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Original Research

Correlation of Cytology-Positive Tuberculosis with TB PCR: A Prospective Observational Study

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Abstract:

Background: Cytological identification of granulomatous inflammation is widely used for the diagnosis of tuberculosis, particularly in extrapulmonary cases. However, cytology alone cannot provide definitive etiological confirmation, and Ziehl–Neelsen staining often shows low sensitivity. Molecular techniques such as tuberculosis polymerase chain reaction (TB PCR) enable rapid and sensitive detection of Mycobacterium tuberculosis and may complement cytological diagnosis.

Objective: To evaluate the correlation between cytology-positive granulomatous lesions suggestive of tuberculosis and TB PCR results.

Methods: This prospective observational study was conducted in the Department of Pathology & microbiology, Patna Medical College and Hospital, Patna, from August 2024 to December 2025. A total of 135 patients with cytological evidence of granulomatous inflammation on fine-needle aspiration cytology were included. Cytological findings were assessed using May–Grünwald–Giemsa and Ziehl–Neelsen staining. Samples were subsequently subjected to TB PCR for detection of Mycobacterium tuberculosis complex DNA. Cytology findings were correlated with TB PCR results, and statistical analysis was performed to assess diagnostic agreement.

Results: TB PCR detected Mycobacterium tuberculosis DNA in a significant proportion of cytology-positive cases. Higher PCR positivity was observed in lesions showing granulomas with necrosis compared to those without necrosis. TB PCR demonstrated additional diagnostic value in cytology-positive but Ziehl–Neelsen–negative cases. A statistically significant correlation was found between cytological features suggestive of tuberculosis and TB PCR positivity.

Conclusion: There is a significant correlation between cytology-positive granulomatous lesions and TB PCR results. TB PCR serves as a valuable adjunct to cytology by improving diagnostic confirmation, particularly in smear-negative cases. The combined use of cytology and molecular testing enhances diagnostic accuracy for tuberculosis in high-burden settings.

Keywords: Tuberculosis; Granulomatous inflammation; Fine-needle aspiration cytology; TB PCR; Extrapulmonary tuberculosis

Introduction

Tuberculosis is still a serious public health issue, especially in low- and middle-income nations, with India accounting for a substantial share of the global disease burden. While pulmonary tuberculosis remains the most frequently encountered form, extrapulmonary tuberculosis constitutes a significant proportion of cases and poses unique diagnostic challenges [1]. The clinical presentation of extrapulmonary disease is often nonspecific, and radiological findings may be inconclusive. Delayed or inaccurate diagnosis can lead to disease progression, increased morbidity, and inappropriate treatment. Consequently, there is a persistent need for reliable, rapid, and accessible diagnostic modalities that can facilitate early detection of tuberculosis, especially in resource-constrained settings [2,3].

Fine-needle aspiration cytology has emerged as a cornerstone in the diagnostic evaluation of suspected extrapulmonary tuberculosis due to its minimally cost-effectiveness, invasive nature, and rapid turnaround time [4]. Cytological features such as epithelioid cell granulomas, Langhans-type giant cells, and caseous necrosis are highly suggestive of tuberculous etiology and are commonly used to establish a presumptive diagnosis [5]. However, granulomatous inflammation is not exclusive to tuberculosis and may be encountered in a variety of infectious and non-infectious conditions, including sarcoidosis, fungal infections, and foreign body reactions. Additionally, Ziehl–Neelsen staining for acid-fast bacilli, although specific, has limited sensitivity in paucibacillary specimens, which are frequently encountered in extrapulmonary disease. These limitations reduce the diagnostic certainty of cytology when used as a standalone modality [6,7].

Advances in molecular diagnostic techniques have significantly improved the ability to detect Mycobacterium tuberculosis directly from clinical samples. Tuberculosis polymerase chain reaction (TB PCR) allows rapid identification of mycobacterial DNA with high sensitivity, even in specimens with low bacillary load. Unlike culture methods, which require prolonged incubation periods, TB PCR provides results within a shorter timeframe, enabling earlier initiation of appropriate therapy. The application of TB PCR to cytological samples has gained increasing attention, as it offers etiological confirmation in cases where conventional microscopy fails to demonstrate acid-fast bacilli. Moreover, molecular testing has the potential to reduce diagnostic ambiguity in granulomatous lesions by distinguishing tubercular from non-tubercular causes [8,9].

In high tuberculosis burden settings, integrating cytological evaluation with molecular techniques may offer a pragmatic and efficient diagnostic approach. Correlating cytology-positive granulomatous lesions with TB PCR results can help validate cytological diagnosis, enhance diagnostic confidence, and guide clinical management. Despite the widespread use of FNAC and increasing availability of molecular assays, data on the correlation between cytological findings and TB PCR positivity remain limited, particularly in tertiary care centers in Eastern India. The present study was therefore undertaken to evaluate the relationship between cytology-positive granulomatous inflammation and TB PCR results, and to assess the utility of TB PCR as an adjunct to cytology in the diagnosis of tuberculosis.

Methods

Study Design and Setting

This prospective observational study was conducted in the Department of Pathology & Microbiology, Patna Medical College and Hospital, Patna, over a period of 17 months from August 2024 to December 2025.

Study Population and Sample Size

135 consecutive patients with granulomatous inflammation on fine-needle aspiration cytology (FNAC) and clinical suspicion of tuberculosis were included in the study. During the trial period, patients of both sexes and all age groups were enrolled.

Inclusion and Exclusion Criteria

Patients were included if cytological examination revealed granulomatous inflammation with or without necrosis and if adequate material was available for TB PCR testing. Patients who were already receiving anti-tubercular therapy, those with inadequate or poorly preserved samples, and cases with confirmed non-tubercular granulomatous etiology were excluded from the study.

Sample Collection and Cytological Evaluation

A 22- to 24-gauge needle connected to a 10-mL disposable syringe was used for the aseptic FNAC procedure. Clean glass slides were covered with aspirated substance. To find acid-fast bacilli, air-dried smears were stained with May-Grünwald-Giemsa, and alcohol-fixed smears were stained using the Ziehl-Neelsen method. The presence of epithelioid cell granulomas, Langhans large cells, and/or caseous necrosis provided the basis for the cytological diagnosis of tuberculosis.

TB PCR Analysis

Samples showing cytological features suggestive of tuberculosis were subjected to TB PCR for detection of Mycobacterium tuberculosis complex DNA. PCR testing was performed using standardized, commercially available kits following the manufacturer's instructions. Strict quality control measures were maintained throughout the procedure to prevent contamination and ensure reliability of results.

Data Collection

Clinical and laboratory data including age, sex, site of aspiration, cytological findings, Ziehl–Neelsen staining results, and TB PCR results were recorded in a predesigned proforma for each patient.

Statistical Analysis

Microsoft Excel was used to enter the data, and the relevant statistical software was used for analysis. The chi-square test was used to evaluate the relationship between cytological findings and TB PCR results. TB PCR was used as the reference standard to calculate the sensitivity, specificity, positive predictive value, and negative predictive value of cytology. Statistical significance was defined as a p-value of less than 0.05.

Results

A total of 135 cytology-positive cases with granulomatous inflammation were included in the study. The study population comprised patients from a wide age range with a slight male predominance. Lymph nodes constituted the most common site of aspiration, followed by lung and other extrapulmonary sites. All cases demonstrated cytological features suggestive of tuberculosis, including epithelioid cell granulomas with or without necrosis.

TB PCR detected Mycobacterium tuberculosis DNA in 90 of the 135 cases, yielding an overall PCR positivity rate of 66.7%. Ziehl–Neelsen staining for acid-fast bacilli was positive in a smaller proportion of cases. TB PCR identified several additional cases that were negative on Ziehl–Neelsen staining, thereby increasing diagnostic confirmation in cytology-positive samples.

When cases were categorized based on cytological pattern, TB PCR positivity was significantly higher in lesions showing granulomas with necrosis compared to granulomas without necrosis. This difference was statistically significant,

indicating a strong association between the presence of necrosis and PCR positivity. Chi-square analysis revealed a significantly significant connection ($p < 0.05$) between cytological diagnosis and TB PCR results.

Table 1: Correlation of Cytological Pattern with TB PCR Results

Cytological Pattern	Total Cases (n=135)	TB PCR Positive	TB PCR Negative
Granuloma with necrosis	78	62	16
Granuloma without necrosis	57	28	29
Total	**135**	**90**	**45**

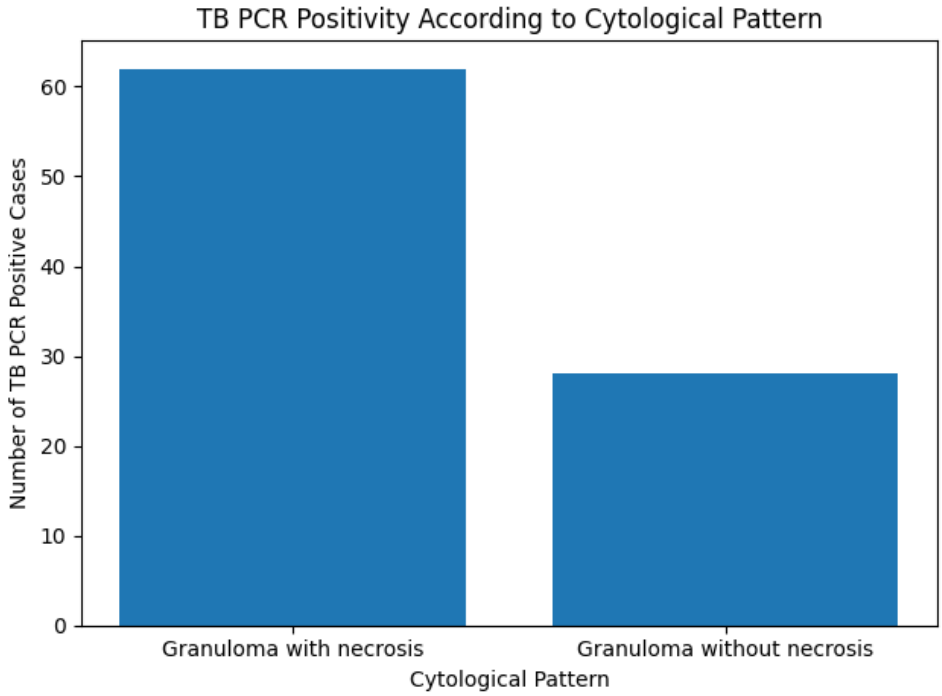

Figure 1: TB PCR Positivity According to Cytological Pattern

Discussion

The present study demonstrates a significant correlation between cytology-positive granulomatous lesions and TB PCR positivity, reinforcing the diagnostic relevance of cytological findings in suspected tuberculosis. Among the 135 cases evaluated, TB PCR confirmed Mycobacterium tuberculosis infection in a substantial proportion of cytology-positive samples, supporting the premise that granulomatous inflammation detected on FNAC frequently represents true tuberculous etiology. The statistically significant association observed in this study highlights the value of combining cytological assessment with molecular testing to improve diagnostic confidence, particularly in cases where microbiological confirmation is challenging [10].

A notable observation in this study was the higher TB PCR positivity among cases exhibiting granulomas with necrosis compared to those without necrosis. This finding represents an association between necrotizing granulomatous inflammation and TB PCR positivity and should not be interpreted as a causal relationship. The presence of necrosis likely reflects a higher mycobacterial burden, which may increase the probability of detecting mycobacterial DNA by PCR. Similar associations between necrotizing granulomas and increased molecular detection rates have

been reported in earlier studies. Importantly, TB PCR positivity was also observed in nearly 50% of non-necrotizing granulomas, indicating that the absence of necrosis does not exclude tuberculous etiology and underscoring the value of TB PCR as an adjunct to cytomorphological evaluation in suspected tuberculosis cases [7,11,12].

The study also highlights the limited sensitivity of Ziehl–Neelsen staining in cytology samples, particularly in extrapulmonary tuberculosis. A significant proportion of cases that were negative for acid-fast bacilli on microscopy were subsequently confirmed by TB PCR. This reinforces the well-recognized limitation of smear microscopy in paucibacillary disease and emphasizes the importance of molecular diagnostics in enhancing case detection. The ability of TB PCR to identify mycobacterial DNA in smear-negative specimens has important clinical implications, as it allows earlier initiation of anti-tubercular therapy and reduces diagnostic delays [13,14].

From a diagnostic perspective, the findings suggest that TB PCR serves as a valuable confirmatory tool in cytology-positive cases, rather than a replacement for cytological evaluation [15]. FNAC remains indispensable as a rapid, minimally invasive, and cost-effective initial investigation, especially in resource-limited settings. The addition of TB PCR strengthens the diagnostic pathway by providing etiological confirmation, thereby reducing uncertainty in granulomatous lesions that may otherwise be attributed to non-tubercular causes. Together, these methods improve diagnostic precision and facilitate better clinical decision-making.

The strengths of this study include its prospective design, uniform cytological evaluation, and inclusion of a well-defined study population over an extended period. The systematic correlation of cytological features with TB PCR results provides a comprehensive assessment of the diagnostic interplay between morphology and molecular testing. Conducting the study in a tertiary care center catering to a high TB-burden population further increases the clinical relevance of the findings and reflects real-world diagnostic challenges encountered in routine practice [16].

Despite these strengths, certain limitations must be acknowledged. Mycobacterial culture, considered the gold standard for tuberculosis diagnosis, was not performed due to logistical constraints and prolonged turnaround time. Consequently, TB PCR was used as the reference standard, which may have resulted in false-negative or false-positive results in a small subset of cases. Additionally, drug resistance profiling was not included, which could have provided further insights into the clinical utility of molecular testing. The study also did not assess patient outcomes following diagnosis, limiting the ability to correlate diagnostic findings with treatment response [17,18].

The findings of this study support the integration of TB PCR into routine diagnostic workflows for cytology-positive granulomatous lesions, particularly in high TB-burden settings. Future studies with larger sample sizes, inclusion of culture and drug susceptibility testing, and longitudinal follow-up may further clarify the role of molecular diagnostics in tuberculosis management. Expanding the use of molecular testing in conjunction with cytology has the potential to improve early diagnosis, optimize treatment strategies, and ultimately contribute to better disease control outcomes.

Conclusion

In this prospective observational study, cytology-positive granulomatous lesions demonstrated a significant correlation with TB PCR positivity, confirming the diagnostic relevance of cytological evaluation in suspected tuberculosis. TB PCR provided etiological confirmation in a

substantial proportion of cases, including those that were negative on Ziehl–Neelsen staining, thereby enhancing diagnostic accuracy in paucibacillary disease. Lesions exhibiting granulomas with necrosis showed higher PCR positivity, supporting the association between necrosis and increased mycobacterial burden. These findings indicate that cytology remains an effective initial diagnostic modality, while TB PCR serves as a valuable adjunct for confirmation. The combined use of cytology and molecular testing offers a pragmatic and reliable diagnostic approach, particularly in high tuberculosis burden settings where rapid and accurate diagnosis is essential. Incorporation of TB PCR into routine evaluation of cytology-positive granulomatous lesions may facilitate timely initiation of appropriate therapy and improve patient management.

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