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Сравнение теста амплификации нуклеиновых кислот на основе картриджей с тонкоигольной аспирационной цитологией при подозрении на туберкулезный лимфаденит (опыт Индии)

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АННОТАЦИЯ

Введение. Диагностика туберкулезного лимфаденита является сложной задачей, поскольку существуют различные клинические проявления и отсутствует единый «золотой стандарт» исследования. Тест амплификации нуклеиновых кислот на основе картриджей (англ.: *cartridge-based nucleic acid amplification test*, CBNAAT) — это быстрый молекулярный диагностический анализ для одновременного подтверждения туберкулеза и определения резистентности к рифампицину.

Цель. Оценить эффективность теста CBNAAT для выявления *M. tuberculosis* в образцах лимфатических узлов по сравнению с тонкоигольной аспирационной цитологией (англ.: *fine needle aspiration cytology*, FNAC).

Материалы и методы. Исследование выполнено в сельской больнице третичного звена в Центральной Индии. Было включено 180 пациентов с клиническим подозрением на туберкулезный лимфаденит. Соотношение мужчин и женщин составило 1:1,3; средний возраст — 33,3 года, наибольшее число случаев было зафиксировано в возрастной группе 21–40 лет. Наиболее частыми жалобами пациентов были повышение температуры тела (29,4%), с последующей потерей аппетита (9,5%), снижение веса (9,5%) и кашель (6,6%). Однако, большинство пациентов обратились в больницу только по поводу лимфаденопатии (44,4%). Наиболее часто поражался передний шейный лимфатический узел (78,8%), за которым по частоте следуют подмышечные (10,5%), подчелюстные (2,8%), паховые (2,8%), надключичные (2,2%), субментальные (1,7%) и подключичные (1,1%) лимфатические узлы. У всех пациентов выполнено как FNAC, так и на CBNAAT. Результаты на *M. tuberculosis* представлены как положительные или отрицательные, поскольку CBNAAT дает полуколичественную оценку концентрации бацилл. Результаты о резистентности к рифампицину были представлены как «выявлена» или «не выявлена».

Результаты. Цитологическое исследование аспиратов из лимфатических узлов показало, что в большинстве случаев это были случаи туберкулезного лимфаденита. Цитоморфологический анализ случаев туберкулезного лимфаденита выявил преобладающий тип 6 (туберкулезный абсцесс). Тестирование CBNAAT выявило 26 случаев *M. tuberculosis* и три случая резистентности к рифампицину. Специфичность (92,92%) комбинации методов FNAC и CBNAAT значительно выше по сравнению с использованием только метода CBNAAT при низкой чувствительности комбинированного применения методов (26,86%).

Заключение. CBNAAT наряду с FNAC является ценным дополнением в исследованиях первой линии при туберкулезном лимфадените для своевременного подтверждения диагноза.

Ключевые слова: *CBNAAT; FNAC; микобактерии туберкулеза; лимфаденопатия; устойчивость к рифампицину*

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Cartridge-Based Nucleic Acid Amplification Test Compared to Fine Needle Aspiration Cytology in Suspected Cases of Tubercular Lymphadenitis (the Indian Experience)

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ABSTRACT

INTRODUCTION: Diagnosis of tubercular lymphadenitis is daunting as there are varied clinical presentations and no single confirmatory gold standard test. Cartridge-based nucleic acid amplification test (CBNAAT) of the lymph node is a rapid molecular diagnostic test for simultaneously detecting tuberculosis (TB) and rifampicin resistance.

AIM: To evaluate the performance of the CBNAAT test for detecting *M. tuberculosis* in lymph node specimens compared to fine needle aspiration cytology (FNAC).

MATERIALS AND METHODS: The study was conducted in a rural tertiary care hospital in central India. A total of 180 patients clinically suspected of tubercular lymphadenitis were included. The male-to-female ratio was 1:1.3. The average age was 33.3 years. The age group 21–40 years had the highest number of cases. The most common complaints among the patients were fever (29.4%), followed by loss of appetite (9.5%), weight loss (9.5%), and cough (6.6%). However, most patients presented to the hospital with only lymphadenopathy (44.4%). The most common site involved was the anterior cervical lymph node (78.8%), followed by the axillary group (10.5%), submandibular (2.8%), inguinal (2.8%), supraclavicular (2.2%), submental (1.7%) and infraclavicular (1.1%) group of lymph nodes. The patients were subjected to both FNAC and CBNAAT testing. Results were reported as positive or negative for *M. tuberculosis* as CBNAAT gives a semiquantitative estimate of the concentration of bacilli. Rifampicin resistance results were reported as detected or not detected.

RESULTS: Cytological examination of the lymph node aspirates revealed that most were tubercular lymphadenitis cases. Cytomorphological analysis of the cases of tubercular lymphadenitis revealed Type 6 (tubercular abscess) as the predominant pattern. CBNAAT testing detected 26 cases of *M. tuberculosis* and three cases of rifampicin resistance. The study reported a specificity of 92.92% and low sensitivity of 26.86% of combined FNAC and CBNAAT is much higher compared to only CBNAAT.

CONCLUSION: CBNAAT, along with FNAC, is a valuable addition in first-line investigations of tubercular lymphadenitis to make a timely diagnosis.

Keywords: *CBNAAT; FNAC; Mycobacterium tuberculosis; lymphadenopathy; rifampicin resistance*

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LIST OF ABBREVIATIONS

CBNAAT — cartridge-based nucleic acid amplification test
FNAC — fine needle aspiration cytology
HIV — human immunodeficiency viruses
NAATs — nucleic acid amplification tests
RNTCP — Revised National Tuberculosis Control Programme (India)
TB — tuberculosis
WHO — World Health Organization

INTRODUCTION

Tuberculosis (TB) still accounts for most of the morbidity and mortality in the world, especially in developing countries like India. There were 5.8 million newly diagnosed TB cases in 2020, according to the World Health Organization (WHO) Global TB report 2021 (next — the Report). It also reported 1.3 million human immunodeficiency viruses (HIV) negative TB deaths and an additional 214 thousand HIV-positive TB death. Geographically, most TB cases in 2021 were in the WHO regions of South-East Asia, Africa, and the Western Pacific countries. The Report also stated that India accounts for 26% of the global TB burden [1]. India is ranked the world's highest TB burden country in the absolute number of incidence cases yearly. TB continues to kill approximately 480 thousand Indians every year [2].

Diagnosis of tubercular lymphadenitis is daunting as there are varied clinical presentations, and no single confirmatory gold standard test exists for its diagnosis. Moreover, the paucibacillary nature of extra-pulmonary specimens is a big hurdle in establishing the diagnosis [3]. Delay in appropriate diagnosis leads to delay in initiating anti-tubercular therapy leading to an increased transmission in the community. Thus, there is a need for a rapid and accurate diagnostic tool for tubercular lymphadenitis. To overcome these limitations, more rapid and reliable methods are the need of the hour. Molecular diagnostic methods are a potential candidate for efficient and timely diagnosis of tubercular lymphadenitis.

Several studies [4–7] have assessed the utility of nucleic acid amplification tests (NAATs) in diagnosing tubercular lymphadenitis. These studies suggest that although NAATs cannot fully replace traditional tests like fine needle aspiration cytology (FNAC), microscopy, culture, and histopathology for tubercular lymphadenitis, they could be utilized and interpreted in correlation with available clinical data and conventional tests. The cartridge-based nucleic acid amplification test (CBNAAT) is an automated deoxyribonucleic acid test that identifies *M. tuberculosis* and rifampicin resistance within two hours. The CBNAAT (Xpert) assay uses heminested real-time polymerase chain reaction to amplify an *M. tuberculosis*-specific sequence of the *rpoB* gene. The rifampin resistance is determined by probing the rifampin resistance-determining region of the *rpoB* gene with molecular beacons [5].

In December 2010, WHO recommended CBNAAT (Cepheid, USA) for TB laboratories to diagnose TB. CBNAAT was initially introduced in India by Revised National Tuberculosis Control Programme in 2012 to diagnose pulmonary TB on sputum samples. Current Indian INDEX-TB guideline states that for diagnosis of tubercular lymphadenitis, Xpert *M. tuberculosis*/rifampin resistance should be used as an additional test to cytology in FNAC specimens, conventional smear microscopy, and culture [6–8]. However, only a few studies from rural populations focused on aspirates from lymph nodes and their role in diagnosing tubercular lymphadenitis by CBNAAT. In addition, the correlation of morphological patterns of tubercular lymphadenitis with the CBNAAT data was also evaluated by only a few studies in the literature.

The **aim** of this study to compared the efficacy of cartridge-based nucleic acid amplification test assay from lymph node aspirates for diagnosing tubercular lymphadenitis with fine-needle aspiration cytology.

MATERIALS AND METHODS

This study has received approval from the Institutional Ethics Committee (MGIMS/IEC/Path/100/2019; October 12, 2019). The cross-sectional study was carried out in the Cytology section of tertiary care rural center located in central India.

During the three-year duration (2019–2021), 1,107 TB patients were diagnosed at our hospital. Among these patients, 182 cases were diagnosed as tubercular lymphadenitis. A total of 180 patients clinically suspected of peripheral tubercular lymphadenitis with no previous history of anti-tubercular drug intake were included in the study.

The male-to-female ratio in the study's 180 patients was 1:1.3. The average age was 33.3 years. The age group 21–40 years had the highest number of cases. The most common complaints among the patients were fever (29.4%), followed by loss of appetite (9.5%), weight loss (9.5%), and cough (6.6%). However, most patients presented to the hospital with only lymphadenopathy (44.4%). The most common site involved was the anterior cervical lymph node (78.8%), followed by the axillary group (10.5%), submandibular (2.8%), inguinal (2.8%), supraclavicular (2.2%), submental (1.7%) and infraclavicular (1.1%) group of lymph nodes. Most patients presented to the hospital

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within the first six months of lymph node enlargements.

FNAC of the lymph nodes was done with the help of 22–26-gauge disposable needles and 10 ml syringes with a Cameco® syringe holder with standard precautions. Smears made from the aspirates were air-dried and fixed in 95% ethyl alcohol. We reviewed the fine needle aspiration smears stained with Papanicolaou and Giemsa stains. In addition, the Ziehl–Neelsen stain was done in cytologically diagnosed cases of tubercular lymphadenitis. A repeat pass was done, and the aspirate was rinsed in 1 ml of sterile phosphate buffered saline in a 10 ml glass vial and sent for CBNAATing to the District TB Center. The presence of epithelioid cell granulomas with or without multinucleated giant cells and caseation necrosis was used to diagnose tubercular lymphadenitis [9]. Tubercular lymphadenitis was subdivided into six patterns depending on the cytomorphological appearances [10].

Results were reported either positive or negative for *M. tuberculosis* as CBNAAT gives a semiquantitative estimate of the concentration of bacilli as defined by the cycle threshold range (high, < 16; medium, 16–22; low, 22–28; very low, > 28). In addition, rifampicin resistance results were reported as detected or not detected.

Data was collected and analysed in EPI INFO, version 7 (USA). The study involved the analysis of de-identified patient data. The diagnostic accuracy of CBNAAT for tubercular lymphadenitis compared to FNAC was estimated using the sensitivity, specificity, predictive value, and likelihood ratios.

RESULTS

Cytological examination of the lymph node aspirates revealed that most were tubercular lymphadenitis cases. The clinically suspected cases were diagnosed as abscess, malignancy, suppurative lesion, and non-tubercular granulomatous lymphadenitis. Most patients diagnosed with tubercular lymphadenitis belonged to the second, third, and fourth decades of life. The most common site in diagnosed cases was still the anterior cervical lymph node group by a staggering majority (86.6%). They presented with either lymphadenopathy alone or with fever in most cases.

Cytomorphological analysis of the cases of tubercular lymphadenitis revealed Type 6 (tubercular abscess) as the predominant pattern (32.8%). This was followed by type 1, which showed the classical tubercular pattern with well-formed epithelioid granulomas, Langhans giant cells, and caseous necrosis in 19 (28.4%) cases. In addition, 10 (14.9%) cases showed caseous necrosis with few lymphocytes and histiocytes, 9 (13.4%) cases showed numerous clusters of epithelioid cells, and 7 (10.4%) patients mainly showed caseous necrosis with few epithelioid cells. Acid-fast bacilli staining for the 67 cases diagnosed as tubercular lymphadenitis showed positivity in 4 (6.0%) cases (Tables 1 and 2, Figure 1).

Out of the 180 suspected cases of tubercular lymphadenitis subjected to CBNAAT testing, *M. tuberculosis* was identified in 26 (14.4%) cases. Cytomorphological diagnosis of these cases included 18 (69.2%) cases of tubercular lymphadenitis. Other cytological diagnoses included non-specific lymphadenitis (11.5%), abscess (11.5%), and acute suppurative lesion (7.7%). The cytomorphological pattern analysis of the CBNAAT detected cases with a cytological diagnosis of tubercular lymphadenitis showed type 6 as the predominant pattern (43.8%). This was followed by type 2 (33.3%), type 4 (18.8%), and type 1 (12.5%). None of the cases with only caseous and mostly caseous necrosis were positive for CBNAAT. In the present study, 3 (11.5%) cases of rifampicin resistance were detected by CBNAAT.

The sensitivity and specificity of CBNAAT from aspirate with cytology (FNAC) were 26.9% and 92.9%, and positive and negative predictive values were 69.2% and 68.1%, respectively (Table 3).

DISCUSSION

Tubercular lymphadenitis is the commonest cause of lymphadenopathy in developing countries and is the most typical manifestation of extra-pulmonary TB, contributing to around 25% of all cases of TB [9–11]. Extra-pulmonary TB contributes to a significant burden of mortality and morbidity due to its complex and varied presentations, leading to a delay in diagnosis.

Table 1. Cytomorphological diagnosis in the studied group of patients (n = 180)

Cytomorphological diagnosis	FNAC detected cases	CBNAAT detected cases
Non-specific lymphadenitis, n (%)	63 (35.00)	3 (11.53)
Suppurative lesion, n (%)	7 (3.88)	2 (7.69)
Non-tubercular granulomatous lymphadenitis, n (%)	5 (2.77)	0
Abscess, n (%)	24 (13.33)	3 (11.53)
Malignancy, n (%)	14 (7.77)	0
Tubercular lymphadenitis, n (%)	67 (37.22)	18 (69.23)
Total, n	180	26

Notes: CBNAAT — cartridge-based nucleic acid amplification test, FNAC — fine needle aspiration cytology

Table 2. Classification of smears according to cytomorphological pattern in the studied group of patients (n = 180)

Cytomorphological pattern types	Number of cases detected on FNAC	Number of cases detected on CBNAAT
Type 1 — Epithelioid granulomas, Langhans giant cells, and caseous necrosis, n (%)	19 (28.35)	2 (12.50)
Type 2 — Numerous clusters of epithelioid cells, n (%)	9 (13.43)	6 (33.33)
Type 3 — Mostly caseous necrosis with few epithelioid cells, n (%)	7 (10.44)	0
Type 4 — Caseous necrosis with few lymphocytes and histiocytes, n (%)	10 (14.92)	3 (18.75)
Type 5 — Only caseous necrosis, n (%)	0	0
Type 6 — Tubercular abscess, n (%)	22 (32.83)	7 (43.75)
Total, n (%)	67	18

Notes: CBNAAT — cartridge-based nucleic acid amplification test, FNAC — fine needle aspiration cytology

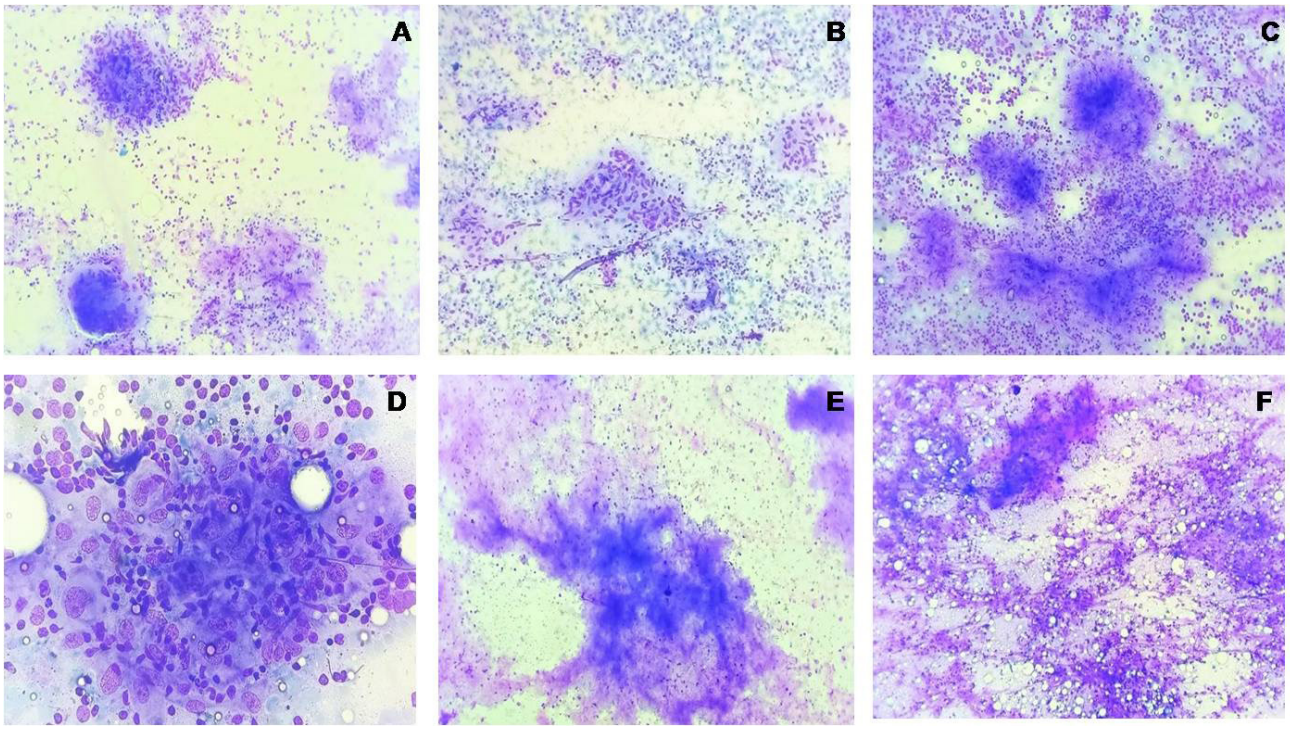

Fig. 1. Cytomorphological patterns: epithelioid granulomas with Langhans giant cells and caseous necrosis (Giemsa, ×10) (A); only numerous epithelioid cells and granulomas in a reactive background (Giemsa, ×10) (B); caseous necrosis with few epithelioid cells (Giemsa, ×10) (C); caseous necrosis with few epithelioid cells (Giemsa, ×40) (D); caseous necrosis with few lymphocytes and histiocytes, no epithelioid cells (Giemsa, ×10) (E); tubercular abscess showing predominantly neutrophils along with epithelioid cells (Giemsa, ×10) (F).

Table 3. Sensitivity, specificity, predictive values, and likelihood ratios of cartridge-based nucleic acid amplification test with cytology as the gold standard

Sensitivity	26.86%	2 (12.50)
Specificity	92.92%	6 (33.33)
Positive Predictive Value	69.23%	0
Negative Predictive Value	68.18%	3 (18.75)
Positive Likelihood Ratio	3.25	0
Negative Likelihood Ratio	0.80	7 (43.75)

Maximum cases (71.64%) were reported in ages 21–50. TB primarily affects people in their most economically productive years of life with important socioeconomic impacts on the household, such as increased debt burden, particularly for the poor and marginalized sections of the population. A. Gupta, et al. also reported 18-45 years as the most affected age group (63.1%) [12].

Among the clinically suspected cases, almost equal occurrence was seen in both sexes, with a slight female predominance (57.22%). In their research, C. V. Srinivas, et al. reported a male predominance (56%) in the clinico-pathological profile of cervical tubercular lymphadenitis. Though there is variation in the predominant gender involved in various studies, it can be assumed that the disease affects both sexes equally [13].

The current study's most common lymph node group was the anterior cervical (86.56%). Many studies reported similar findings [6, 7, 10, 12–14]. This could result from lung lymphatics draining the supraclavicular lymph nodes and lower cervical chain. Also, the tuberculosis bacilli may drain to cervical lymph nodes from extra-thoracic sources in the pharynx and larynx [15]. The cytological analysis reported 37.22% of cases as tubercular lymphadenitis. Many patients were also diagnosed with non-specific lymphadenitis (35.0%). V. Gupta, et al. [6] study assessing clinically suspected tubercular lymphadenopathy on lymph node aspirates found most cases to be reactive lymphadenitis (52.3%), followed by tubercular lymphadenitis in 33.2% of cases. S. Dasgupta, et al., in their study on the shifting trend of tubercular lymphadenitis over a decade in the eastern region of India, concluded that tubercular lymphadenopathy had reduced [16].

The 67 cytologically diagnosed cases of tubercular lymphadenitis were classified based on the cyto-morphological patterns according to studies in the literature [10, 14]. Most cases were grouped under Type 6 — tubercular abscess (32.83%). N. Gangane, et al. reported Type 1 as predominant [14], and C. Nanlinimohan, et al. reported Type 3 as the commonest (27%) [10]. A. Jamsheed, et al. found the predominant pattern of epithelioid granulomas with caseous necrosis [17]. However, no predominant cytomorphological pattern was consistent in the literature for all the studies. In tuberculous lymphadenitis, the morphologic spectrum varies significantly depending on the host's immunity and the stage of the disease. Among the many traditional diagnostic techniques available, mycobacterial culture is often considered the gold standard due to its high sensitivity and specificity, but *results take 2–6 weeks*, which is undesirable [9]. Diagnosis of tubercular lymphadenitis by FNAC is based on identifying epithelioid granulomas and caseous necrosis. It is ideal for use in resource-limited settings, including more remote and rural areas, and is a minimally invasive, pain-free procedure. However, it has *low specificity* as many conditions are associated with granuloma formation [4].

CBNAAT of the lymph node aspirates detected 26 cases (14.4%) in our study out of the 180 clinically suspected cases of tubercular lymphadenitis. Compared to other studies, [4, 7, 18] the present study showed a lower detection rate of *M. tuberculosis* by the CBNAAT testing. The study could have had a higher detection rate on CBNAAT if inclusion criteria for the clinical suspicion of tubercular lymphadenitis had been stringent. However, since India is endemic to TB, we need to include a more significant portion of patients in clinical suspicion to combat the disease. The 26 CBNAAT-detected cases in our study on cytomorphological examination revealed that the majority (69.2%) had the features of tubercular lymphadenitis, followed by 3 points each of non-specific lymphadenitis and abscess and two cases of the acute suppurative lesion.

The eight cases detected on CBNAAT and missed on cytological evaluation may be due to sampling error missing the granulomatous area of the lymph node, thus giving a cytological picture of non-specific lymphadenitis in three cases. The cytological picture of the abscess and the suppurative lesion may be due to a tubercular abscess. A combined approach using clinical suspicion, microscopy, acid-fast bacilli staining, culture, and CBNAATing is needed to diagnose tubercular lymphadenitis.

Various studies [7, 18] in the literature reported consistently high specificity of CBNAAT for detecting *M. tuberculosis* in tubercular lymphadenitis. However, the sensitivity among various studies shows varied results. In the present study, though the specificity was high (92.92%), there was low sensitivity (26.86%) for the CBNAAT (Table 3). The lymph node aspirates, if blood mixed, would not contain representative material; therefore, the bacilli would not be detected on CBNAAT. Also, the solid cheesy nature of aspirate has a low bacillary load and may lead to CBNAAT negativity [19]. Despite performing repeat passes for the CBNAAT sample to avoid low CBNAAT detection of *M. tuberculosis*, the present study had low sensitivity, which could be attributed to the refrigeration of samples before testing [3]. Similar to our study, various studies [7, 18, 20] report low detection rates of rifampicin resistance. The rapid detection of rifampicin resistance by CBNAAT gives added advantage to CBNAAT compared to other modalities of detecting tubercular lymphadenitis. The benefit to patients regarding immediate and accurate initiation of specific anti-tubercular therapy is invaluable.

Strength. This study highlights the necessity, limitations, inaccuracy of utilizing only FNAC and only CBNAAT individually to diagnose tubercular lymphadenopathy in locations with a high frequency of the disease. It also emphasizes the need for further supporting investigations, such as Ziehl–Neelsen staining. In addition, according to the study, FNAC must be combined with CBNAAT samples from lymph nodes and should be the initial examination in lymphadenopathy cases to boost the TB discovery rate. Finally, this study shows how well FNAC and CBNAAT work together in high-frequency areas.

Limitations. Limited sample sizes in the study must be replaced with a larger sample. By doing a separate pass for CBNAAT samples, the need for more sampling for CBNAAT was eliminated in the study. Despite this, our study's sensitivity was modest. This can be because the samples were refrigerated for 1–2 days before the test. The timing and preservation of tests after collecting CBNAAT samples from lymph nodes require more research.

CONCLUSION

Cartridge-based nucleic acid amplification test from lymph node aspirate is a useful tool to diagnose tubercular lymphadenitis. At the same time, a negative result should be followed by investigating various modalities in patients with strong clinical suspicion of tubercular lymphadenitis. Cartridge-based nucleic acid amplification test combined with fine needle aspiration cytology is a valuable addition in first-line investigations of tubercular lymphadenitis to make a timely diagnosis and start the appropriate anti-tubercular treatment.

ADDITIONALLY

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Contribution of the authors: *S. A. Oommen , B. U. Patil* — design of study, collection and analysis of data, writing the text; *P. Ghongade* — design of study, writing the text; *N. Gangane* — concept and design of study, editing. The authors confirm the correspondence of their authorship to the ICMJE International Criteria. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.
Вклад авторов: *Oommen S. A., Patil B. U.* — дизайн исследования, сбор и анализ данных, написание текста; *Ghongade P.* — дизайн исследования, написание текста; *Gangane N.* — концепция и дизайн исследования, редактирование. Авторы подтверждают соответствие своего авторства международным критериям ICMJE (все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией).

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