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Research Article

Evaluation of Diagnostic Modalities and Clinical Profiles of Cervical Tuberculous Lymphadenitis in a Medical College in Jharkhand

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A B S T R A C T

Introduction: Tuberculosis (TB) is a major global health issue, with extrapulmonary TB (EPTB) making up 15–20% of cases, and tuberculous lymphadenopathy being the most common form. Diagnosing cervical lymphadenitis, often presenting as painless neck lumps, is difficult due to its paucibacillary nature. Traditional methods like smear microscopy and culture have low sensitivity, so advanced diagnostics like PCR, histopathology, FNAC, and Xpert MTB/ RIF are needed. This study aimed to assess the clinical features and diagnostic accuracy of these methods in smear-negative cervical tuberculous lymphadenitis.

Materials and Method: A total of 100 individuals with 10–80 years of age with cervical lymphadenopathy were included in the study in the Department of Microbiology of a medical college in Dumka, Jharkhand. Samples from FNAC or incision biopsy were obtained and prepared for Ziehl-Neelsen (ZN) staining, culture using the MGIT 960 system, Xpert MTB/ RIF, and PCR. A histopathological examination was also conducted. The diagnostic performance of each modality was assessed against a composite reference standard including culture, histopathology, radiological findings, or treatment response. SPSS version 25 was used to examine the data.

Results: The study population's mean age was 59.55 years, and the male-to-female ratio was 1:1.17. Xpert MTB/ RIF identified 26% of cases, PCR detected 21%, and MGIT 960 identified 18%. The combined use of these modalities improved diagnostic accuracy. Sensitivity and specificity were highest for PCR compared to the composite reference standard.

Conclusion: The enhanced diagnosis of *Mycobacterium* TB in neck tuberculous lymphadenitis is possible when a multimodal diagnosis strategy combining conventional and molecular methods is used.

Keywords: Extrapulmonary Tuberculosis, Fnac, Xpert/ Rif

Introduction

Tuberculosis (TB), as the primary cause of illness and mortality in developing nations, remains a serious health concern worldwide. Globally, about 9.6 million individuals are diagnosed with TB each year, which leads to 1.5 million deaths. Out of all the reported TB cases, about 15–20% are Extra Pulmonary Tuberculosis (EPTB) with tuberculous lymphadenopathy being the most prevalent form constituting 35% of EPTB cases.[1–3] In 60–90% of cases of tuberculous lymphadenopathy, the afflicted cervical lymph nodes are the most frequently found. However, cervical tuberculous lymphadenitis, or scrofula, is difficult to diagnose since the specimens are paucibacillary, rendering sensitive diagnostic methods such as culture and microscopy with smears ineffective. Smear microscopy yields positive results in less than 10% of samples, while culture sensitivity ranges from 39% to 80%.[4,5] On a histological examination, granular inflammation with caseation necrosis is usually observed. Although suggestive, this condition is not limited to tuberculosis; it can also arise in other situations, including malignancies and some fungal infections. Because depending just on one modality might result in delayed diagnosis, greater morbidity, and higher mortality rates, these diagnostic constraints highlight the necessity for a multimodal approach.

The diagnostic challenges are further complicated when EPTB occurs alongside pulmonary TB, posing a risk of wider transmission.[6] Cervical tuberculous lymphadenitis presents as painless, progressively enlarging neck masses, often accompanied by generalised symptoms like chills, fever, and loss of appetite. However, many patients may remain asymptomatic or present without significant systemic signs, complicating early detection. Diagnostic evaluation typically includes clinical assessment, imaging, and microbiological testing, with fine-needle aspiration cytology (FNAC) offering a quick, minimally invasive diagnostic tool. Polymerase chain reaction (PCR) is valuable for its high sensitivity and specificity in detecting mycobacterial DNA in lymph node samples, whereas culture, for all its time-consuming character, is still the gold standard.[7–9] Using a combination of traditional and molecular diagnostic methods is essential to improve diagnostic accuracy. Integrating methods such as smear microscopy, histopathological analysis, and advanced molecular in cervical tuberculous lymphadenitis, methods such as nucleic acid amplification (NAA) test by GeneXpert® Instrument Systems and resistance to rifampicin (Xpert MTB/ RIF), PCR, and Mycobacteria Growth Indicator Tube (MGIT) enhance the diagnosis of *Mycobacterium tuberculosis* (MTB). The purpose of this study was to investigate the diagnostic efficacy and clinical characteristics of several modalities, such as Xpert MTB/ RIF, conventional PCR, MGIT, histopathology, and clinical follow-up, in smear-negative cases of cervical tuberculous lymphadenitis. By evaluating these methods, the study seeks to enhance diagnostic accuracy and inform better clinical management strategies for this challenging condition.

Materials and Method

This study was carried out at the Department of Microbiology of a medical college in Jharkhand. The participants were aged between 10 and 80 years. Patients with lymphadenopathy were assessed for tuberculosis-related symptoms. A comprehensive evaluation was conducted on 100 patients (based on prevalence in our hospital) who presented to different specialities for cervical lymph node expansion, neck oedema, or leaking sinus.The study was done retrospectively between 2020-2021. The National TB Elimination Program (NTEP) guidelines state that all patients undergo fine-needle aspiration (FNA) following a comprehensive clinical history and physical examination. For cases with negative or inconclusive FNAC results, an excision biopsy was performed. Additional diagnostic tests included Erythrocyte Sedimentation Rate (ESR), tuberculin skin test, and chest radiography, which were conducted on all patients. FNA or excision biopsy samples from the 100 patients were gathered and prepared for PCR, Xpert MTB/ RIF, Ziehl-Neelsen (ZN) staining, and culture using the MGIT 960 system. A different section of the material was sent for histopathological examination. The conventional NALC-NaOH method (N-acetyl-L-cysteine-sodium hydroxide method) was utilised for sample processing, smear preparation, culture, Xpert MTB/ RIF, and PCR testing.[10]

Diagnostic Procedures

Smear Examination

The processed samples underwent smear examination using the ZN staining method and were analysed under a light microscope. The results were interpreted as per the guidelines set by the NTEP.[11]

The decontaminated samples were placed into MGIT tubes and processed by the use of the MGIT 960 Systems (Becton Dickinson, Sparks, MD, USA). Finally, the TBc Identity Tests (TBcID, Becton Dickinson, Sparks, MD, USA) were used to confirm the positive cultures.[12]

Xpert MTB/ RIF Assay

The Xpert MTB/ RIF assay is a qualitative, nested real-time PCR used for the detection of *Mycobacterium tuberculosis* complex DNA in a sputum sample. In the test, if *Mycobacterium tuberculosis* complex (MTBC) is detected, the Xpert MTB/ RIF assay also detects the rifampin-resistance-associated mutations of the rpoB gene (Cepheid, Sunnyvale, CA).[13–15] The clinical sample was mixed with a sample reagent and put into the cartridge. After inserting the cartridges into the testing apparatus, the results were generated in around ninety minutes.[13–15]

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Sample Preparation and PCR Amplification

To avoid cross-contamination, the extraction of DNA and amplification by PCR were carried out in different, assigned rooms. The tissue phenol-chloroform-isoamyl alcohol method was used to isolate DNA. A lysis buffer containing 20 mM Tris-HCl, 0.5% Peg 20, and 1 mg/mL of proteinase K was used, and the mixture was incubated for 16 hours at 56 °C. Primers MPT1 (5'-TCC GCT Cgc AGT CGT CTT CC-3') and MPT2 (5'-GTC CTC GCG AGT CTA the GGC CA-3') were used for the amplification process generating 240 bp amplicons specific for the MPT-64 gene of *Mycobacterium tuberculosis*, following established protocols.[9]

PCR Controls and Analysis

Each PCR run included appropriate controls: sterile distilled water as the negative control and 100 pg of H37Ra DNA as the positive control to ensure assay accuracy. The amplified PCR products were analysed via gel electrophoresis.[9]

Composite Reference Standards

To address diagnostic challenges, Composite Reference Standards (CRS) were used as the gold standard in this study. For both aspirates and biopsy samples, CRS included a combination of any two positive results from culture, histopathology, radiological findings, or response to treatment.[16] Treatment response was evaluated based on clinical improvement, including resolution of symptoms such as fever, weight gain, enhanced general well-being, and reduction in lymph node size.

Statistical Analysis

The statistical program SPSS 25.0 was used to analyse the data. Following tabulation, the categorical variable data were shown as percentages and frequencies. The chi-square test was used to assess the statistical significance of descriptive statistics expressed as percentages, and p values were employed to establish the degree of significance.

Results

Clinical and Demographic Characteristics

A total of 100 participants with cervical lymphadenopathy were involved in the research study. The male-to-female ratio among these patients was 1:1.17, with 46 (46%) men and 54 (54%) women. The patients were between the ages of 10 and 80, with an average age of 59.55 ± 14.46 years. Out of the 100 patients, 87 (87%) had solid lymph nodes, 10 (10%) had abscesses, and 3 (3%) had sinuses that were draining. There were 87 (87%) cases of unilateral cervical lymph node involvement, with 59 (68%) patients primarily on the right side and 28 (32%) on the left. The diameters of the lymph nodes varied: 53 (53%) patients had a diameter of 3–6 cm, 30 (30%) had a diameter greater than 6 cm, and 17 (17%) had a diameter smaller than 3 cm. Furthermore, an X-ray revealed related lung abnormalities in 12 (12%) of the cases.

The patients' gender and the location of involvement did not significantly correlate. Fever was prevalent in 75 (75%), weight loss was observed in 59 (59%), and night sweats were particularly common in 58 (58%) patients. Table 1 shows that 31 (31%) cases had a positive Mantoux test result, and 47 (47%) had an elevated rate of ESR. The results of smear microscopy were negative for each sample.

Microorganism Growth Indicator Tube 960, Polymerase Chain Reaction, Fine-Needle Aspiration Cytology, and Xpert MTB/ RIF Diagnostic Performance

Among the 100 patients suspected of having cervical tuberculous lymphadenitis, the following were detection rates for MTBC: Expert MTB/ RIF identified 26 cases (26%), conventional PCR detected 21 cases (21%), and the MGIT 960 identified 18 cases (18%). Notably, Xpert MTB/ RIF identified 16 cases that were missed by MGIT 960, while five cases positive by MGIT were not detected by Xpert MTB/ RIF. Additionally, eight cases were culture-positive but negative on PCR, and 12 culture-negative cases returned positive results on PCR. The combinations of positive results were as follows: Xpert MTB/ RIF and PCR in 16% of cases, PCR and MGIT 960 in 16%, and Xpert MTB/ RIF and MGIT 960 in 11% of cases. Importantly, all microbiological tests (MGIT 960, Xpert MTB/ RIF, and PCR) were positive in 11% of the cases. GeneXpert and PCR's sensitivity and specificity in relation to the gold standard are displayed in Table 2.

Table 1.Clinical and Demographic Characteristics of the Study Population

N = 100

Characteristic	Number of Patients	Percentage of Patients
Gender		
Male	46	46
Female	54	54
Male-to-female ratio	-	1:1.17
Age		
Age range (years)	10 to 80	-
Mean age (± SD)	59.55 ± 14.46	-
Presentation		
Solid lymph nodes	87	87
Abscess	10	10
Discharging sinus	3	3

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Cervical lymph node involvement		
Unilateral involvement	87	87
Right-side involvement	59	68
Left-side involvement	28	32
Lymph node size (diameter in cm)		
3–6	53	53
> 6	30	30
< 3	17	17
Associated lung lesions (X-ray)	12	12
Systemic features		
Fever	75	75
Weight loss	59	59
Night sweats	58	58
Laboratory findings		
Elevated erythrocyte sedimentation rate	47	47
Positive Mantoux test	31	31

Table 2.Diagnostic Performance of GeneXpert and PCR Against Gold Standard

Test	Sensitivity (%)	Specificity (%)
Xpert MTB/ RIF	79.17	67.85
PCR	85.86	90.16

Treatment Response

According to RNTCP criteria, 60% of the patients in this study received Category I treatment. Out of them, 74% replied in less than six months, 14% in a shorter period, and 12% took longer than a year. Every single Xpert MTB/ RIF-positive patient was susceptible to rifampicin. After treatment, 4% of patients had no decrease in lymph nodes but did exhibit improvements in overall well-being and weight gain; ultimately, surgical excision of the lymph nodes was necessary.

Discussion

Globally, TB continues to be a major source of disease and mortality with tuberculous lymphadenopathy being one of the most prevalent forms in India.[17] Both tuberculous and nontuberculous mycobacteria can lead to cervical lymphadenitis, posing diagnostic and therapeutic challenges despite the rising global incidence of the disease.[18–20] TB is notably the most frequent opportunistic infection in regions with high HIV prevalence.[21] The male-to-female ratio (1:1.17) observed in our study aligns with similar research conducted in Pakistan and India, though variations exist in other studies from the UK and Pakistan.[22–25] Jha et al. reported a low occurrence of cervical abscesses or sinuses, which aligns with our findings of abscesses in 10% and discharging sinuses in 3% of cases.[23] A study in Bangladesh reported higher rates, with abscesses in 21.5% and sinus formation in 9.2% of cases.[26] Our study identified unilateral neck swelling in 87% of patients, a common finding observed in other studies.[23,27] Associated lung lesions on chest radiographs were found in 12% of our cases, compared to 16% and 7.5% in other studies, while Choudhury et al. reported a higher incidence of 48.48%.[23–25] Additionally, elevated ESR was seen in 47% of our patients, consistent with findings by Umer et al., (28)but higher than the 12.5% reported by Magsi et al.[24]

EPTB diagnosis is fraught with difficulties, chief among which are specimens that are paucibacillary, a small sample volume, and the requirement to divide samples for a variety of diagnostic tests, including PCR, histology, cytology, biochemical testing, and microbiology, all of which can result in an uneven distribution of microorganisms. The purpose of this study was to assess the clinical characteristics and methods of diagnosis for tuberculous lymphadenopathy. Using Xpert MTB/ RIF, PCR, and MGIT 960, MTBC was found in 26%, 21%, and 18% of 100 patients, respectively, with suspected cervical tuberculous lymphoma. While Xpert MTB/ RIF did not find five MGIT-positive cases, it did identify 16 instances that MGIT 960 had missed. Twelve cases had a negative culture but a PCR result, while eighty-two cases showed the converse. Xpert MTB/ RIF and PCR had a combined positivity rate of 16%, MGIT and PCR of 16%, and Xpert MTB/ RIF and MGIT 960 of 11%. The positive results of all three tests were observed in 11% of cases, which is probably because of sample inhibition.

Although histopathology remains an affordable and effective tool in low-resource settings, it has limitations in distinguishing TB from other conditions like lymphomas. Conventional methods like smear microscopy and culture, used as reference standards, do not capture all TB cases, as evidenced in our study. Relying solely on a single diagnostic test could result in missed diagnoses, underscoring the importance of clinical judgment in initiating antitubercular therapy.

Antituberculous chemotherapy remains the cornerstone of managing TB lymphadenitis, with a 6-month regimen proving sufficient for most patients (74%). However, establishing a definitive “endpoint” for treatment

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effectiveness in EPTB can be challenging due to potential delayed responses. In this study, 4 patients ultimately required surgical intervention for lymph node removal. Similarly, Jha et al. reported that while most patients responded well to a 6-month course of chemotherapy, surgery was occasionally necessary for management.[23]

Limitation

This study had several limitations. The single-centre approach and small sample size could restrict how far the results can be applied. The paucibacillary nature of EPTB specimens affected diagnostic accuracy, and the diagnostic tests used had varying sensitivity and specificity. Additionally, the lack of long-term follow-up hindered the assessment of treatment outcomes, and drug resistance patterns were not thoroughly evaluated. In some cases, treatment was initiated based on clinical judgment rather than microbiological confirmation, raising concerns about potential overtreatment. Larger, multi-centre studies are needed for more accurate results.

Conclusion

Diagnosing TB lymphadenitis is challenging due to the limitations of individual diagnostic methods. In line with national TB control goals for EPTB cases, combining clinical, radiographic, and microbiological techniques can enhance early diagnosis and treatment. Given the significant possibility of concomitant pulmonary involvement, early antitubercular therapy reduced tuberculosis transmission, and the CRS outperformed conventional approaches in this investigation.

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Conflict of Interest: None

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