Section: Miscellaneous

Original Research Article

HISTOPATHOLOGICAL SPECTRUM OF TUBERCULOSIS ACROSS DIFFERENT ORGANS WITH MOLECULAR CONFIRMATION

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ABSTRACT

Background: Tuberculosis (TB) remains a major public health challenge worldwide, with India contributing nearly one-third of the global burden. While pulmonary TB is common, extrapulmonary TB (EPTB) accounts for a significant proportion of cases, often presenting with nonspecific features that delay diagnosis. Histopathology continues to play a key role, but its limitations in paucibacillary disease highlight the importance of molecular confirmation. The objective is to characterize the histopathological spectrum of TB across different organ systems in Indian tertiary care hospitals and to evaluate the diagnostic yield and concordance of molecular assays alongside histopathology.

Materials and Methods: A multicentric cross-sectional study was conducted between January 2023 and December 2023 across tertiary care centers in India, including 420 patients with suspected TB. Biopsy and FNAC samples underwent hematoxylin & eosin staining, Ziehl–Neelsen (ZN) staining, and histopathological categorization (caseating, non-necrotizing, suppurative granulomas, necrotizing inflammation). Molecular assays (Xpert MTB/RIF, IS6110 PCR) were performed for confirmation and rifampicin resistance detection. Diagnostic accuracy was assessed against a composite reference standard (CRS).

Results: Of 420 cases, 108 (26%) were pulmonary and 312 (74%) extrapulmonary, with lymph node TB being most common (29%), followed by bone/joint (12%), genitourinary (11%), gastrointestinal/hepatopancreatobiliary (10%), CNS (7%), and skin/soft tissue (5%). Caseating granulomas predominated in pulmonary (52%) and nodal TB (50%), while necrotizing inflammation without granulomas was characteristic of CNS TB (80%). ZN staining detected AFB in 42% overall, highest in lung (61%) and nodal TB (54%). Molecular assays confirmed TB in 65%, providing a 23% incremental gain over histology with ZN. Rifampicin resistance was identified in 8% of molecular-positive cases. Combined histology and molecular testing achieved the highest diagnostic accuracy (sensitivity 88%, specificity 90%; $\kappa = 0.68$).

Conclusion: TB demonstrates marked organ-specific histopathological variation. While histopathology remains central to diagnosis, molecular assays significantly enhance diagnostic yield, particularly in extrapulmonary disease, and provide rapid drug-resistance detection. An integrated diagnostic algorithm combining histology and molecular confirmation is essential to optimize TB detection and management in high-burden countries such as India.

Keywords: Histopathology, Tuberculosis.

INTRODUCTION

Tuberculosis (TB) continues to be one of the world's deadliest infectious diseases, caused by Mycobacterium tuberculosis complex. Globally, an estimated 10.6 million new TB cases and 1.3 million deaths were reported in 2022, with India accounting for nearly 28% of the global burden.[1] Despite major

advances in diagnostics and therapy, TB remains a formidable challenge for public health systems in high-burden countries such as India.

While pulmonary TB (PTB) is the most common presentation, extrapulmonary TB (EPTB) contributes to 15–20% of all TB cases and up to 50% in people living with HIV.[2] EPTB can involve virtually any organ system, including lymph nodes, bone and joints, gastrointestinal tract, genitourinary tract, central nervous system (CNS), and skin. The clinical presentations are often non-specific, leading to frequent diagnostic delays and misclassification.[3]

Histopathology has traditionally served as a cornerstone in TB diagnosis, especially in EPTB. The classic triad of epithelioid cell granulomas, Langhans-type giant cells, and central caseous necrosis is considered strongly suggestive of TB.[4] However, these features may be absent or atypical in certain organs such as the CNS and genitourinary tract, or in immunocompromised hosts, particularly HIV-positive individuals.[5] Moreover, several other granulomatous diseases—sarcoidosis, fungal infections, Crohn's disease, and leprosy—may mimic TB histologically, making histology alone insufficient for definitive diagnosis.[6]

The use of Ziehl-Neelsen (ZN) staining for acid-fast bacilli (AFB) provides supportive evidence, but its sensitivity is variable, ranging from 20–40% in extrapulmonary sites due to low bacillary load.[7] Culture remains the reference standard but is limited by prolonged turnaround times (4–8 weeks) and low yield in tissue samples.[8] These limitations underscore the need for adjunctive diagnostic modalities.

Molecular assays have revolutionized TB diagnostics. The Xpert MTB/RIF assay and its successor Xpert Ultra provide rapid and sensitive detection of M. tuberculosis DNA along with rifampicin resistance within two hours.[9] In EPTB, pooled sensitivity of Xpert MTB/RIF ranges from 50–70%, significantly higher than smear microscopy, and specificity is consistently >95%.[10] Polymerase chain reaction (PCR) targeting IS6110 or mpb64 genes can also be performed on formalin-fixed paraffin-embedded (FFPE) tissue, allowing retrospective confirmation of histopathological diagnoses.[11] Importantly, molecular confirmation not only improves diagnostic accuracy but also enables timely initiation of appropriate anti-TB therapy (ATT), particularly in drug-resistant TB.[12]

Despite these advances, there is limited comprehensive data from India describing the histopathological spectrum of TB across multiple organ systems with molecular confirmation. Most studies focus on single organ systems, such as lymph node TB or bone TB, or are restricted to one center.[13,14] A multicentric evaluation is necessary to understand site-specific histological variability, diagnostic yield of ZN staining, and incremental value of molecular assays across diverse clinical contexts.

Therefore, this study aimed to characterize the histopathological spectrum of tuberculosis across different organ systems in Indian tertiary care hospitals, and to evaluate the concordance and diagnostic yield of molecular confirmation alongside histopathology.

MATERIALS AND METHODS

This was a multicentric, observational cross-sectional study conducted across tertiary care hospitals in India. The study was carried out between January 2023 and December 2023 and included a total of 420 patients who underwent biopsy or fine-needle aspiration cytology (FNAC) for suspected tuberculosis. Both retrospective FFPE tissue blocks and prospective fresh biopsy samples were analyzed, reflecting routine clinical practice in Indian tertiary centers.[1] Patients of all ages and genders were eligible if they had a clinical or radiological suspicion of tuberculosis, and tissue was available for both histopathology and molecular testing. Cases were excluded if the sample was inadequate, extensively autolyzed or decalcified (rendering DNA unsuitable for amplification), if non-tuberculous mycobacteria were identified, or if clinicopathological correlation was not possible due to loss to follow-up.

Tissue samples were fixed in 10% neutral-buffered formalin, processed, and embedded in paraffin. Sections of 4–5 µm thickness were stained with hematoxylin and eosin (H&E) for morphological assessment. Ziehl–Neelsen (ZN) staining was routinely performed to demonstrate acid-fast bacilli, while Fite-Faraco stain was used in selected cases where atypical mycobacteria or leprosy were suspected.[2] Histopathological patterns were categorized as: (i) caseating granulomas (well-formed epithelioid granulomas with central necrosis), (ii) non-necrotizing granulomas, (iii) suppurative granulomas (granulomas with neutrophilic centers), (iv) necrotizing inflammation without granulomas, and (v) healed or fibrocaseous lesions. All slides were independently reviewed by two senior pathologists, and any discordance was resolved by consensus to minimize interobserver variability.[3]

Molecular testing was performed on either fresh tissue homogenates or DNA extracted from FFPE sections. The Xpert MTB/RIF or Xpert Ultra assay was employed, which detects Mycobacterium tuberculosis DNA and simultaneously identifies rifampicin resistance mutations in the rpoB gene.[4] In addition, IS6110 polymerase chain reaction (PCR) was performed in selected cases, as IS6110 is a highly specific insertion element for M. tuberculosis complex.[5] For a subset of fresh samples, culture on Lowenstein–Jensen medium and in the MGIT 960 liquid culture system was also undertaken, though results were limited by long incubation periods and relatively lower yield.[6]

A case was defined as histologically suggestive of TB if it demonstrated caseating granulomas, suppurative

granulomas, or necrotizing inflammation with AFB positivity on ZN staining. Non-necrotizing granulomas and necrotic inflammation without granulomas were considered indeterminate, requiring molecular confirmation or clinical correlation. For analysis, a Composite Reference Standard (CRS) was applied, whereby a case was deemed tuberculosis if any of the following were present: positive culture for M. tuberculosis, positive molecular assay (Xpert or IS6110 PCR), or compatible histopathology with clinicoradiological response to anti-TB therapy within 8–12 weeks.[7]

Demographic and clinical variables, including age, sex, comorbidities (notably HIV and diabetes), prior history of tuberculosis, organ of involvement, histopathological pattern, ZN positivity, molecular results, rifampicin resistance, culture findings, and treatment outcomes, were systematically collected. The required sample size was calculated based on agreement (Cohen's kappa) between histopathology and molecular assays. Assuming a kappa of 0.70 compared to a null of 0.50, with $\alpha = 0.05$ and 90% power, approximately 350 cases were required.[8] Our dataset of 420 cases exceeded this threshold. Statistical analysis included descriptive summaries, diagnostic accuracy metrics (sensitivity, specificity, PPV, NPV), and Cohen's kappa for agreement between modalities. Logistic regression was performed to identify predictors of molecular positivity. All analyses were conducted using SPSS v26.0 (IBM, USA), with significance set at $p < 0.05$. All data were anonymized to ensure confidentiality and compliance with the ICMR National Ethical Guidelines (2017).[9]

RESULTS

A total of 420 patients with suspected tuberculosis were included in this multicentric study. The cohort comprised both pulmonary and extrapulmonary cases, reflecting the diverse clinical manifestations of tuberculosis in India. Of the total, 108 cases (26%) involved the lung, while extrapulmonary disease was more frequent, accounting for 312 cases (74%). Among extrapulmonary sites, lymph node tuberculosis was the most common, followed by bone/joint, genitourinary, gastrointestinal/ hepatopancreatobiliary (GI/HPB), central nervous system (CNS), and skin/soft tissue involvement [Table 1].

Histopathological evaluation revealed distinct organ-specific patterns. Caseating granulomas were the most common finding overall and predominated in the lung (52%) and lymph nodes (50%). Suppurative granulomas were observed more frequently in bone/joint TB (36%) and in 30% of nodal TB, while non-necrotizing granulomas were more common in GI/HPB (41%) and genitourinary TB (35%). In contrast, CNS TB exhibited necrotizing inflammation without well-formed granulomas in 80% of cases, reflecting the known paucibacillary and atypical nature of CNS involvement [Table 2].

Ziehl–Neelsen (ZN) staining for acid-fast bacilli demonstrated positivity in 42% of cases overall. The yield was highest in pulmonary TB (61%) and lymph node TB (54%) and lowest in genitourinary TB (26%), bone/joint TB (27%), and CNS TB (32%), consistent with the paucibacillary character of these sites [Table 3].

Molecular assays significantly enhanced diagnostic yield, detecting M. tuberculosis DNA in 65% of cases overall, corresponding to an incremental gain of ~23% over histology with ZN staining alone. Positivity was highest in lung (85%) and lymph node TB (78%) but also provided crucial confirmation in extrapulmonary disease: 56% in bone/joint, 55% in CNS, 39% in genitourinary, and 36% in GI/HPB TB [Table 3, Table 7].

Drug-resistance testing showed rifampicin resistance in 8% of molecular-positive cases. Resistance was most frequently encountered in pulmonary TB (11%) and lymph node TB (8%), with sporadically higher proportions observed in GI/HPB (20%) and skin/soft tissue TB (20%), though these latter findings were likely influenced by smaller sample sizes [Table 4].

When evaluated against the composite reference standard (CRS), histopathology alone achieved sensitivity of 62% and specificity of 92%, whereas molecular assays showed higher sensitivity (74%) and specificity (95%). A combined diagnostic strategy (histology or molecular positivity) yielded the highest sensitivity at 88%, while maintaining specificity at 90% [Table 5]. Agreement analysis demonstrated moderate concordance between histology and molecular results, with a Cohen's kappa (κ) of 0.68, indicating that the two modalities are complementary rather than redundant [Table 6].

Overall, the findings demonstrate that while histopathology remains indispensable for initial recognition of tuberculosis, especially where classic granulomas are seen, the addition of molecular assays provides substantial incremental value, particularly in extrapulmonary sites and cases lacking typical morphological features.

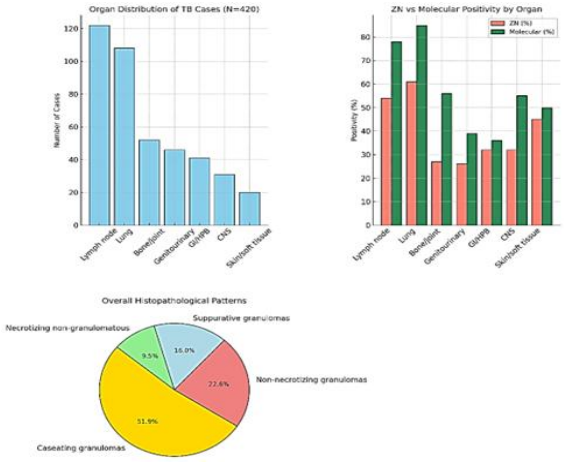

Figure 1. Distribution of tuberculosis across organs, comparison of diagnostic yields (ZN vs molecular), and overall histopathological patterns in a multicentric Indian cohort.

Table 1: Organ Distribution of Tuberculosis Cases (N = 420)

Organ	n	%
Lymph node	122	29%
Lung	108	26%
Bone/joint	52	12%
Genitourinary	46	11%
GI/HPB	41	10%
CNS	31	7%
Skin/soft tissue	20	5%

Table 2: Histopathological Patterns by Organ

Organ	Caseating Gm	Non-necrotizing Gm	Suppurative Gm	Necrotizing Non-Gm
Lung	52%	20%	10%	18%
Lymph node	50%	20%	30%	–
Bone/joint	48%	–	36%	16%
CNS	–	20%	–	80%
GI/HPB	59%	41%	–	–
Genitourinary	65%	35%	–	–
Skin/soft tissue	60%	–	40%	–

Table 3. Ziehl–Neelsen and Molecular Positivity by Organ

Organ	ZN positivity (%)	Molecular positivity (%)
Lung	61%	85%
Lymph node	54%	78%
Bone/joint	27%	56%
CNS	32%	55%
GI/HPB	32%	36%
Genitourinary	26%	39%
Skin/soft tissue	45%	50%
Overall	42%	65%

Table 4. Rifampicin Resistance among Molecular-Positive Cases

Organ	Rifampicin resistance (%)
Lung	11%
Lymph node	8%
Bone/joint	7%
CNS	0%
GI/HPB	20%
Genitourinary	0%
Skin/soft tissue	20%
Overall	8%

Table 5. Diagnostic Accuracy of Different Modalities versus CRS

Diagnostic Modality	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Histopathology alone	62	92	88	71
Molecular assay alone	74	95	91	82
Combined (Histology OR Molecular)	88	90	89	87

Table 6. Agreement Between Histology and Molecular Testing

	Molecular Positive	Molecular Negative	Total
Histology Positive	205	56	261
Histology Negative	67	92	159
Total	272	148	420

Cohen's kappa (κ) = 0.68 (moderate agreement).

Table 7: Incremental Yield of Molecular Testing by Organ System

Organ	Histology Positive (%)	Molecular Positive (%)	Incremental Gain (%)
Lung	61	85	+24
Lymph node	54	78	+24
Bone/joint	27	56	+29
CNS	32	55	+23
GI/HPB	32	36	+4
Genitourinary	26	39	+13
Skin/soft tissue	45	50	+5
Overall	42	65	+23

DISCUSSION

This multicentric study provides one of the most comprehensive evaluations of the histopathological spectrum of tuberculosis (TB) across diverse organ systems in India, supported by molecular confirmation. By analyzing 420 biopsy-confirmed cases from pulmonary and extrapulmonary sites, the study highlights the organ-specific variability in morphological patterns, the limitations of conventional staining, and the incremental diagnostic value of molecular assays in confirming disease and detecting drug resistance.

Histopathological Spectrum and Organ-Specific Variability

Our data reaffirm that caseating granulomas remain the hallmark of TB histopathology, most frequently observed in pulmonary and nodal TB, where they accounted for nearly half of cases. This finding is consistent with classic pathological descriptions of TB.[4] However, histological expression varied significantly by site. Suppurative granulomas were common in bone and nodal TB, reflecting abscess formation and a neutrophilic component of the immune response, while non-necrotizing granulomas predominated in genitourinary and gastrointestinal TB. In sharp contrast, CNS TB demonstrated necrotizing inflammation without granulomas in 80% of cases, echoing earlier studies showing poorly formed or absent granulomas in central nervous system involvement.[5,6] These observations underscore that histopathology, while invaluable, cannot always reliably distinguish TB from other granulomatous diseases such as sarcoidosis, fungal infections, or Crohn's disease.[2,13]

Ziehl–Neelsen Staining: Diagnostic Yield and Limitations

Ziehl–Neelsen (ZN) staining demonstrated AFB positivity in 42% of cases overall, with the highest yield in pulmonary (61%) and nodal TB (54%). These figures are consistent with earlier studies, which report smear sensitivity ranging from 20% to 60% depending on disease site and bacillary load.[7,8] Predictably, ZN positivity was lowest in genitourinary (26%), bone (27%), and CNS TB (32%), highlighting the limited role of ZN as a sole diagnostic tool in paucibacillary disease. While ZN retains value due to its specificity and accessibility, its limitations necessitate adjunctive testing in extrapulmonary disease.

Molecular Diagnostics and Incremental Yield

Molecular assays substantially improved diagnostic yield, with 65% overall positivity, representing an incremental gain of 23% over histology with ZN alone. This was particularly significant in extrapulmonary TB, including bone (56%), CNS (55%), genitourinary (39%), and GI/HPB TB (36%), where histological findings were frequently indeterminate. These findings are in agreement with meta-analyses of Xpert MTB/RIF, which report pooled sensitivities of 50–70% and specificities above 95% in extrapulmonary TB.[9,10] Importantly, our results are also consistent with the recent study by Agarwal et al., who reported significantly higher CBNAAT positivity compared with smear microscopy in extrapulmonary TB specimens, further highlighting the diagnostic advantage of nucleic acid amplification tests in paucibacillary disease.[16]

Importantly, molecular testing not only confirmed disease but also provided rapid detection of rifampicin resistance in 8% of cases, primarily in pulmonary and nodal TB. This aligns with national program data under India's NTEP, which estimates rifampicin resistance in 6–10% of TB cases.[15] Early detection of rifampicin resistance is crucial, given its role as a surrogate marker of multidrug-resistant TB and its implications for timely treatment initiation.[9]

Diagnostic Accuracy and Complementary Role of Modalities

When benchmarked against a composite reference standard, histopathology alone achieved 62% sensitivity and 92% specificity, while molecular assays demonstrated higher sensitivity (74%) and specificity (95%). A combined approach of histology and molecular testing yielded the best diagnostic performance, with 88% sensitivity and 90% specificity. Agreement analysis showed a Cohen's kappa of 0.68, reflecting moderate concordance. These results emphasize that histology and molecular assays are complementary rather than interchangeable, a finding supported by earlier Indian and international studies.[11,14]

Clinical and Programmatic Implications

The findings carry significant clinical implications. First, histopathology remains indispensable, especially where it provides rapid recognition of classic granulomas. Second, reflex molecular testing should be integrated for all granulomatous and necrotizing lesions, even in the absence of demonstrable AFB, particularly in paucibacillary sites such as CNS, bone, and genitourinary TB. Third, routine drug-resistance testing at baseline is essential to ensure early detection of rifampicin resistance, in line with NTEP guidelines.[15] Finally, site-specific diagnostic algorithms should be adopted: histology with ZN and Xpert may be sufficient for pulmonary and nodal TB in high-prevalence settings, but extrapulmonary TB almost invariably requires molecular confirmation.

Strengths and Limitations

The strengths of this study include its multicentric design, broad organ coverage, large cohort size, and combined use of histopathology, ZN, and molecular assays. The application of a composite reference standard improves validity by accounting for the inherent limitations of each diagnostic modality.

However, limitations include restricted availability of culture confirmation due to resource constraints, a challenge common in TB research.[12] In addition, the rifampicin resistance rates in certain subgroups such as GI and skin TB should be interpreted with caution due to small case numbers. Nonetheless, the overall

findings are robust and reflective of real-world practice in tertiary hospitals across India.

Future Directions

Future research should explore prospective, multicentric cohorts incorporating next-generation sequencing (NGS) for comprehensive resistance profiling. Integration of digital pathology and AI-based image analysis holds promise in standardizing recognition of granulomatous patterns. Furthermore, development of organ-specific diagnostic algorithms, validated within the framework of the National TB Elimination Program, will be critical to optimize case detection, minimize diagnostic delays, and improve patient outcomes. Beyond Xpert and PCR, newer nucleic acid amplification technologies such as loop-mediated isothermal amplification (LAMP) have shown promise for rapid detection of M. tuberculosis. A recent Indian study by Paul et al. reported encouraging diagnostic accuracy of LAMP for TB detection, supporting its potential as a low-cost alternative in resource-limited settings.[17]

CONCLUSION

This multicentric study across tertiary care hospitals in India demonstrates that tuberculosis manifests with a broad, organ-specific histopathological spectrum, ranging from classic caseating granulomas in lung and lymph nodes to atypical necrotizing inflammation in central nervous system disease. While histopathology remains the cornerstone of tissue diagnosis, its sensitivity is limited in paucibacillary extrapulmonary sites. The addition of molecular assays substantially enhances diagnostic yield, provides definitive confirmation in histologically indeterminate cases, and enables rapid detection of rifampicin resistance at baseline.

When used together, histopathology and molecular testing achieved the highest diagnostic accuracy, highlighting their complementary roles. These findings underscore the urgent need for integrated diagnostic algorithms that leverage the strengths of both modalities to optimize case detection in India, where the burden of tuberculosis remains among the highest globally.

Clinical Recommendations

Integrate Histopathology with Molecular Testing: All biopsy and resection specimens showing granulomatous or necrotizing inflammation should undergo reflex molecular testing (e.g., Xpert MTB/RIF or PCR), regardless of Ziehl–Neelsen status.

Adopt Site-Specific Diagnostic Pathways:

- Pulmonary and lymph node TB: Histopathology combined with ZN and Xpert may suffice in most cases.
- CNS, bone/joint, genitourinary, and GI TB: Molecular confirmation should be mandatory given the frequent absence of classic granulomas and low AFB yield.

Baseline Drug-Resistance Testing: All molecular-positive cases should be assessed for rifampicin resistance, and when feasible, subjected to line probe assay (LPA) or culture-based drug susceptibility testing, in alignment with National TB Elimination Program (NTEP) guidelines.

Programmatic Integration: Laboratories should establish standardized reporting templates that incorporate histology, ZN, and molecular results to ensure clear communication with clinicians and facilitate rapid treatment initiation.

Future Strategy: Expansion of next-generation sequencing and AI-assisted histopathology should be prioritized for more precise diagnosis and comprehensive drug-resistance profiling in the coming decade.

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