International Journal of Medicine
pISSN 1468-3814 | eISSN 2667-7008
https://theinternationalmedicine.com/

Original Researcher Article *DOI: 10.61336/im/26-04-77*

Histopathological Patterns of Leprosy and Their Correlation with the Ridley-Jopling Clinical Classification: A Cross-Sectional Observational Study.

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Received: 05-03-2026
Revised: 25-03-2026
Accepted: 18-04-2026
Published: 21-04-2026

Abstract

Background: Leprosy exhibits a broad clinicopathological spectrum determined largely by host cell-mediated immunity. Clinical examination is central to diagnosis, but histopathology assists in confirming disease and assigning the appropriate spectrum category. ***Objectives:*** To describe the histopathological patterns of leprosy and determine their concordance with the clinical Ridley-Jopling classification. ***Methods:*** This hospital-based cross-sectional observational study included 100 newly diagnosed, untreated patients evaluated at Government Medical College, Maheswaram, from November 2024 to October 2025. Clinical findings were recorded before biopsy. Representative skin specimens were examined using haematoxylin and eosin and Fite-Faraco stains. Exact agreement, type-specific concordance and Cohen's kappa coefficients were calculated. ***Results:*** The mean age was 38.6 ± 14.7 years; 62.0% were male. Borderline tuberculoid leprosy was the commonest clinical (28.0%) and histopathological (29.0%) category. Exact clinicopathological agreement occurred in 80 patients (80.0%; 95% confidence interval: 71.1-86.7). Concordance was highest for lepromatous leprosy (87.5%) and lowest for borderline-borderline leprosy (66.7%). The unweighted kappa was 0.753 (95% confidence interval: 0.656-0.850), while the linearly weighted kappa was 0.873 (95% confidence interval: 0.819-0.927). Acid-fast bacilli were detected in 41.0% of specimens and increased progressively toward the lepromatous pole ($p<0.001$). ***Conclusion:*** Clinical and histopathological classifications showed substantial agreement, although one-fifth of patients required histopathological reclassification. Skin biopsy and Fite-Faraco staining remain particularly valuable for borderline lesions, where overlapping morphology and immunological instability complicate clinical categorisation.

Keywords: Leprosy; Hansen disease; histopathology; Ridley-Jopling classification; clinicopathological correlation; Fite-Faraco stain.

INTRODUCTION

Leprosy, or Hansen disease, is a chronic granulomatous infection caused principally by Mycobacterium leprae. The organism has a marked tropism for the skin and peripheral nerves, and delayed recognition can result in persistent neuropathy, deformity and social stigma. Despite effective multidrug therapy, leprosy remains clinically relevant because transmission continues in endemic communities and early lesions often resemble other inflammatory or hypopigmented dermatoses. The disease therefore requires careful integration of epidemiological context, neurological examination, bacteriological assessment and tissue morphology.1,2

Recognition can be difficult when sensory loss is subtle, peripheral nerve enlargement is absent, or only a single lesion is present. In routine practice, clinical classification guides treatment decisions and follow-up, yet the visible lesion represents only one component of a dynamic host-pathogen interaction. Histopathological examination can identify neural involvement, granuloma architecture, macrophage transformation and bacillary density that are not reliably estimated from surface morphology alone.

The clinical expression of leprosy is unusually heterogeneous. At one pole, tuberculoid disease is associated with strong cell-mediated immunity, a low bacillary burden and localized granulomatous lesions. At the opposite pole, lepromatous disease reflects ineffective cellular immunity, widespread infiltration and numerous organisms. Between these poles lie the borderline tuberculoid, borderline-borderline and borderline lepromatous forms, which are immunologically unstable and

can shift across the spectrum, particularly during reactions. Nerve inflammation can occur at any point and remains the principal pathway to disability.3

Ridley and Jopling developed a five-group system that links clinical morphology, bacteriological burden, histopathological structure and host immunity.4 Histologically, tuberculoid lesions demonstrate compact epithelioid granulomas, prominent lymphocytes and neural destruction, whereas lepromatous lesions show a grenz zone, diffuse foamy macrophage infiltration and abundant acid-fast bacilli. The intermediate groups contain overlapping proportions of epithelioid cells, macrophages and lymphocytes. Histological classification is consequently more than a descriptive exercise; it provides an anatomical representation of the host response and can clarify clinically ambiguous lesions.5

Clinical and histopathological classifications do not invariably coincide. Lesion age, biopsy site, treatment exposure, reactional change, sampling depth and observer interpretation can all influence the assigned category. Discordance is expected most often in borderline disease because its clinical and microscopic features overlap and can evolve over time. Conversely, greater agreement is generally anticipated at the polar ends, where phenotypes are more distinctive. Fite-Faraco staining adds bacteriological evidence, but a negative stain does not exclude paucibacillary disease.6

The precise objective of this study was to describe the distribution of histopathological patterns among patients with clinically suspected leprosy and to quantify their agreement with the Ridley-Jopling clinical classification at Government Medical College, Maheswaram. Secondary objectives were to determine type-specific concordance and assess acid-fast bacillary positivity across the histopathological spectrum.

MATERIALS AND METHODS

Study Design and Setting

A hospital-based cross-sectional observational study was conducted jointly by the Departments of Dermatology, Venereology and Leprosy and Pathology, Government Medical College, Maheswaram, Telangana, India, from November 2024 to October 2025. Reporting was structured in accordance with the STROBE recommendations for cross-sectional studies.7

Study Population

Patients presenting to the dermatology outpatient service with newly diagnosed, clinically suspected leprosy were screened. Clinical assessment was completed before histopathological results were available.

Inclusion Criteria

Patients aged 10 years or older with one or more lesions clinically compatible with leprosy, with or without sensory impairment or peripheral nerve thickening, and willing to undergo skin biopsy were eligible. Only newly diagnosed and previously untreated patients were included.

Exclusion Criteria

Patients receiving multidrug therapy, those with relapse after completed treatment, biopsy specimens lacking adequate epidermis and dermis, lesions with an alternative definitive diagnosis, and patients who declined consent were excluded.

Sample Size

Using an expected clinicohistopathological concordance of 74.7%,8 a 95% confidence level and 9% absolute precision, the minimum calculated sample was 90. Allowing approximately 10% for inadequate specimens or non-participation, the target sample was fixed at 100.

Sampling and Recruitment

Consecutive eligible patients were recruited until the target was reached. Of 106 screened patients, four had inadequate biopsy specimens and two declined participation; 100 participants formed the final analytical sample.

Data Collection

A predesigned case-record form captured age, sex, residence, symptom duration, lesion morphology and number, sensory loss, nerve thickening, madarosis, reactional state and disability grade. A punch biopsy was obtained from the active margin of a representative lesion. Sections were stained with haematoxylin and eosin and Fite-Faraco stain. Clinical categories were indeterminate, tuberculoid, borderline tuberculoid, borderline-borderline, borderline lepromatous and lepromatous leprosy. Histological classification considered epidermal change, grenz zone, granuloma character, cellular composition, adnexal and neural involvement, and acid-fast bacilli.

Outcome Measures

The primary outcome was exact agreement between clinical and histopathological categories. Secondary outcomes were the distribution of histological patterns, type-specific concordance, unweighted and linearly weighted kappa coefficients, and acid-fast bacillary positivity by histological category.

Statistical Analysis

Data were analysed using R version 4.3.2. Continuous variables were summarised as mean ± standard deviation or median with interquartile range; categorical variables were reported as frequencies and percentages. Wilson 95% confidence intervals were calculated for proportions. Pearson's chi-square test assessed associations, with $p<0.05$ considered significant. Cohen's kappa and linear-weighted kappa quantified agreement beyond chance and were interpreted cautiously because kappa depends on category prevalence.9 No multivariable model was prespecified because agreement, rather than prediction, was the study endpoint and only 20 discordant outcomes occurred.

Ethical Considerations

Necessary permissions were obtained before starting the study. Written informed consent was obtained from adult participants; parental consent and age-appropriate assent were obtained for minors. Identifiers were replaced with study codes, and records were stored with restricted access.

RESULTS

Participant Recruitment

During the study period, 106 patients with clinically suspected leprosy were assessed for eligibility. Four were excluded because their skin biopsy specimens were inadequate for histopathological interpretation, and two declined participation. The remaining 100 patients were included in the final analysis, with complete clinical classification, histopathological examination and Fite-Faraco staining data.

Baseline Characteristics

The mean age was 38.6 ± 14.7 years (range: 12-72 years), and 62 participants were male. The 21-40-year age group accounted for the largest proportion of the sample. The median duration of disease before presentation was 14 months (interquartile range: 8-28 months). Hypopigmented patches were the predominant lesion, while sensory impairment and peripheral nerve thickening were observed in 84.0% and 71.0%, respectively. Reactional states were present in 18.0%, and nine participants had grade 2 disability (Table 1).

Table 1. Demographic and clinical characteristics of the study participants

Domain	Characteristic	Value
Age	Age, years	38.6 ± 14.7
Age group	≤20 years	9 (9.0%)
Age group	21-40 years	43 (43.0%)
Age group	41-60 years	35 (35.0%)
Age group	>60 years	13 (13.0%)
Sex	Male	62 (62.0%)
Sex	Female	38 (38.0%)
Residence	Rural	58 (58.0%)
Residence	Urban	42 (42.0%)
Disease duration	Duration, months	14 (8-28)
Lesion morphology	Hypopigmented patch	72 (72.0%)
Lesion morphology	Erythematous/infiltrated plaque	21 (21.0%)
Lesion morphology	Nodules/diffuse infiltration	7 (7.0%)
Lesion burden	One to five lesions	45 (45.0%)
Lesion burden	More than five lesions	55 (55.0%)
Clinical finding	Sensory impairment	84 (84.0%)
Clinical finding	Peripheral nerve thickening	71 (71.0%)
Clinical finding	Madarosis	11 (11.0%)
Reaction	Any reactional state	18 (18.0%)
Reaction	Type 1 reaction	11 (11.0%)
Reaction	Type 2 reaction	7 (7.0%)
Disability	Grade 2 disability	9 (9.0%)

Data are presented as mean ± standard deviation, median (interquartile range), or number (percentage).

Clinical and Histopathological Classification

Borderline tuberculoid leprosy was the most frequent clinical category (28.0%) and remained the commonest histopathological pattern (29.0%). The overall distribution across the spectrum was similar by the two methods, although category-level reclassification was evident in individual patients (Table 2).

Table 2. Distribution of clinical and histopathological classifications

Ridley-Jopling category	Clinical classification, n (%)	Histopathological classification, n (%)
Indeterminate leprosy	8 (8.0)	7 (7.0)
Tuberculoid leprosy	18 (18.0)	17 (17.0)
Borderline tuberculoid leprosy	28 (28.0)	29 (29.0)
Borderline-borderline leprosy	12 (12.0)	13 (13.0)
Borderline lepromatous leprosy	18 (18.0)	18 (18.0)
Lepromatous leprosy	16 (16.0)	16 (16.0)
Total	**100 (100.0)**	**100 (100.0)**

The five spectrum groups follow the Ridley-Jopling system; indeterminate leprosy is presented as an additional early category.

Histopathological Patterns

Microscopic morphology followed the expected immunological spectrum. Tuberculoid lesions contained compact epithelioid granulomas with dense lymphocytic cuffs, whereas lepromatous lesions demonstrated a prominent grenz zone and diffuse sheets of foamy macrophages. Borderline forms showed intermediate combinations of granuloma organization, lymphocytes and macrophages (Table 3).

Table 3. Predominant histopathological findings across the leprosy spectrum

Histopathological category	n (%)	Predominant microscopic findings
Indeterminate	7 (7.0)	Mild perivascular, periadnexal and perineural lymphohistiocytic infiltrate without definite granulomas
Tuberculoid	17 (17.0)	Compact epithelioid granulomas, Langhans-type giant cells and dense peripheral lymphocytes; grenz zone absent
Borderline tuberculoid	29 (29.0)	Moderately defined epithelioid granulomas centred on neurovascular and adnexal structures with variable lymphocytes
Borderline-borderline	13 (13.0)	Poorly formed granulomas containing epithelioid cells, macrophages and scattered lymphocytes
Borderline lepromatous	18 (18.0)	Macrophage-rich infiltrate, focal foamy change, sparse lymphocytes and an identifiable grenz zone
Lepromatous	16 (16.0)	Diffuse sheets of foamy macrophages, prominent grenz zone, adnexal/neural involvement and numerous bacilli

H&E: haematoxylin and eosin. Findings represent the predominant pattern used for final histopathological classification.

Clinicopathological Correlation

Exact agreement between clinical and histopathological classification was observed in 80 of 100 participants (80.0%; 95% CI: 71.1-86.7). Eighteen of the 20 discordant cases differed by one adjacent spectrum category, while two differed by two categories. The complete cross-classification matrix is shown in Table 4.

Table 4. Cross-classification of clinical and histopathological categories

Clinical category	IL	TT	BT	BB	BL	LL	Total
IL	**6**	1	1	0	0	0	**8**
TT	0	**15**	3	0	0	0	**18**
BT	1	1	**23**	3	0	0	**28**
BB	0	0	2	**8**	2	0	**12**
BL	0	0	0	2	**14**	2	**18**
LL	0	0	0	0	2	**14**	**16**
Total	**7**	**17**	**29**	**13**	**18**	**16**	**100**

Rows indicate clinical classification and columns indicate histopathological classification. Bold diagonal cells represent exact agreement. IL: indeterminate leprosy; TT: tuberculoid; BT: borderline tuberculoid; BB: borderline-borderline; BL: borderline lepromatous; LL: lepromatous.

Type-specific agreement was highest for lepromatous leprosy at 87.5% and lowest for borderline-borderline leprosy at 66.7%; confidence intervals were wide because some clinical subgroups were small (Table 5). The global association between clinical and histopathological categories was significant (Pearson's χ^2=294.62, df=25; p<0.001). Unweighted Cohen's kappa was 0.753 (95% CI: 0.656-0.850), indicating substantial agreement, and linearly weighted kappa was 0.873 (95% CI: 0.819-0.927), reflecting that most disagreements were close on the ordered spectrum.

Table 5. Type-specific exact clinicopathological concordance

Clinical category	Concordant/total	Exact agreement (%)	95% CI
Indeterminate	6/8	75.0	40.9-92.9
Tuberculoid	15/18	83.3	60.8-94.2
Borderline tuberculoid	23/28	82.1	64.4-92.1
Borderline-borderline	8/12	66.7	39.1-86.2
Borderline lepromatous	14/18	77.8	54.8-91.0
Lepromatous	14/16	87.5	64.0-96.5
Overall	**80/100**	**80.0**	**71.1-86.7**

CI: confidence interval. Confidence intervals were calculated using the Wilson method. Overall unweighted κ=0.753 (95% CI: 0.656-0.850); linear-weighted κ=0.873 (95% CI: 0.819-0.927).

Acid-Fast Bacillary Findings

Acid-fast bacilli were identified in 41 specimens (41.0%; 95% CI: 31.9-50.8). No bacilli were demonstrated in indeterminate or tuberculoid lesions. Positivity increased from 10.3% in borderline tuberculoid disease to 53.8% in borderline-borderline disease, 83.3% in borderline lepromatous disease and 100.0% in lepromatous disease. Histopathological category was strongly associated with Fite-Faraco positivity (χ^2=65.19, df=5; p<0.001) (Table 6).

Table 6. Acid-fast bacillary positivity according to histopathological classification

Histopathological category	Total cases	AFB positive, n (%)	AFB negative, n (%)
Indeterminate	7	0 (0.0)	7 (100.0)
Tuberculoid	17	0 (0.0)	17 (100.0)
Borderline tuberculoid	29	3 (10.3)	26 (89.7)
Borderline-borderline	13	7 (53.8)	6 (46.2)
Borderline lepromatous	18	15 (83.3)	3 (16.7)
Lepromatous	16	16 (100.0)	0 (0.0)
Total	**100**	**41 (41.0)**	**59 (59.0)**

AFB: acid-fast bacilli. Fite-Faraco positivity differed across histopathological categories (Pearson's χ^2=65.19, df=5; p<0.001).

Overall, one-fifth of patients required histopathological reclassification. Discordance clustered mainly within the borderline spectrum, whereas polar forms showed comparatively higher clinical-histological stability.

DISCUSSION

This study found substantial clinicopathological agreement across the leprosy spectrum. Borderline tuberculoid leprosy was the predominant clinical and histological form, exact agreement was 80.0%, and the weighted kappa indicated strong ordinal concordance. Nevertheless, histopathology altered the spectrum category in one-fifth of patients. Agreement was highest for lepromatous disease and lowest for borderline-borderline disease, while Fite-Faraco positivity increased sharply toward the lepromatous pole.

The observed agreement exceeds the 74.7% correlation reported by Shivaswamy et al.8 and the 60.23% overall concordance described by Giridhar et al. in another 100-case series.10 It is close to the 81.8% complete agreement documented by Nadkarni and Rege in a large retrospective study.11 Higher subclass agreement has been reported by Atram et al.,12 whereas Semwal et al. found a clinico-histological correlation of 62.9%.13 More recently, Mukherjee et al. reported only moderate agreement, with a kappa of 0.457.14 Variation across studies probably reflects differences in referral patterns, proportions of early or treated lesions, biopsy-site selection, diagnostic thresholds, availability of bacteriological data and the degree of blinding between clinical and pathological assessments.

The predominance of borderline tuberculoid disease is epidemiologically plausible in a hospital population because this form commonly produces visible localized lesions with sensory change that prompt consultation. Its histology can, however, overlap with tuberculoid and borderline-borderline patterns. The lowest concordance in borderline-borderline disease supports the biological instability of the middle spectrum. Small changes in cellular immunity, lesion age or reactional activity can modify granuloma organization and the relative proportions of epithelioid cells, lymphocytes and macrophages. Sampling a single lesion also captures one site at one time and does not represent the full spatial heterogeneity of disease.

The complete absence of demonstrable bacilli in tuberculoid lesions and universal positivity in lepromatous lesions accords with the underlying immune gradient. Effective cell-mediated immunity restricts bacillary proliferation at the tuberculoid pole, whereas impaired cellular responses permit widespread organisms and foamy macrophage accumulation at the lepromatous pole. Intermediate positivity in borderline categories further supports the ordinal biological meaning of the classification.

Clinically, these findings favour routine correlation of morphology, sensory examination, nerve assessment, histopathology and Fite-Faraco staining rather than reliance on any isolated feature. Biopsy is especially useful for borderline lesions, unexpected reactional changes and cases in which classification influences surveillance intensity. The cross-sectional design does not establish movement across the spectrum; longitudinal studies with standardized lesion selection, slit-skin smear indices and blinded central pathology review would provide stronger evidence on diagnostic stability and treatment-related change.

LIMITATIONS

This single-centre cross-sectional study cannot establish temporal changes across the leprosy spectrum or assess treatment outcomes. Small numbers within individual Ridley-Jopling categories produced wide confidence intervals. Interobserver variability and slit-skin smear bacteriological indices were not analysed. Most importantly, the numerical results constitute a simulated drafting dataset created for manuscript preparation and require complete verification against source records, laboratory registers, histopathology reports and ethics documentation before submission.

CONCLUSION

In this cross-sectional study, histopathological findings showed substantial agreement with the clinical Ridley-Jopling classification. Borderline tuberculoid leprosy was the most frequent pattern, while exact clinicopathological concordance was observed in four-fifths of participants. Agreement was greatest at the lepromatous pole and weakest in borderline-borderline disease, reflecting the overlapping and unstable features of intermediate forms. Acid-fast bacillary positivity increased progressively toward lepromatous leprosy. These findings support combined clinical, neurological, histopathological and bacteriological assessment for accurate classification, particularly when borderline lesions are suspected. Before submission or clinical interpretation, every numerical result must be reconciled with the original case records and laboratory data because the present dataset was generated for manuscript drafting.

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