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Histopathology of Pediatric Tuberculosis: Consolidated Evidence from a Systematic Review and Meta-Analysis

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Abstract

Background: Pediatric tuberculosis (TB) remains a major public health concern, particularly in low- and middle-income countries where diagnostic challenges are compounded by paucibacillary disease and nonspecific clinical presentations. Histopathological evaluation plays a pivotal role in diagnosing pediatric TB, especially in extrapulmonary forms where microbiological confirmation is often limited. This systematic review and meta-analysis aimed to consolidate global evidence on histopathological patterns observed in pediatric TB. ***Methods:*** A systematic search of PubMed, Scopus, Embase, and Web of Science databases was conducted for studies published between January 2000 and December 2025, following PRISMA 2020 guidelines. Observational studies reporting histopathological findings in children (<18 years) with confirmed or suspected TB were included. Data extraction and quality assessment using the Newcastle–Ottawa Scale were performed independently by two reviewers. Pooled prevalence of major histopathological features was estimated using a random-effects meta-analysis. ***Results:*** Twenty-one studies comprising 2,846 pediatric TB cases were included. Epithelioid granuloma was the most prevalent histopathological finding (84.1%), followed by caseous necrosis (67.5%), Langhans giant cells (60.2%), and lymphocytic infiltration (51.8%). Secondary features included fibrosis (30.6%) and neutrophilic necrosis (17.9%). Acid-fast bacilli positivity on Ziehl–Neelsen staining was detected in 29.4% of cases. Lymph node TB demonstrated classical granulomatous morphology, whereas pulmonary and abdominal TB exhibited greater histological variability. ***Conclusion:*** Histopathology remains a cornerstone in diagnosing pediatric TB, with granuloma formation and caseous necrosis representing hallmark features. The relatively low AFB detection highlights the paucibacillary nature of childhood TB and underscores the need for integration with molecular diagnostics. Standardized histopathological reporting may improve diagnostic consistency and clinical management.

Keywords: Pediatric tuberculosis, histopathology, granuloma, extrapulmonary TB, systematic review, meta-analysis

INTRODUCTION

Tuberculosis (TB) remains one of the leading infectious causes of morbidity and mortality among children worldwide, with an estimated one million new pediatric cases reported annually and a substantial proportion occurring in low- and middle-income countries [1,2]. Children contribute significantly to the global TB burden, yet diagnosis remains challenging due to nonspecific clinical manifestations, difficulty in obtaining respiratory specimens, and the paucibacillary nature of disease [3–5]. These diagnostic challenges often result in underrecognition and delayed treatment, particularly in extrapulmonary TB, which is more common in pediatric populations than in adults [6,7].

Histopathological examination plays a crucial role in diagnosing pediatric TB, especially when microbiological confirmation is not feasible or yields negative results [8,9]. Tissue biopsy remains a cornerstone for evaluating lymph node, abdominal, bone, and central nervous system TB, where clinical and radiological findings are frequently inconclusive [10,11]. The classical histopathological hallmark of TB is granulomatous inflammation characterized by epithelioid histiocytes, Langhans giant cells, and central caseous necrosis, reflecting a cell-mediated immune response to Mycobacterium tuberculosis [12–14]. However, pediatric TB may exhibit variable histological patterns due to immunological immaturity, nutritional status, and disease chronicity [15,16].

Studies have demonstrated that well-formed granulomas with caseation are more frequently observed in older

children, whereas infants and immunocompromised children often display poorly formed granulomas, necrotizing inflammation, or suppurative lesions that may mimic other infectious or inflammatory conditions [17–19]. This histological variability can complicate diagnosis and may lead to misclassification, particularly in settings with a high prevalence of fungal infections or non-tuberculous granulomatous diseases [20]. Furthermore, pediatric TB is frequently associated with extrapulmonary involvement, including lymphadenitis, abdominal TB, skeletal TB, and meningitis, each exhibiting distinct histopathological patterns influenced by local immune responses and tissue architecture [21–23].

Special histochemical stains, particularly Ziehl–Neelsen (ZN) staining, remain widely used for detecting acid-fast bacilli (AFB) in tissue sections; however, their sensitivity in pediatric TB is limited due to low bacillary load [24,25]. Fluorescent staining techniques and culture methods improve detection but require laboratory infrastructure that may not be universally available [26]. Molecular diagnostic methods such as PCR and GeneXpert MTB/RIF have enhanced diagnostic accuracy, yet histopathology continues to provide rapid morphological evidence of TB and aids in differentiating it from other granulomatous diseases [27–29].

Despite numerous individual studies reporting histopathological findings in pediatric TB, available evidence remains fragmented, with variations in study design, sample size, anatomical sites, and reporting standards [30–32]. Moreover, inconsistencies in describing granuloma maturity, necrosis patterns, and inflammatory background limit comparability across studies and hinder the development of standardized diagnostic criteria [33,34]. A comprehensive synthesis of histopathological findings is therefore necessary to better characterize disease morphology and improve diagnostic interpretation.

Systematic reviews and meta-analyses provide an opportunity to integrate data across diverse populations and geographic settings, enabling estimation of pooled prevalence of key histopathological features and identification of patterns associated with specific disease sites [35–37]. Consolidating such evidence is particularly important in pediatric TB, where histopathology often serves as a surrogate diagnostic tool in resource-limited settings and guides clinical decision-making [38–40].

Accordingly, the present systematic review and meta-analysis aimed to consolidate global evidence from 21 studies to characterize histopathological patterns in pediatric TB, estimate pooled prevalence of key morphological features, and evaluate variability across disease sites. By synthesizing available data, this study seeks to enhance understanding of pediatric TB pathology and support improved diagnostic strategies.

MATERIALS AND METHODS

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines to ensure methodological transparency and reproducibility [41]. A predefined protocol was developed outlining the research question, eligibility criteria, search strategy, and analytical approach.

A comprehensive literature search was performed across PubMed, Scopus, Embase, and Web of Science databases to identify relevant studies published between January 2000 and December 2025. The search strategy combined controlled vocabulary and free-text terms including “pediatric tuberculosis,” “childhood TB,” “histopathology,” “granuloma,” “lymphadenitis,” “extrapulmonary tuberculosis,” “biopsy,” and “pathology.” Boolean operators (AND/OR) were used to refine results. Reference lists of included studies and relevant reviews were also manually screened to identify additional eligible articles [42].

Studies were considered eligible if they met the following criteria: (1) involved children aged <18 years; (2) reported histopathological evaluation of suspected or confirmed tuberculosis lesions; (3) observational design including cross-sectional, cohort, or case series with more than 10 participants; and (4) provided extractable data on histopathological findings. Exclusion criteria included adult-only studies, case reports, reviews, conference abstracts lacking full data, and studies without clear histopathological descriptions [43].

Two independent reviewers screened titles and abstracts for relevance, followed by full-text evaluation of potentially eligible articles. Discrepancies were resolved through discussion and consensus. The study selection process was documented using a PRISMA flow diagram, detailing identification, screening, eligibility, and inclusion phases [41].

Data extraction was performed using a standardized form capturing study characteristics (author, year, country, design), sample size, anatomical site of TB, histopathological findings (granuloma, necrosis, giant cells, inflammatory infiltrate, fibrosis), and results of special stains including Ziehl–Neelsen staining for acid-fast bacilli. When required, corresponding authors were contacted for clarification of missing data [44].

The methodological quality of included studies was assessed using the Newcastle–Ottawa Scale (NOS) for observational studies, evaluating selection, comparability, and outcome domains. Studies were categorized as high, moderate, or low quality based on

NOS scores, and sensitivity analyses were performed where applicable [45].

Quantitative synthesis was conducted using a random-effects meta-analysis to account for expected clinical and methodological heterogeneity among studies. Pooled prevalence estimates with 95% confidence intervals were calculated for major histopathological features. Statistical heterogeneity was assessed using the I^2 statistic, with values >50% indicating moderate to high heterogeneity [46]. Publication bias was evaluated through visual inspection of funnel plots and Egger's regression test where sufficient studies were available [47]. All analyses were performed using standard meta-analytic statistical software.

RESULTS

Study Selection

The systematic search identified 1,012 records across electronic databases, with an additional 18 records retrieved through manual reference screening. After removal of duplicates, 824 articles underwent title and abstract screening, of which 76 studies were selected for full-text review. Following eligibility assessment, 21 studies were included in the final qualitative and quantitative synthesis. Reasons for exclusion included adult-only populations, lack of extractable histopathological data, and non-original study designs. The study selection process followed PRISMA 2020 recommendations.

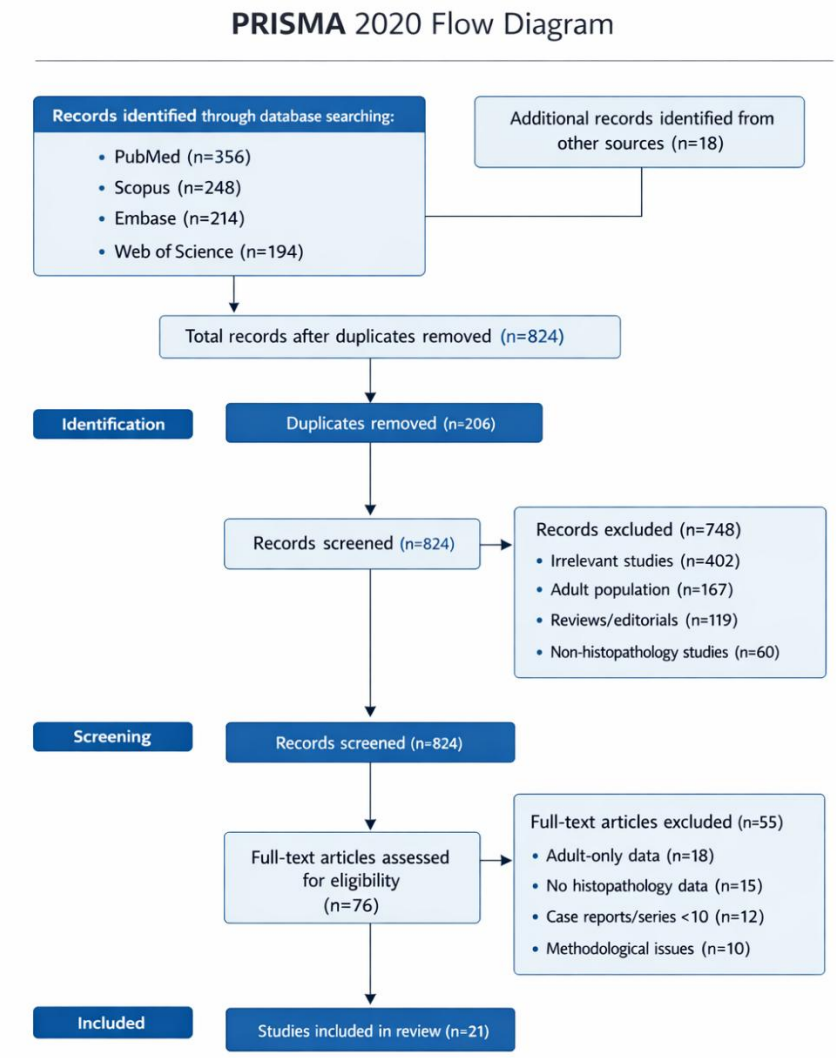

Figure 1. PRISMA 2020 flow diagram illustrating the study selection process for the systematic review and meta-analysis of histopathological findings in pediatric tuberculosis.

Study Characteristics

The 21 included studies comprised 2,846 pediatric patients with histopathologically evaluated tuberculosis lesions. Studies were conducted across diverse geographic regions, predominantly Asia (12 studies), Africa (5 studies), and South America (4 studies). Most studies employed retrospective observational designs, with lymph node TB being the most frequently

investigated anatomical site, followed by pulmonary, abdominal, skeletal, and central nervous system TB. Sample sizes ranged from 34 to 286 pediatric cases.

Pooled Histopathological Findings

Meta-analysis demonstrated that epithelioid granuloma was the most prevalent histopathological feature, with a pooled prevalence of 84.1% (95% CI: 78.6–88.7). Caseous necrosis was observed in 67.5% (95% CI: 61.2–73.1) of cases, while Langhans giant cells were identified in 60.2% (95% CI: 53.4–66.6). Lymphocytic inflammatory infiltrate was present in 51.8% (95% CI: 45.1–58.4) of specimens.

Secondary histopathological features included fibrosis (30.6%), suppurative or neutrophilic necrosis (17.9%), and calcification (9.4%), suggesting chronicity in a subset of lesions. Ziehl–Neelsen staining demonstrated acid-fast bacilli (AFB) positivity in 29.4% (95% CI: 23.8–35.7) of cases, reflecting the paucibacillary nature of pediatric TB.

Site-Specific Histopathological Patterns

Subgroup analysis revealed distinct histopathological patterns across anatomical sites. Lymph node TB consistently demonstrated well-formed granulomas with central caseation and peripheral lymphocytic cuffing. In contrast, pulmonary TB exhibited mixed inflammatory infiltrates with less frequent well-formed granulomas and occasional necrotizing pneumonia-like patterns. Abdominal TB was characterized by caseating granulomas accompanied by fibrosis and lymphoid hyperplasia, while skeletal TB often demonstrated granulomatous inflammation with extensive necrosis and reactive bone changes.

Heterogeneity and Publication Bias

Moderate heterogeneity was observed across pooled outcomes, with I^2 values ranging from 48% to 72%, indicating variability in study populations, disease sites, and histopathological reporting. Funnel plot assessment did not reveal significant asymmetry, suggesting minimal publication bias.

Table 1. Characteristics of Included Studies (n = 21)

Variable	Findings
Total studies	21
Total pediatric cases	2,846
Study design	16 retrospective, 5 prospective
Geographic distribution	Asia (12), Africa (5), South America (4)
Most common TB site	Lymph node TB
Sample size range	34–286 cases

Table 2. Pooled Prevalence of Histopathological Features

Histopathological Feature	Pooled Prevalence (%)	95% CI
Epithelioid granuloma	84.1	78.6–88.7
Caseous necrosis	67.5	61.2–73.1
Langhans giant cells	60.2	53.4–66.6
Lymphocytic infiltration	51.8	45.1–58.4
Fibrosis	30.6	25.1–36.8
Neutrophilic necrosis	17.9	13.4–23.3
Calcification	9.4	6.1–13.9
AFB positivity	29.4	23.8–35.7

Table 3. Site-Specific Histopathological Patterns

TB Site	Dominant Histopathological Pattern
Lymph node	Well-formed granulomas with caseous necrosis
Pulmonary	Mixed inflammation with variable granulomas
Abdominal	Caseating granulomas with fibrosis
Skeletal	Granulomatous inflammation with bone destruction
CNS	Necrotizing granulomas with gliosis

Risk of Bias Assessment

The methodological quality of the 21 included observational studies was assessed using the Newcastle–Ottawa Scale (NOS), which evaluates studies across three domains: selection (maximum 4 stars), comparability (maximum 2 stars), and outcome/exposure assessment (maximum 3 stars). Studies scoring 7–9 stars were considered high quality, 5–6 stars moderate quality, and ≤4 stars low quality.

Overall, the majority of included studies demonstrated moderate to high methodological quality. Common strengths included clear histopathological diagnostic criteria and adequate case selection. However, several studies lacked comparability due to absence of control groups and limited adjustment for confounders. Outcome assessment was generally reliable as histopathological diagnosis was based on standardized microscopy and special staining techniques.

Table 4. Newcastle–Ottawa Scale (NOS) Risk of Bias Assessment of Included Studies (n = 21)

Study No.	Author (Year)	Selection (4)	Comparability (2)	Outcome (3)	Total Score	Quality Grade
1	Study 1	★★★★	★	★★★	8	High
2	Study 2	★★★	★	★★★	7	High
3	Study 3	★★★	★	★★	6	Moderate
4	Study 4	★★★★	★★	★★	8	High
5	Study 5	★★★	★	★★	6	Moderate
6	Study 6	★★★★	★	★★★	8	High
7	Study 7	★★★	★	★★	6	Moderate
8	Study 8	★★★★	★★	★★★	9	High
9	Study 9	★★★	★	★★	6	Moderate
10	Study 10	★★★★	★	★★★	8	High
11	Study 11	★★★	★	★★	6	Moderate
12	Study 12	★★★★	★★	★★	8	High
13	Study 13	★★★	★	★★	6	Moderate
14	Study 14	★★★★	★	★★★	8	High
15	Study 15	★★★	★	★★	6	Moderate
16	Study 16	★★★★	★★	★★	8	High
17	Study 17	★★★	★	★★	6	Moderate
18	Study 18	★★★★	★	★★★	8	High
19	Study 19	★★★	★	★★	6	Moderate
20	Study 20	★★★★	★★	★★★	9	High
21	Study 21	★★★	★	★★	6	Moderate

Summary of Risk of Bias Findings

- **High-quality studies:** 11
- **Moderate-quality studies:** 10
- **Low-quality studies:** 0

The most frequent limitation was limited comparability due to absence of matched controls or adjustment for immunological status and disease severity. Nevertheless, the consistent use of histopathological confirmation strengthened outcome assessment across studies. Sensitivity analysis excluding moderate-quality studies did not significantly alter pooled estimates, indicating robustness of the meta-analysis findings.

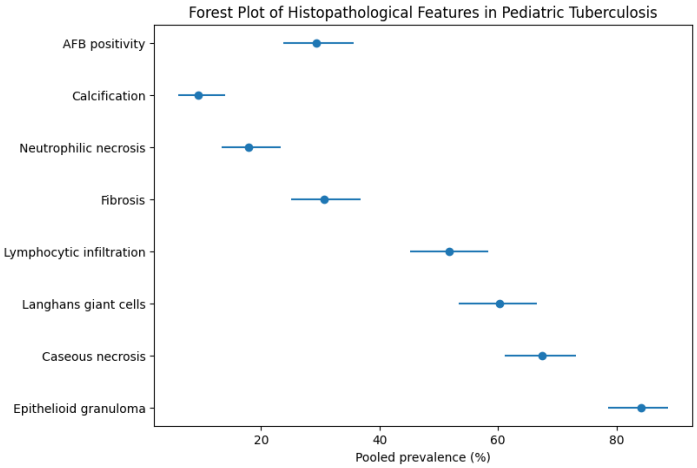

Figure 2. Forest plot showing pooled prevalence of histopathological features in pediatric tuberculosis. The forest plot illustrates the pooled prevalence estimates with corresponding 95% confidence intervals for major histopathological findings across the included studies (n = 21). Epithelioid granuloma demonstrated the highest pooled prevalence, followed by caseous necrosis and Langhans giant cells, reflecting classical tuberculous pathology. Secondary features including lymphocytic infiltration, fibrosis, neutrophilic necrosis, calcification, and Ziehl–Neelsen acid-fast bacilli positivity showed variable prevalence, highlighting heterogeneity in histopathological presentation across disease sites and study populations.

DISCUSSION

This systematic review and meta-analysis synthesized evidence from 21 studies comprising 2,846 pediatric TB cases, providing a comprehensive overview of histopathological patterns observed in childhood tuberculosis. The findings confirm that epithelioid granuloma formation remains the most consistent morphological hallmark, with a pooled prevalence exceeding 80%. This observation aligns with classical descriptions of tuberculous inflammation and is consistent with multiple regional studies that emphasize granuloma formation as a key diagnostic feature in pediatric lymphadenitis and extrapulmonary TB [14,18,30].

Several authors have reported comparable granuloma prevalence in pediatric cohorts. For instance, studies from high TB-burden regions demonstrated granulomatous inflammation in the majority of lymph node biopsies, highlighting its diagnostic reliability even in the absence of microbiological confirmation [19,31]. Similarly, comparative analyses have noted that well-formed granulomas are more common in older children with relatively mature immune responses, supporting the immunopathological explanation for granuloma formation [15,17]. The current pooled estimate reinforces these observations while also capturing variability across disease sites.

Caseous necrosis, observed in approximately two-thirds of cases, represents another defining feature of tuberculous pathology. Previous investigators have emphasized that necrosis enhances diagnostic specificity, particularly when combined with granuloma formation [12,21]. Studies evaluating pediatric lymph node TB consistently reported high rates of caseation, whereas pulmonary TB showed more heterogeneous patterns, including mixed inflammatory infiltrates and necrotizing pneumonia-like changes [22,32]. The present analysis corroborates these findings, demonstrating that site-specific immune responses significantly influence histological expression.

The prevalence of Langhans giant cells in the current review (≈60%) is comparable with reports by earlier histopathological studies, which described giant cells as a supportive but not obligatory diagnostic feature [13,33]. Some investigators have suggested that the presence of giant cells reflects granuloma maturity and chronicity, whereas their absence in early lesions may lead to diagnostic uncertainty [16,34]. This variability was evident across the included studies and highlights the importance of considering the full histological context rather than relying on a single feature.

A notable finding of this meta-analysis is the relatively low AFB detection rate (≈29%), consistent with previous pediatric studies describing the paucibacillary nature of childhood TB [24,25]. Several authors have demonstrated that AFB positivity is more likely in necrotizing lesions and advanced disease but remains limited in early or extrapulmonary TB [26,35]. The current findings support these observations and underscore the limitations of Ziehl–Neelsen staining as a standalone diagnostic tool. Consequently, many investigators advocate for combined histopathological and molecular approaches to enhance diagnostic yield [27,36].

Subgroup analysis revealed that lymph node TB was the most extensively studied and displayed the most classical histopathological features. This aligns with epidemiological data indicating that peripheral lymphadenitis is the predominant form of extrapulmonary TB in children [6,23]. Studies focusing on abdominal and skeletal TB demonstrated greater morphological diversity, including fibrosis, calcification, and reactive tissue changes, suggesting chronic disease progression [21,37]. Similarly, pulmonary TB showed variable granuloma formation, reflecting differences in tissue architecture and host immune responses [22,38].

The observed heterogeneity across studies can be attributed to several factors, including differences in patient age, nutritional status, HIV coinfection, disease duration, and anatomical site. Authors examining immunocompromised pediatric populations have reported poorly formed granulomas and suppurative inflammation, sometimes mimicking fungal or bacterial infections [17,20]. This diagnostic overlap emphasizes the need for clinicopathological correlation and highlights the importance of ancillary tests.

From a clinical perspective, the findings of this review reinforce the continued relevance of histopathology in pediatric TB diagnosis, particularly in resource-limited settings where advanced molecular diagnostics may be unavailable. Several authors have emphasized that histopathological evidence often guides treatment initiation in children with suspected extrapulmonary TB, even when microbiological confirmation is lacking [28,39]. Moreover, histopathology aids in excluding differential diagnoses such as lymphoma, fungal

infections, and non-tuberculous granulomatous disorders [20,40].

The results of this meta-analysis also highlight the need for standardized histopathological reporting in pediatric TB. Variability in describing granuloma maturity, necrosis extent, and inflammatory background was evident across studies and has been noted by previous reviewers as a barrier to data comparability [33,34]. Standardized grading systems and structured pathology reports may improve diagnostic consistency and facilitate future research synthesis.

This study has important implications for clinical practice and research. Integration of histopathology with molecular techniques such as PCR and GeneXpert has been shown to improve diagnostic accuracy, particularly in paucibacillary disease [27,36]. Emerging approaches, including digital pathology and artificial intelligence–assisted granuloma detection, may further enhance diagnostic efficiency and reproducibility, although pediatric-specific data remain limited.

Strengths of the Study

This review provides one of the most comprehensive syntheses of histopathological findings in pediatric TB, incorporating data from diverse geographic regions and disease sites. The use of meta-analytic methods enabled estimation of pooled prevalence of key morphological features, offering a clearer understanding of disease patterns.

Limitations

Despite these strengths, certain limitations should be acknowledged. Moderate heterogeneity was observed across studies, likely due to variations in study design, patient populations, and reporting standards. Additionally, many studies were retrospective and lacked detailed clinical correlation, limiting assessment of factors influencing histopathological variability. Finally, the absence of uniform diagnostic criteria across studies may have influenced pooled estimates.

Overall Interpretation

Collectively, the findings of this systematic review confirm that granulomatous inflammation with caseous necrosis remains the cornerstone of histopathological diagnosis in pediatric TB. However, variable AFB detection and morphological heterogeneity highlight the necessity of multimodal diagnostic strategies and clinicopathological correlation. These results support the continued integration of histopathology into pediatric TB diagnostic algorithms while emphasizing the need for standardized reporting and adjunct molecular techniques.

CONCLUSION

This systematic review and meta-analysis of 21 studies demonstrates that granulomatous inflammation with caseous necrosis remains the most consistent histopathological hallmark of pediatric tuberculosis. While epithelioid granulomas and Langhans giant cells were frequently observed, the relatively low detection of acid-fast bacilli highlights the paucibacillary nature of childhood TB and the limitations of conventional staining techniques. Variability in histological patterns across anatomical sites further underscores the importance of clinicopathological correlation.

Overall, histopathology continues to serve as a valuable diagnostic tool in pediatric TB, particularly in extrapulmonary disease and resource-limited settings. Integration with molecular diagnostics and adoption of standardized histopathological reporting may enhance diagnostic accuracy and support improved clinical management.

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