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A Study of Clinico-histopathological Correlation in Patients of Hansen's Disease

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Abstract

Background: Hansen's disease (Leprosy), caused by Mycobacterium leprae, is a chronic granulomatous condition with varied clinical presentations reflecting the host's immune response. Clinical and histological classifications may differ, leading to diagnostic errors. Histopathology offers definitive information on granulomas, bacillary load, and tissue changes. Thus, CLINICO-HISTOPATHOLOGICAL correlation is crucial for accurate diagnosis and appropriate treatment.

Objectives: To study the clinic-histopathological comparison in patients with Hansen's disease and evaluate the concordance between clinical and histopathological findings.

Materials and Methods: This retrospective observational study analyzed records of patients with Hansen's disease who underwent skin biopsy at a tertiary care center in Nepal during a two-year study period. Cases with complete clinical and histopathological data were included. Clinical and histopathological classifications were performed according to the Ridley-Jopling spectrum. H&E staining, Fite-Faraco stain for bacilli was done. Clinico-histopathological correlation was assessed by comparing clinical and histopathological diagnoses. Data were analyzed using SPSS, with categorical variables expressed as frequencies, percentages and means. Clinicopathological correlation between clinical and histopathological classification of leprosy was assessed using Cohen's kappa statistic.

Results: A total of 150 patients aged 11-85 years were included, with a mean age of 43.75 ± 15.89 years and male predominance. Clinically, lepromatous leprosy was most common, while histopathology most often showed tuberculoid leprosy. The overall agreement was moderate ($\kappa = 0.48$) and was statistically significant ($p < 0.001$). The observed agreement between the two methods was 57.3%.The agreement of tuberculoid leprosy was 76.66% and lepromatous leprosy 75.75%, while it was moderate in borderline tuberculoid (54.83%); and low in borderline (30%) and borderline lepromatous (33.33%). Substantial reclassification occurred particularly within the borderline spectrum, with BB being clinically overestimated and IL being underestimated.

Conclusion : A combined clinic-histopathological approach is essential for accurate classification, especially in borderline cases. While clinical features provide an initial impression, histopathology remains the gold standard for confirmation. A combined approach enhances diagnostic precision, ensures appropriate therapy, and contributes to better patient outcomes.

Key words: Biopsy, Histological Techniques, Leprosy, Skin Diseases

Introduction

Hansen's disease is a chronic granulomatous infectious disease caused by Mycobacterium leprae. The disease mainly affects skin, the peripheral nervous system and certain other tissues such as the

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reticulo-endothelial system, bones and joints, mucous membranes, eyes, testes, muscles, adrenals, etc.[1] Depending on the degree of immunity, clinical and histopathological features of various types of leprosy may develop gradually.[2] Its clinical manifestations are remarkably diverse, ranging from localized hypopigmented patches with minimal sensory loss to widespread nodular lesions and severe deformities. This spectrum of presentations reflects the complex host–parasite interactions and the underlying immunological status of the affected individual.[3,4]

In Nepal, though Leprosy has been on decline, with the government declaring elimination of leprosy, after achieving a prevalence rate of 0.89 per 10,000 persons, the disease is still prevalent.[1,5] While several studies have examined this correlation, data from the eastern region of Nepal are limited. This study aims to evaluate clinic-histopathological concordance in leprosy cases at our tertiary center to assess local diagnostic accuracy and challenges.

Materials and Methods

This retrospective observational study reviewed records of patients with Hansen's disease who underwent skin biopsy at a tertiary care center in Nepal during February 2022 and March 2024. Patients with complete clinical and histopathological data were included. Inclusion criteria included patients of all ages with a clinical diagnosis of leprosy across the Ridley-Jopling spectru, new, untreated cases and availability of a diagnostic skin biopsy. Exclusion criteria included patients on anti-leprosy treatment before biopsy, inadequate biopsy material and cases where clinical data were incomplete

Sample size was calculated using the Kappa (κ) statistic to assess agreement between clinical and histopathological diagnoses of Hansen's disease. Based on a study by Mathur et al., ~80% clinicopathological correlation (κ ≈ 0.8) at an expected κ of 0.70, null κ of 0.40, 95% confidence level, and 80% power, the minimum required sample size was 125 patients (Donner and Eliasziw method). Allowing for 20% attrition, a total of 150 patients were included. A convenience sample of all new, untreated cases meeting the inclusion criteria was included. Clinical classification was done according to the Ridley–Jopling spectrum. Histopathological examination was performed using H&E staining and Fite–Faraco stain for bacilli, where available and classified by pathologists of the same center. Agreement between clinical and histopathological diagnosis was evaluated using Cohen's kappa statistic. A p-value <0.05 was considered statistically significant. Data were analyzed using SPSS version 27. Categorical variables were expressed as frequencies, percentages and means. Ethical approval was obtained from the Institutional Review Committee.

Results

One hundred and fifty new cases of leprosy were included in this study. Out of that, 96(64%) of cases were male and 54(36%) were female. There was a significant male preponderance, with a male-to-female ratio of 1.7:1.

The age distribution ranged from 11 to 85 years. Mean age was 43.75±15.89. The most common age group involved was 21-30 years, followed by 41-50 years. The most common clinical type of leprosy was Lepromatous Leprosy (LL) (22%), followed by borderline tuberculoid (BT) (20.7%) and tuberculoid (TT) (20.0%). Indeterminate leprosy (IL) constituted 2% of cases, followed by histoid leprosy (HL), which comprised 1.3% of total cases. LL was the most common clinical diagnosis amongst males, followed by BT. TT was the most common clinical diagnosis amongst females, followed by BB. (Table 1) (Figure1-4)

Table 1: Clinical case distribution according to age

Age (years)	TT	BT	BB	BL	LL	HL	IL
11-20	0	1	0	0	0	0	0
21-30	8	8	2	7	8	0	3
31-40	4	4	1	5	12	1	5
41-50	8	11	3	4	6	0	1
51-60	9	3	4	4	3	0	0
61-70	6	2	2	2	2	2	0
71-80	2	1	1	0	2	1	1
81-90	0	0	0	0	1	0	0

The most common histopathological case was TT type (24.7%), followed by LL type (22.7%). BT, BL and BB constituted 20%, 14.7% and 8.7%, respectively. IL comprised of 6.7%, whereas HL comprised of 2.7 %. Out of 150 cases, only 86 cases (57.33%) showed clinical and histopathological correlation. Correlation was seen in 23 out of 30 patients (76.66%) in TT cases, 17 out of 31 cases (54.83%) in BT, 9 out of 30 cases (30%) in BB, 7 out of 21 cases (33.33%) in BL and 25 out of 33(75.5%) in LL. Two out of 2 in histoid and 3 out of 3 IL cases showed correlation. (Table 2) (Figure 5-6)

Table 2: Clinico-histopathological correlation of leprosy

Clinical types	Clinical diagnosis (n)	Histopathological diagnosis (n)							Agreement (%)	Kappa measurement of agreement	p-value
		TT	BT	BB	BL	LL	HL	IL			
TT	30	23	4	1	1	0	0	1	76.66	0.48	0.001
BT	31	9	17	1	1	1	0	2	54.83		
BB	30	1	8	9	6	1	2	3	30		
BL	21	4	0	2	7	7	0	1	33.33		
LL	33	0	1	0	7	25	0	0	75.5		
HL	2	0	0	0	0	0	2	0	100		
IL	3	0	0	0	0	0	0	3	100		
Total	**150**	**37**	**30**	**13**	**22**	**34**	**4**	**10**			

Fite-Faraco staining was positive in 59 cases (39.3%) out of 150 histopathologically confirmed cases. (Figure 7) Positivity of Fite- Faraco and Slit skin smear increased progressively towards the lepromatous pole, with maximum positivity observed in lepromatous leprosy.(Table 3)

Table 3: Showing the association between histopathological diagnosis and Fite-Faraco stain

Clinical type	Clinically diagnosed(n)	HPE confirmed(n)	Fite -Faraco Positivity(n)	Slit Skin Smear(n)
TT	30	37	0	0
BT	31	30	2	0
BB	30	13	9	1
BL	21	22	15	10
LL	33	34	30	21
HL	2	4	3	3
IL	3	10	0	0
Total	**150**	**150**	**59**	**35**

Diagnostic shifts were observed between clinical and histopathological classification. BB, initially accounting for 20% of provisional diagnosis, decreased to 8.7% after biopsy, indicating frequent clinical overestimation. In contrast, IL increased from 2% clinically to 6.7% on histopathology, demonstrating that early or indeterminate lesions were commonly missed on clinical evaluation. BT, BL, and LL showed relatively good correlation between clinical and histopathological findings, with only minor variations in frequency. TT cases demonstrated a slight reduction from 20% to 18%, and HL cases increased from 1.3%to 2.7% on histopathological confirmation. The comparison of provisional and histopathological diagnoses demonstrates that while borderline tuberculoid, borderline lepromatous, and lepromatous forms show good clinico- histopathological correlation, substantial discrepancies exist in the diagnosis of BB and IL forms. BB was clinically overdiagnosed (20% vs 8.7%), whereas IL was underdiagnosed (2% vs 6.7%).

Figure 1: Single hypopigmented patch seen in tuberculoid leprosy.

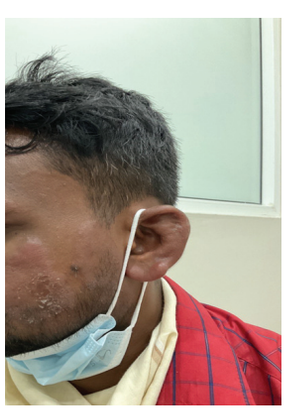

Figure 2: Infiltrated plaques over cheek and infiltrated nodules over ear in lepromatous leprosy.

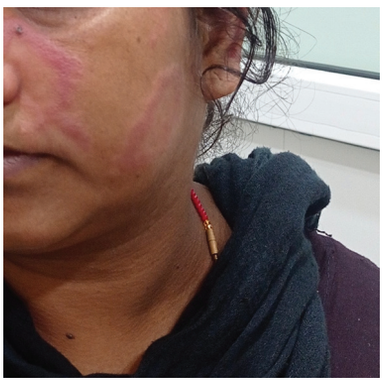

Figure 3: Annular plaque seen in borderline leprosy.

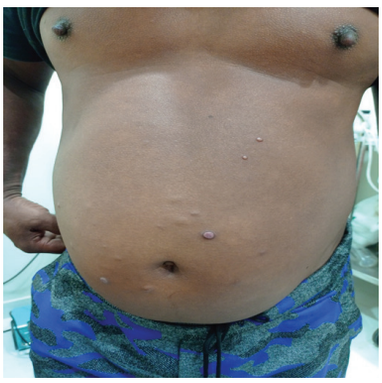

Figure 4: Histoid leprosy showing succulent papules and nodules.

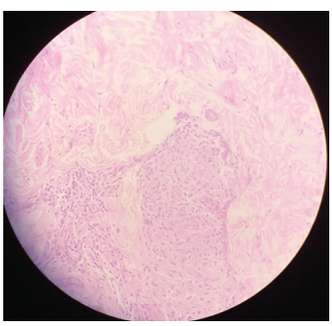

Figure 5: Borderline lepromatous leprosy showing mixed inflammatory infiltrates, predominantly lymphocytes and a few ill-defined epitheloid cells. Perivascular lymphocytes infiltrate and perineural fibrosis is noted. Underlying stroma consists of skin appendages with numerous foamy macrophages and multinucleated giant cells. (H&E, 40X)

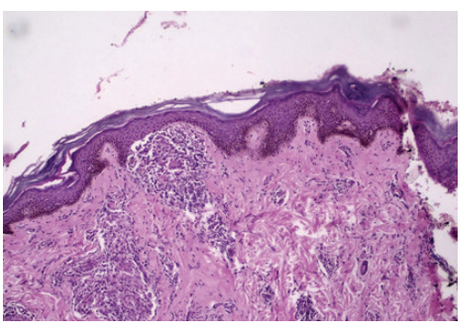

Figure 6: Histopathological section of Borderline Tuberculoid (BT) leprosy. Beginning of the Grenz zone seen(A). Well-formed epithelioid granuloma demonstrating a central core of histiocytes. Langhans-type multinucleated giant cell with peripherally arranged nuclei (B). Lymphocytic mantle surrounding the granulomatous core. (H&E, x100)

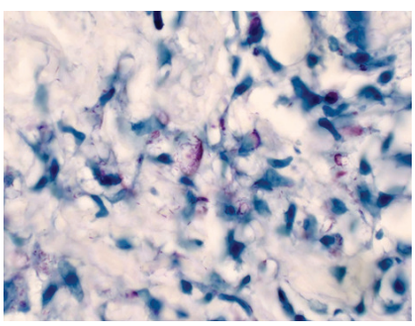

Figure 7: Showing clumps of lepra bacilli (arrow) in Fite-Faraco stain.

Discussion

Hansen disease remains endemic across South-East Asia, including Nepal, and presents with a broad clinical spectrum, from small hypopigmented patches with little sensory change to diffuse nodular disease with marked deformities. Histopathological appearances likewise vary with host immunity, ranging from compact granulomas to diffuse dermal infiltration, so individual cases frequently differ both clinically and microscopically. Male preponderance was seen in our study with 64% (96/150) of cases affecting male and 36% (54/150) female. Similar male preponderance was seen in studies done by Mathur et al, Thapa et al, Tiwari et al., Gupta et al., and Rad F et al.[1, 5–8] This male preponderance may be due to greater occupational and outdoor exposure, increasing contact with Mycobacterium leprae. Additionally, health-seeking behavior differs by gender; males tend to present more frequently to healthcare facilities, whereas females may experience delayed reporting due to social, cultural or economic barriers.

The mean ages of the cases in our study were 43.75±15.893. In a study done by Thapa et al., the mean age was 37.85±2.021, while in a study by Tiwari et al, Soni et al, and Shrestha et al mean age was 32.64, 32.66 and 38.14±16.35, respectively.[5,6,9,10] In our study, the youngest age of a leprosy patient was 11 years and the oldest was 85 years. In a study by Mathur et al, the minimum age was 8 years and the maximum age was 86 years. Likewise, in a study by Thapa et al, the youngest age with leprosy was 12 years and the oldest was 80 years, which was almost similar to our study.[1,5]

The most common age group involved in our study was 21-30 years. According to Mathur et al, Manandhar et al, Moorthy et al, Soni et al and Giridhar et al, the common age group affected in leprosy was 20-30 years.[1,9,11–13] Whereas in a study by Ramesh et al, the 30 - 50 years of age group was affected the most.14 In our study, the most common clinical type of leprosy was LL (22%), followed by BT (20.7%) and TT (20%). IL and HL constituted 2% and 1.3% of cases, respectively.

Table 5: Showing common clinical type and histological type of various authors

Author	Common clinical type	Common histological type
Mathur et al. 1	TT>BT>LL	TT>BT>BL>LL
Thapa et al.5	unspecified type>BT>TT>	TT>BT>IL>LL>BL
Manandhar U. et al. 11	TT>BT>LL>	BT>BL>TT>LL>BB>IL
Shrestha A et al. 10	TT>BT>LL	TT>IL>LL>BT>BB>HL>BL
Giridhar et al. 13	BT>TT>LL>BL	BT>IL>LL>TT>BL
Kalla et al. 15	LL>TT>BL>BT>BB	LL>TT>BL>BT>BB
Present study	LL>BT>BL>BT>BB	TT>LL>BT>BL>BB>IL>HL

In our study, we observed a substantial diagnostic shift between clinical and histopathological classification. Out of 150 cases, only 86 cases (57.33%) show clinical and histopathological correlation. Association was seen in 23 out 30 patients (76.66%) in TT cases, 17 out of 31 cases (54.83%) in BT, 9 out of 30 cases (30%) in BB, 7 out of 21 cases (33.33%) in BL and 25 out of 33(75.5%) in LL. 2 out of 2 in histoid and 3 out of 3 IL cases showed concordance.

Mathur et al, reported an overall clinic-histopathological concordance of 80.4%, with the highest agreement in LL (95.2%), followed by BT (89.7%), TT (73.2%), BL (72.4%) and BB (64.7%).[1] Thapa et al, found the greatest parity in TT, followed by BT and LL.[3] Manandhar et al observed maximum correlation in BT and LL with poor correlation in TT, which is in contrast to our study.[6] Shrestha A et al., noted the highest correlation in indeterminate and histoid leprosy, followed by LL, TT, BB and BT, with no agreement in BL; overall concordance was 39.58%.[12] Giridhar et al, reported the highest agreement in LL, followed by borderline leprosy, TT and BT, with the least in IL.[14] Kalla et al, recorded the highest correlation in LL (76.7%) and TT(75.6%), followed by BT(44.2%), BL(43.7%) and BB(37%).[16] Ridley and Jopling found complete agreement in 56% cases, with the highest concordance in TT(87.5%) and LL(71.4%), followed by IL(81.2%), BT(60.9%), BB(54.5%), and BL(53.8%).[16]

In the present study, clinico-histopathological correlation was highest in IL and HL, with both demonstrating 100% concordance. Similar findings have been consistently reported in previous studies, where IL showed the highest rate of agreement between clinical and histopathological diagnoses, underscoring its relatively distinctive clinical and microscopic features.[10,17,18]

After excluding indeterminate and histoid leprosy cases from the analysis, TT and LL appeared to present the least difficulty in classification, with clinico-histopathological agreement rates of 76.6% and 75.5%, respectively. Similar trends have been noted in earlier studies. Mathur et al, Shrestha et al and Moorthy et al reported the highest correlation in LL.1,10,12 Whereas Kalla et al and Kar et al observed maximum concordance in the tuberculoid spectrum.[15,19]

The disparity between clinical and histopathological observations is expected, as the criteria used for histopathological classification result from the spectrum-based nature of disease, heterogeneous lesional activity, early non-specific changes, reactional episodes, and inherent instability of borderline forms. Overall, histopathology resulted in significant reclassification within the borderline spectrum, particularly for BB and IL, underscoring the limitations of clinical diagnosis alone and reinforcing the importance of histopathological examination for accurate categorization of leprosy. These findings highlight the limitations of clinical assessment alone and reinforce the pivotal role of histopathology in accurately classifying leprosy, particularly in early and borderline cases.

The present study demonstrated a moderate level of clinicopathological agreement ($\kappa = 0.48$, $p < 0.001$), which is consistent with earlier studies by Poudel et al., who reported moderate agreement ($\kappa = 0.505$), with statistically significant concordance.20 Similar to previous reports, lower agreement was noted in borderline forms of leprosy, highlighting the diagnostic difficulty in these categories and emphasizing the importance of histopathological confirmation

Conclusion

This study underscores the importance of clinic-histopathological correlation in improving diagnostic accuracy and treatment decisions in leprosy. While clinical evaluation guides initial classification, histopathology offers crucial confirmation, especially in borderline cases with overlapping features. The frequent discrepancies between clinical and histological findings highlight the need for routine biopsies in resource-limited settings. Strengthening this correlation enables timely multidrug therapy, reduces complications, and supports better public health control.

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Conflict of Interest : None.

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