Original Article

A study on the multidisciplinary diagnostic approach of leprosy: Can we prevent the recrudescence in the post-elimination Indian scenario?

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Abstract

Introduction: Leprosy also widely known by the name Hansen's disease is a chronic disease caused by Mycobacterium leprae affecting mankind with various clinico-pathological forms. It remained a major public health issue due to associated case load, morbidity and stigma attached to it. India declared elimination of leprosy in the year 2005. However, it is surprising to see that in some parts of the country, the prevalence is still significant. The objective of the study is to describe the spectrum of histopathological profile of leprosy and compare its correlation with clinical diagnosis in this post elimination era. **Methods:** A 24-months prospective study was conducted with clinically diagnosed leprosy cases in a tertiary care hospital in eastern India. Lesions were graded and the histopathological slides along with its bacteriological index (BI) on slit skin smears where possible was reviewed and analyzed. Agreement of histopathological finding with clinical finding was established. **Results:** A total of 220 cases were included in the study. On histopathology, borderline category was the most frequently reported with borderline tuberculoid the most common subtype. Most common clinical feature was hypopigmented plaque, followed by erythematous skin lesions, nodules, macules etc. Bacteriological index was studied in 192 slit skin smears. Moderate agreement between clinical and histopathological diagnosis with kappa measure of inter-rater agreement as 0.457 was noted. **Conclusion:** Clinico-histopathological correlation is pivotal in the accurate diagnosis of leprosy to prevent, treat, and control the resurgence of the disease in the post-elimination era.

Keywords: Clinical diagnosis, histopathological diagnosis, leprosy, renaissance

Introduction

Leprosy is one of the potential community health concerns in India and takes various morphological forms depending on the host's degree of immune response.[1] Because of this, making a confirmatory diagnosis is challenging for both the clinician and the pathologist. The relevance of leprosy diagnosis in the practice of primary care physicians cannot be overstated, as it plays a crucial role in the early detection and treatment of this chronic infectious disease. Primary care physicians are often the first point of contact for individuals seeking medical care, making them essential in the identification of leprosy cases.[1]

Mycobacterium leprae causes leprosy, which can be spread by inhaling bacilli that may be expelled from a patient's nasal

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passages. The specific route of transmission is yet unknown. When inhaled as droplets, the organisms are phagocytosed by the macrophages in the lung and disseminated throughout the circulatory system. It only replicates in tissues with comparatively lower temperature, so it typically affects the skin and nerves, though cases have also been reported involving the muscles, eyes, bones, testicles, and other deep-seated organs.[2] The clinical spectra of presentation range from minor skin lesions to severe disease that may result in significant deformities.[2]

According to a modified version of Ridley and Jopling's classification, leprosy is divided into five clinico-pathologic groups: TT—Tuberculoid Polar (High resistance), BT—Borderline Tuberculoid, BB—Mid Borderline (dimorphic), BL—Borderline Lepromatous, and LL—Lepromatous Polar (Low resistance).[3] Considering cutaneous lesions and/or nerve trunk involvement, the WHO suggested classifying these lesions as paucibacillary (PB) and multibacillary (MB) in 1982.[4,5]

This disease presents in a variety of ways both clinically and histologically, which makes it difficult to diagnose in clinical practice. Primary care physicians are responsible for referring suspected cases of leprosy to specialized healthcare facilities for confirmation of the diagnosis and initiation of appropriate treatment. Leprosy diagnosis typically involves clinical evaluation, skin smears for acid-fast bacilli, and histopathological examination of skin biopsy samples. Primary care physicians should be aware of these diagnostic procedures and ensure that patients receive the necessary follow-up care. Clinically, it may appear as hypoesthetic papules, macules, or plaques; therefore, accurate diagnosis of these lesions necessitates the use of a variety of techniques, including careful examination of the affected area of skin and peripheral nerves, slit skin smears for the demonstration of acid-fast bacilli by Ziehl–Neelsen staining, and further confirmation with histopathology and bacilli demonstration by Fite.[6] The bacillary index is crucial for determining the disease's severity.[4] Histopathology aids in disease classification and shows how a lesion may advance or regress, as well as how a drug may cause reaction the skin.[6]

Leprosy is still a health concern in some regions of India, with Bihar, Maharashtra, Uttar Pradesh, Odisha, Chhattisgarh, Madhya Pradesh, West Bengal, and Jharkhand accounting for about 76% of new leprosy cases, according to data from the National Leprosy Eradication Programme (NLEP). This is despite the country being declared "leprosy-free" in 2005.[7] The World Health Organization (WHO) reports that 114,451 new leprosy cases were found in the nation in 2019-20, making up 80% of the cases in southeast Asian nations.[8] There are 4.56 cases detected annually for every 10,000 people. Leprosy affects 0.4 people out of every 10,000 in the nation.[8]

Therefore, the objectives of the study were to evaluate the clinical and histopathological features (along with bacillary index) of leprosy in skin biopsies and assess the degree of agreement between clinical and histopathological diagnosis in a tertiary teaching hospital of Northern Bihar in this post-elimination era.

Materials and Methods

During the 24 months from August 2020 to July 2022, a prospective hospital-based study was carried out at the Department of Pathology of a tertiary care facility in Northern Bihar. All age groups and both sexes of leprosy patients with a clinical diagnosis were included. Dermatologists took skin punch biopsies from lesions that were 3 mm or larger. These biopsies were delivered to the Department of Pathology, where they underwent standard protocols for processing and staining. The Ridley–Jopling classification was used to assign a grade to the lesions. When assessing the patients, Wade's new variety of leprosy, known as histoid leprosy, was also considered. The histopathological features were examined and agreement between histopathological and clinical findings was evaluated.

Patients were also advised by dermatologists to get their slit-skin smears examined in the Department of Microbiology. A minimum of five smears from each patient were taken from both earlobes, forehead and lesions/nodules and evaluated for the bacillary index (BI) after staining with ZN stain.

When appropriate, frequency and percentages were used to evaluate and portray descriptive statistics. To find out the extent of agreement between the clinical and histological diagnoses, inter-rater agreement was conducted using the kappa measure of agreement. The following are the kappa values and their interpretations: 0 means there is no agreement; 0 to 0.19 means it is extremely weak; 0.20 to 0.39 means it is weak; 0.40 to 0.59 means it is moderate; 0.60 to 0.79 means it is substantial; and 0.8 to 1.0 means it is good. For all analyses, a *P* value less than 0.05 was regarded as significant. Microsoft Excel and SPSS Version 16.0 were used as the statistical software for all studies (Chicago, IL, SPSS Inc.).

Results

A total of 220 cases were studied. Sex ratio was observed to be 1.93:1 (Male: Female), with 145 cases of males and 75 females. The age of the patients ranged from 9 years

Table 1: Age distribution of cases as per histopathological types

Age (in yrs)	IL	TT	BT	BB	BL	LL	Histoid	Type 1	Type 2
1-10	0	2	5	0	0	0	0	0	0
11-20	6	8	32	1	12	2	1	1	1
21-30	10	5	24	2	18	7	0	2	2
31-40	5	3	12	1	12	3	0	1	1
41-50	3	1	8	0	10	1	1	0	0
51-60	1	0	4	0	3	1	1	0	0
61-70	0	0	2	0	0	2	0	0	1
71-80	0	1	1	0	0	0	0	0	0

to 78 years with highest incidence noted in the age band of 21–30 years, followed by 11–20 years and 31–40 years, respectively [Table 1 and Figure 1].

Most common clinical feature was hypopigmented plaque (43.18%), followed by erythematous skin lesions (29.55%), nodules (18.18%), macules (5%), papules (3.64%), and claw hand (0.45%).

Bacteriological index could be studied in 192 slit skin smears. The other 28 cases did not turn up in the Department of Microbiology for getting the test done. BI when correlated with their corresponding histopathological diagnosis was observed to be 0 (zero) in case of TT and mostly 5+/6+ in cases of LL and its variant of histoid leprosy [Table 2].

On histopathology, borderline category was the most frequently reported with borderline tuberculoid the most common subtype (88/220; 40%) followed by borderline lepromatous, intermediate leprosy, tuberculoid leprosy, and lepromatous type [Figure 2]. We also found 4 (1.8%) cases of mid borderline leprosy in our study. Three cases (1.36%) of histoid leprosy were also noted along with 9 (4.09%) cases of lepra reaction.

Histopathology of lepromatous leprosy (LL) showed an atrophied epidermis with grenz zone and dermis showing foamy macrophages (called as lepra cells) surrounding blood vessels, nerves, and adnexa structures. Lepra cells contained lepra bacilli. ZN staining demonstrated acid-fast bacilli in globi. Borderline lepromatous leprosy (BL) showed inflammatory infiltrate mostly lymphocytes few histiocytes and perineural fibrosis. Lepra bacilli were seen. Tuberculoid leprosy (TT) showed dermis consisting of granulomas composed of epithelioid cells and Langhans' giant cells. No grenz zone was noted. Lepra bacilli were few in number. Borderline tuberculoid leprosy (BT) showed epithelioid cells and many lymphocytes. ZN stain was negative for acid fast bacilli. Mid-borderline leprosy (BB) showed epithelioid cells and few lymphocytes. Histoid leprosy showed atrophy of epidermis with grenz zone. Dermis showed spindle cells arranged in whorled or storiform pattern. Acid-fast stain showed numerous bacilli.

Histological findings of cases showing mixed dermal inflammatory infiltrate composed of lympho-histiocytes along with polymorphs and evidence of vasculitis were diagnosed as type 2 reaction (erythema nodosum leprosum), cases showing edema among epithelioid granuloma in upper and mid-dermis were diagnosed as type 1 reaction. ZN staining in both cases for acid fast bacilli were negative.

Agreement between clinical and histopathological diagnosis was evaluated. Overall, there was moderate agreement (56.82%) between clinical and histopathological diagnosis with kappa measure of inter-rater agreement as 0.457 which was statistically significant (*P* value < 0.05) [Table 3]. Figure 3 shows microscopic

Table 2: Bacteriological index in slit skin smears in relation to their histopathological types

BI	IL	TT	BT	BB	BL	LL	Histoid	Type 1	Type 2	Total (*n*=192)
0	11	17	0	1	0	0	0	0	0	29
1+	9	0	48	1	0	0	0	2	0	60
2+	0	0	17	0	0	0	0	0	0	17
3+	0	0	12	0	18	0	0	0	2	32
4+	0	0	0	0	28	2	0	0	0	30
5+	0	0	0	0	7	9	0	0	0	16
6+	0	0	0	0	0	5	3	0	0	8

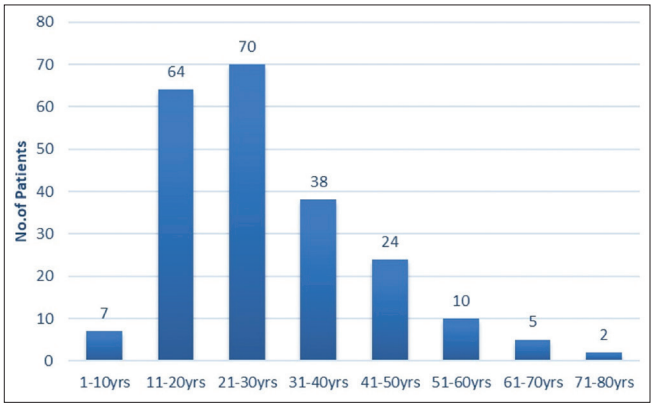

Figure 1: Distribution of cases based on age of the patients

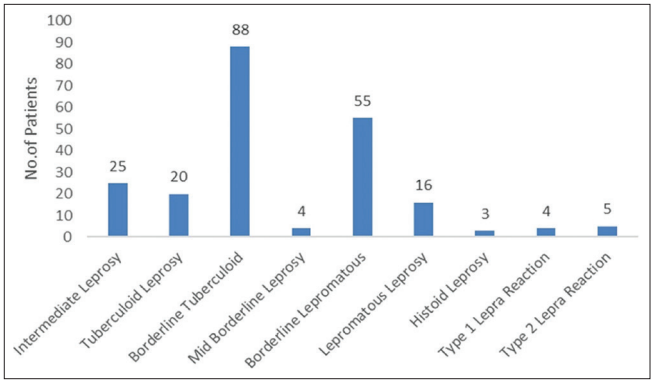

Figure 2: Distribution of cases according to histopathological types

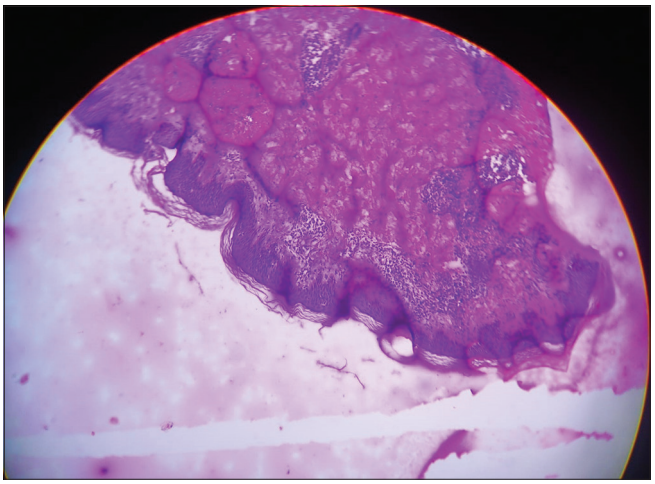

Figure 3: Microscopic picture of a case of indeterminate case of leprosy that was clinically diagnosed as BT (H and E, 100x)

Table 3: Agreement between clinical and histopathological diagnosis

Clinical diagnosis Types of leprosy	No. of patients	Histopathological diagnosis									Agreement	Percentage	Kappa measure of agreement	*P*
		IL	TT	BT	BB	BL	LL	Histoid	Type 1	Type 2				
IL	25	12	1	6	3	2	1	-	-	-	12/25	48.00	0.457	0.001
TT	20	2	10	8	-	-	-	-	-	-	10/20	50.00		
BT	88	25	8	50	-	-	5	-	-	-	50/88	56.82		
BB	4	3	-	-	1	-	-	-	-	-	1/4	25.00		
BL	55	5	-	-	-	33	15	2	-	-	33/55	60.00		
LL	16	-	-	-	2	3	11	-	-	-	11/16	68.75		
Histoid	3	-	-	-	-	-	1	2	-	-	2/3	67.00		
Type 1	4	1	-	-	-	-	-	-	3	-	3/4	75.00		
Type 2	5	2	-	-	-	-	-	-	-	3	3/5	60.00		
Total	220	50	19	64	6	38	33	4	3	3	125/220	56.82		

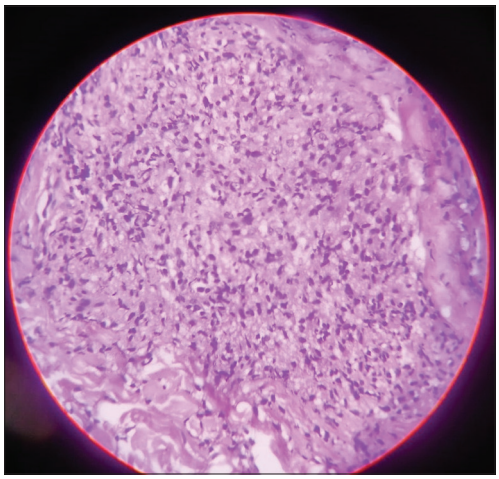

Figure 4: Microscopic picture of a case of LL that was clinically diagnosed as indeterminate (H and E, 400x)

picture of a case of indeterminate case of leprosy, which was clinically diagnosed as BT; Figure 4 shows microscopic picture of a case of LL, which was clinically diagnosed as indeterminate.

Discussion

Leprosy is a persistent granulomatous infection that typically infects the cutaneous and peripheral nervous system and is caused by *M. leprae*. Despite being widespread in many tropical and subtropical nations, the disease is becoming less common due to the advent of multidrug therapy.

The mode of transmission of leprosy is not very clear. Early disease detection and prevention becomes difficult due to the lengthy incubation period. Therefore, leprosy continues to be a significant public health issue.[9] The relevance of leprosy diagnosis in the practice of primary care physicians cannot be underestimated. Their ability to recognize the signs and symptoms of leprosy, initiate appropriate investigations, and refer patients for specialized care is crucial for early detection, treatment, and prevention of further transmission. Primary care physicians play a vital role in the overall management and support of individuals affected by leprosy, ensuring comprehensive care and improving their quality of life. Early disease identification, treatment, and burden reduction can all be of definite benefit to patients. Because a diagnosis based on clinical findings alone is not sufficient, a collaboration between clinical, pathological, and microbiological findings is crucial.[3]

In this study, leprosy was classified according to Ridley–Jopling's system, which is based on clinical, bacterial, pathological, and immunological factors.[10] The study examined 220 cases, of which 145 were men and 75 women, the male to female ratio being 1.93:1, which is consistent with the findings of Manandhar U *et al.* and Shivamurthy *et al.*[11,12] More exposure at work in men and evading treatment due to societal stigma in women are two possible reasons why men experience this condition more frequently than women.[13]

Similar to other studies conducted by Kumar A *et al.*, Roy *et al.* and Rad F *et al.*, the age range of 21–30 years saw the greatest number of cases, followed by 11-20 years with 70 cases (31%) and 64 cases (29%), respectively.[13-15] The reason for more involvement of this age group may be because this group is more active in outdoor activities due to occupational or other reasons.

Clinically, out of 220 cases, 95 (43.1%) had hypopigmented anesthetic plaques as their most prominent clinical feature, followed by 65 (29.5%) cases of erythema. This is similar to studies done by Roy *et al.*[14] and Sinha *et al.*[16]

The cases were histologically classified, and borderline tuberculoid, which accounted for 88 cases and 40% of the total, was the most prevalent histological subtype of leprosy, followed by borderline lepromatous, which accounted for 55 cases and 25% of the total. These results lined up with those of earlier research conducted by Sharma A *et al.* and Barbosa *et al.*[6,17] The study also discovered 20 cases of tuberculoid leprosy with 3 cases of the histoid variety. Our study also included four cases of drug reaction type 1 and five cases of type 2 which was not emphasized in other studies on similar topic.

In contrast to the results of the index study, Kaur *et al.*'s study found that the LL type was the most prevalent type in their series,[18] whereas Mathur *et al.* discovered that the TT type was the most prevalent type.[19] These discrepancies

could be attributed to regional variations, socioeconomic conditions, and immune status of the study population.[20] Leprosy patients have significantly decreased since multidrug therapy (MDT) for leprosy was implemented, but the disease has not yet been eradicated.[21] This is a matter of concern in the north-eastern states of India and its surrounding areas where follow-up and compliance are major obstacles to the achievement of eradication. In our investigation, we included a bacteriological index of slit skin smears that showed that, in contrast to other studies, lepromatous leprosy and its variant histoid leprosy had maximum acid-fast bacilli (5+/6+) while TT had nil (zero).

Leprosy clinicopathological correlation is necessary for tracking therapy effectiveness and determining whether the disease has relapsed or reactivated.[3] Type 1 reaction had the highest correlation in the current study, followed by lepromatous leprosy. Concordance varied considerably with other forms of leprosy, which may be due to more stringent diagnostic standards established in histopathology and newly developed microbiological and immunological procedures. Therefore, observations clearly highlight the significance of histological diagnosis in these cases, as lesions at the lepromatous pole of the disease are quite easy to diagnose clinically. The overall clinicopathological correlation was found to be 56.28% [Table 3]. Other studies in the last 10 years have shown an overall concordance between 55-80%; the highest being obtained by Mathur *et al.*[13,19,20,22-27]

Numerous elements, such as the size of the specimen, the location and depth of the biopsy, the age of the lesion, the patients' immunological condition, and the treatment history, can affect the histological diagnosis of leprosy.[28,29] Better comprehension of the disease is made possible by serial biopsies from the same lesion or from paired lesions.[30] Diagnosis of leprosy must be a collaborative effort involving the dermatologists, the pathologists, and the microbiologists.[2]

Conclusion

Accurate diagnosis is necessary for adequate treatment, avoiding deformities, and medication resistance because leprosy is a slowly progressing infection affecting the cutaneous and peripheral nerve system. Histomorphological analysis is essential for accurate typing and classification along with a slit-skin smear evaluation for bacillary index-based treatment. The clinical characteristics and histological findings of different types of leprosy might significantly overlap. Thus, a rational leprosy management should take into account the concordance of clinical findings, histopathological features, and microbiological examination in order to reduce overall morbidity of this disease as well as to control the "comeback" of this crippling disease in our nation in this postelimination era.[31]

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Conflicts of interest

There are no conflicts of interest.

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