytology diagnosed 35 cases as tubercular lymphadenitis showing typical features of tubercular granuloma consisting epithelioid cells, Langhans giant cells, lymphocytes and caseous necrosis with or without smear positivity for acid fast bacilli. While 73 samples were reported as nonspecific granulomas with epithelioid cells giant cells or lymphocytes which are also considered positive. Such cases are usually treated as TB lymphadenitis by correlating them clinically. Eventually, when such samples were tested by GeneXpert MTB/RIF assay, 34 samples were positive. Similarly 70 were reactive lymphadenitis, 20 among them turned out to be GeneXpert positive. Also, 19 samples were diagnosed as abscess by cytology, among which 8 were found positive by GeneXpert and immediately reported. In 70 samples, the cytological picture was not clear, either hemorrhagic smear, acellular smear and so were reported as inconclusive in cytology reports. These were also tested by GeneXpert and 17 samples were positive.

One sample which showed features of thyroiditis as well as granuloma on a necrotic background was positive by GeneXpert so diagnosed as tuberculous thyroiditis , an uncommon manifestation. Many other etiologies (metastasis, benign tumors, lymphomas) were also diagnosed by cytology.

Table – 3: Cytology reports of all suspects

CYTOLOGY FINDINGS	NO OF SAMPLES (n=282)
Tubercular lymphadenitis	35
Nonspecificgranulomatous lymphadenitis	73
Reactive hyperplasia of lymph node	70
Acute inflammation s/o abscess	19
Inconclusive	70
Metastatic deposits	5
Pleomorphic adenoma	3
Epidermal inclusion cyst	1
Benign tumors	2
Lipoma	1
Lymphoma	2
TB thyroiditis	1
Total	282

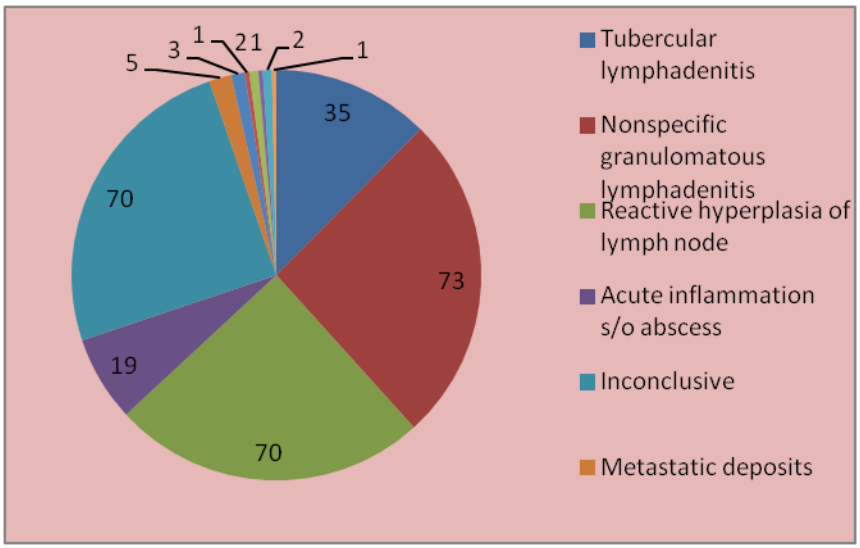


Table – 5: Comparative analysis of cytological diagnoses by molecular methods (XPERT MTB/RIF) in patients with tubercular lymphadenopathy

	GeneXpert MTB/RIF RESULTS		
CYTOLOGY RESULTS	POSITIVE	NEGATIVE	TOTAL
Tubercular lymphadenitis	32	3	35
Nonspecific granulomatous lymphadenitis	34	39	73

Reactive hyperplasia of lymph node	**20**	**50**	**70**
Acute inflammation s/o abscess	**8**	**11**	**19**
Inconclusive	**17**	**53**	**70**
Metastatic deposits	**0**	**5**	**5**
Pleomorphic adenoma	**0**	**3**	**3**
Epidermal inclusion cyst	**0**	**1**	**1**
Benign tumors	**0**	**2**	**2**
Lipoma	**0**	**1**	**1**
Lymphoma	**0**	**2**	**2**
TB thyroiditis	**1**	**0**	**1**
Total	**112**	**170**	**282**

Therefore to summarize, cytology diagnosed 108 cases of TB lymphadenitis (tubercular lymphadenitis and nonspecific granulomas) while GeneXpert MTB/RIF assay diagnosed 112 cases of tubercular lymphadenitis , with 9 MDR- TB cases confirmed by conventional DST later.

Around 117 samples were put on culture out of 282 samples. Remaining samples could not be processed for culture as amount of sample available was very less after performing Xpert test and cytology. Out of 117 samples 74 were confirmed as culture positive for mycobacterium tuberculosis and 40 samples were confirmed as smear positive (smear positive whose culture was not available). Therefore as stated in Table 6, considering culture and smear microscopy as a **composite bacteriological reference standard(CRS) total 114 cases were confirmed TB lymphadenitis cases out of 282 samples(40.42%).Such CRS is used in many studies like one done in a high burden settings where results were comparable [(8)]. Also a series of metanalysis done by Kohli M, Schiller I & Dendukuri N published by Cochrane Database of Systematic Reviews also reviews many studies that have included studies using CRS[(9)].**

Table – 6: Total MTB positive cases in all lymphadenopathy patients by GeneXpert MTB/RIF

TOTAL SAMPLES	**282**
CONFIRMED TBLN (CRS)	114
GeneXpert MTB/RIF POSITIVE	112
CYTOLOGY POSITIVE (TBLN+ NONSPECIFIC GRANULOMA	108

In our study, SENSITIVITY OF GeneXpert MTB/RIF was 96.49% while SPECIFICITY OF GeneXpert MTB/RIF was 98.80% this in in agreement with study by Ankush Raj, Netrapal Singh where sensitivity is 96% and specificity as 99% [(31)] and by Sharma in 2014 where specificity was found to be 91% [(10)] while sensitivity was 88 %.In a series of metanalysis conducted by by Kohli M, Schiller I & Dendukuri N published by Cochrane Database of Systematic Reviews also reviews many studies so that pooled sensitivity was 92.2% (82.9 to 98.1) and pooled specificity was 89.2% (78.9 to 98.2) [(10)].

Table – 7: Total MTB positive cases in all lymphadenopathy patients by GeneXpert MTB/RIF

	CRS present	**CRS ABSENT**	**TOTAL**
GeneXpert MTB/RIF POSITIVE	110	2	112
GeneXpert MTB/RIF NEGATIVE	4	166	170
TOTAL	114	168	282
SENSITIVITY OF XPERT - 96.49% SPECIFICITY OF XPERT - 98.80%			

Table – 8: Total MTB positive cases in all lymphadenopathy patients by GeneXpert MTB/RIF

	CRS PRESENT	**CRS ABSENT**	**TOTAL**
CYTOLOGY POSITIVE	66	42	108
CYTOLOGY NEGATIVE	48	126	174

TOTAL	114	168	282
SENSITIVITY OF CYTOLOGY – 57.89% **SPECIFICITY OF CYTOLOGY – 75.2%**			

IV. Discussion

In the TB-endemic zone, like India tuberculosis is the commonest cause of lymphadenopathy but it can also mimic other diseases. Due to the limitations of procedures for confirming a diagnosis of LNTB, patients are often started on anti-TB therapy and its response is then noted.

Having diagnosed as tuberculosis either by fine needle aspiration cytology or clinically may lead to unnecessary blind anti-tubercular treatment in etiologies which mimic tuberculosis. In these cases apparent initial improvement with ATT finally results in treatment failure. These are the patients of lymphoma, metastatic deposits, reactive lymphadenitis due to bacterial, viral, fungal, foreign body, sarcoidosis, toxoplasmosis, cat scratch fever, collagen vascular diseases, and diseases of the reticuloendothelial system or other etiologies. These also need prompt diagnosis and close monitoring so that they are not missed.

Most of the times, in true positive cases treatment may be started immediately after clinical diagnosis or cytological diagnosis with no information about the patient's MDR status. Conventional methods give the report of MDR status of patient but take a long time, in weeks. While **GeneXpert MTB/RIF** test detects the MDR status in very short time (2 hours) as compared to the conventional methods.

GeneXpert MTB/RIF is a rapid nucleic acid amplification test, a potentially attractive tool for extrapulmonary specimens. A series of meta-analyses has shown that nucleic acid amplification tests (NAATs) have high specificity and positive predictive value with highly variable sensitivity, especially in cases of EPTB[(11)].

In India more than 50% cases of peripheral lymphadenopathy is due to etiologies other than tuberculosis and, in these cases, excision biopsy with histopathology and microbiological examination was the only way to exclude tuberculosis. Such invasive procedure in initial evaluation of lymphadenopathy before starting antitubercular therapy (ATT) is not always possible in all cases. In such cases **GeneXpert MTB/RIF** test can be used to detect TB lymphadenitis and rule out other cases.

Caseation and demonstration of acid fast bacilli on cytology are almost always suggestive of tuberculous etiology. But problems arise when cytological evidences are inconclusive (for example, poorly-formed granuloma, neutrophilic infiltration, absence of acid fast bailli, etc.) and in such cases which are smear negative for acid fast bacilli are often reported as inconclusive reports and patients may face unnecessary repeat FNAC or advised excision biopsy. **GeneXpert MTB/RIF** assay is useful in such inconclusive cases to diagnose tubercle bacilli.

In our study we got 70 cytology reports as inconclusive, among which 17 samples were detected positive for MTB by **GeneXpert MTB/RIF**. Also, 8 out of 11 samples showing acute suppurative inflammation (abscess) turned out positive by **GeneXpert assay**. We found 20 out of 70 samples that were seen as reactive lymphadenitis on cytology but diagnosed positive by **GeneXpert MTB/RIF**. We also found 34 samples out of 73 nonspecific granuloma samples positive by **GeneXpert MTB/RIF**. Remaining may be granuloma due to other causes mentioned above.

This is comparable to a study by Mulualem Tadesse and Gemeda Abebe, which showed Chronic inflammation 18.8%(3/16), Suppurative abscess 66.7%(10/15) , Reactive lymphadenitis 9%(1/11) samples that were Xpert positive[(8)]

The granuloma may occur in regional and/or distant lymph nodes or within the tumour itself. Non-caseating epitheloid granuloma and caseous necrosis both are found in tuberculosis. In lymphoma, development of granulomas may be due to immune or inflammatory reaction to tumour-associated antigenic determinants or to the production of cytokines by the tumour cells. The diagnosis of TB and lymphoma may be difficult due to similarities in the clinical course, laboratory tests, and imaging procedures[(36)]. In such cases, where excision biopsy remains the only option **GeneXpert MTB/RIF** is useful to rule out TB. In our study, few cases like lymphoma(2), metastatic deposits(5), benign tumors(3), pleomorphic adenoma (3) were correctly given negative report by **GeneXpert MTB/RIF** along with cytology which were later confirmed on excision biopsy. This avoided the unnecessary blind anti tubercular treatment and timely diagnosis.

A major hindrance to the diagnosis of LNTB is the atypical presentation. Furthermore the bacterial load is generally very low. The test is currently recommended as "first line" fast diagnostic test in endemic countries when rapid results are crucial for TB diagnosis in HIV infected patients or for appropriate management of multidrug-resistant TB cases.

V. Summary and conclusion

TB is a disease of poverty. Also economic distress, vulnerability, marginalization, stigma and discrimination are often faced by people affected by TB. In this study **GeneXpert MTB/RIF assay** detected 39.70% samples as positive while cytology detected 25.90% samples positive.

GeneXpert MTB/RIF assay for the identification of MTB in EPTB samples should still be done because of its simplicity, reliability, and rapid turnaround time, less biohazard risk and minimal training required. False positivity due to contamination is less likely because the technology uses closed reaction chamber and surfaces where specimens are processed and were extensively cleaned.

GeneXpert has been recently endorsed by the Scientific and Technical Advisory Board of the World Health Organization (WHO) as the most sensitive fast test for TB diagnosis in paucibacillary respiratory samples[(12)] .The test is currently recommended as "first line" fast diagnostic test in endemic countries when rapid results are crucial for TB diagnosis in HIV infected patients or for appropriate management of multidrug-resistant TB cases. Therefore **GeneXpert MTB/RIF assay** can be used as the replacement test for TB lymphadenitis as suggested by new EPTB guidelines.

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