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## A Study of the Histopathological Spectrum of Leprosy in a Tertiary Care Center along with Clinical Correlation

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### ABSTRACT

**Background and aim:** Leprosy (Hansen's disease) is a chronic granulomatous infection by *Mycobacterium leprae*, an acid-fast rod-shaped bacillus, predominantly affecting skin and peripheral nerves. The clinical and pathological manifestations are variable, depending on the immune status of the individual. It could lead to disabilities in a small proportion of patients in the absence of proper treatment. India has eliminated Leprosy as a public health problem, defined as less than 1 case per 10,000 people, at the national level in January 2006. However, cases are still being reported from different regions in varying prevalence. The present study was undertaken to study the clinicopathological spectrum of Leprosy and correlate it with the Bacillary Index (BI).

**Material and methods:** This study was conducted in a tertiary care center teaching hospital. It was a retrospective and prospective study from January 2018 to July 2022 (four and a half years). Fifty skin biopsies of clinically suspicious cases received in our histopathology department were processed and stained with Hematoxylin, and Eosin (H & E) and Fite-Faraco stain. The cases were subtyped based on the findings and correlated with clinical diagnosis.

**Results:** The cases ranged from 11 to 73 years of age, with male predominance. The most common subtype was Borderline Tuberculoid (BT) (32%), followed by Borderline Lepromatous (BL) (20%). The maximum clinicopathological correlation was observed in Lepromatous Leprosy.

**Conclusions:** Accurate and timely diagnosis of Leprosy can be achieved through histopathological examination and clinical correlation.

### 1. Introduction

Leprosy is one of the oldest diseases known to man, also called Hansen disease, after Armauer Hansen, who discovered its causative agent, *Mycobacterium leprae*, in 1873.<sup>[1]</sup> It is a chronic granulomatous infection predominantly affecting skin and peripheral nerves.<sup>[2]</sup> It also affects muscles, eyes, bones, testis, and internal organs.<sup>[3]</sup> India has reached the milestone of eliminating Leprosy, a public health concern, which has been defined as having fewer than 1 case per 10,000 people nationally since January 2006. Nonetheless, instances continue to be reported from different regions of the country with varying prevalence rates.<sup>[4]</sup> India reduced the prevalence rate from 5.27/10,000 in 2000 to 0.66/10,000 in 2016. Despite this, India accounts for 60% of new cases reported globally annually.<sup>[5]</sup> Considering the current scenario, we must try to eradicate the disease consistently. WHO launched a five-year "Global Leprosy Strategy 2016-2020" in April 2016 titled "Accelerating towards a Leprosy-free world".<sup>[6]</sup> Depending on the host's immunity, there are variable clinical and pathological presentations of Leprosy. The clinical presentations can range from single to multiple,

symmetric or asymmetric, hypopigmented, hyperesthetic to anesthetic macules or patches over the skin, and nerve damage leading to weakness, numbness, or paralysis. If appropriate treatment is not available, trauma to the anesthetic limbs could result in ulcerations and loss of fingers or toes. Such physical deformities can evoke severe social stigma, resulting in the abandonment of such patients by their families and society in general. Histopathologically, Leprosy was classified by Ridley and Jopling in 1960 into five types: Tuberculoid (TT), Borderline Tuberculoid (BT), Mid Borderline (BB), Borderline Lepromatous (BL), and Lepromatous Leprosy (LL).<sup>[7]</sup> Based on the number of acid-fast bacilli, it is subdivided and expressed on a logarithmic scale by the Bacillary Index (BI).<sup>[8]</sup> The clinical diagnosis depends on the appearance of the lesions, but it has limitations. The histopathological diagnosis and classification are based on well-defined criteria. It also takes the immunological manifestations of the disease into account. Often, patients presenting with a non-classical presentation can be missed clinically and in epidemiologic studies. Such challenging cases can be confirmed with histopathology. Histopathology is important in confirming the

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diagnosis, subtyping, and assessing the patient's disease under treatment and research.<sup>[3]</sup> This article aims to study the histopathological spectrum of Leprosy in a tertiary care center over four and a half years. We then correlated our findings with the clinical diagnosis to estimate the concordance between the clinical and pathological diagnosis.

## 2. Material and methods

This is a prospective and retrospective study by simple random sampling conducted in our tertiary care hospital and medical college for four and a half years (from January 2018 to July 2022). The Institutional Ethics Committee(IEC) approved the study for Biomedical and Health Research of D. Y. Patil, Deemed to be University School of Medicine, Navi Mumbai, with approval number (DYP/IECBH/2024/164). All skin biopsies received in the Department of Pathology with the clinical diagnosis of Hansen's disease were included in the study. This encompassed biopsies of newly diagnosed cases, clinically suspicious cases, patients on treatment, and relapse cases. Only inadequate biopsies and poorly preserved specimens were excluded from the study. We also excluded the cases wherein the histopathological findings were Non-specific. The skin biopsies were received in a small container in 10% formalin for the prospective samples. A detailed history was collected, including the presentation of the lesions, the duration, skin color or hypopigmented, anesthetic or hypoaesthesia, and whether any prior treatment was received for Hansen's disease or it was newly diagnosed. A history of any associated nerve enlargement or symptoms of nerve involvement, such as paresthesia, tingling, and numbness, was also collected. The biopsies were grossly examined and fixed overnight in 10% neutral buffered formalin. The

specimens were then processed using the standard technique, and serial sections of 4-5 microns were obtained. Hematoxylin and Eosin (H & E) staining was done for the light microscopic study, followed by special staining with Fite-Faraco for Bacillary Index (BI). These findings confirmed or refuted the diagnosis of Leprosy and subtyping according to Ridley and Jopling's classification. Both H and E and Fite Faraco were reviewed for the retrospective samples, records, and histopathology slides, and the findings were recorded for further analysis. Descriptive statistics like mean, median, frequency, and percentage were calculated for the variables and the percentage correlation.

## 3. Results

The present study included 50 skin biopsies that were received from clinically diagnosed cases of Leprosy from January 2018 to July 2022. The patients ranged in age from 11 years to 73 years. Amongst them, maximum number of cases were observed in the age group of 21-30 years 18(35.29%), followed by 41-50 years 9(17.6%) and then by 31-40 years 8(15.7%). Few cases were observed in the age group of 11-20 years 6(12%), 51-60 years 4(8%), 61-70 years 3(5.9%) and 71-80 years 2(3.9%). In the most common age group of 21-30 years, the maximum cases, 4 cases (8%) each, were BT and BL, followed by 3 cases (6%) each of BB, LL, and indeterminate Leprosy. Only 1 case (2%) was of Lepra reaction. (Table 1. Age-wise distribution of histopathological diagnosis). In our study, there were 33(66%) male and 17(34%) female patients, with the male-to-female ratio being 1.9:1. In both sexes, the maximum cases were of BT type. In males, they comprised 11 cases (22%), while in females, they comprised 6 cases (12%).

Table 1. Distribution of Histopathological diagnosis according to age.

No	Age (Years)	Histological Diagnosis							Total N(%)
		TT N(%)	BT N(%)	BB N(%)	BL N(%)	LL N(%)	I N(%)	Lepra Reaction N(%)	
1	0-10	0	0	0	0	0	0	0	0
2	11-20	0	2(4)	0	2(4)	1(2)	1(2)	0	6(12)
3	21-30	0	4(8)	3(6)	4(8)	3(6)	3(6)	1(2)	18(36)
4	31-40	0	1(2)	0	1(2)	4(8)	1(2)	1(2)	8(16)
5	41-50	0	6	0	1(2)	1(2)	1(2)	0	9(18)
6	51-60	0	1(2)	0	1(2)	0	1(2)	1(2)	4(8)
7	61-70	0	1(2)	0	1(2)	0	1(2)	0	3(6)
8	71-80	1(2)	1(2)	0	0	0	0	0	2(4)
	TOTAL	1(2)	16 (32)	3(6)	10(20)	9(18)	8(16)	3(6)	50(100)

TT: Tuberculoid, BT: Borderline Tuberculoid, BB: Mid Borderline, BL: Borderline Lepromatous, LL: Lepromatous Leprosy, I: Indeterminate.

Most patients presented with multiple hypopigmented patches 19(38%), followed by a single hypopigmented patch 11(22%). The other presentations included erythematous nodules 4(8%), erythematous patches 3 (6%), and erythematous plaques 2 (4%). Some of the patients had itchy lesions 2(4%), loss of sensation 2(4%) and tingling sensation 2(4%). Only 1(2%) case of ulnar nerve palsy was observed. On histopathological examination, the most common subtype observed was BT, comprising 16 cases (32%), followed by BL with 10 cases (20%), LL (Fig. 1) with 9 cases (18%), indeterminate

Leprosy has 8 cases (16%), 3 cases (6%) for each BB and Lepra reaction, and only 1 case (2%) of TT leprosy (Fig. 2).

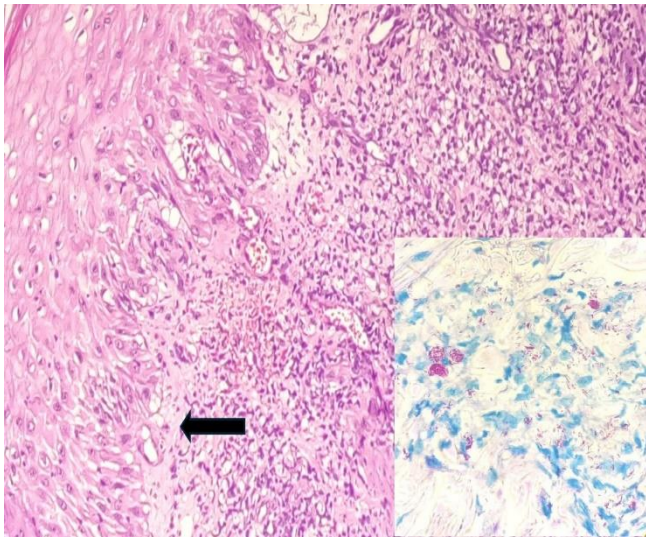


Fig. 1. Lepromatous leprosy (LL) displaying sheets of foamy macrophages in the dermis separated from the epidermis by Grenz zone (black arrow) (H & E; 40x) Inset: Bacillary Index 5+ (Fite Faraco stain, 100x).

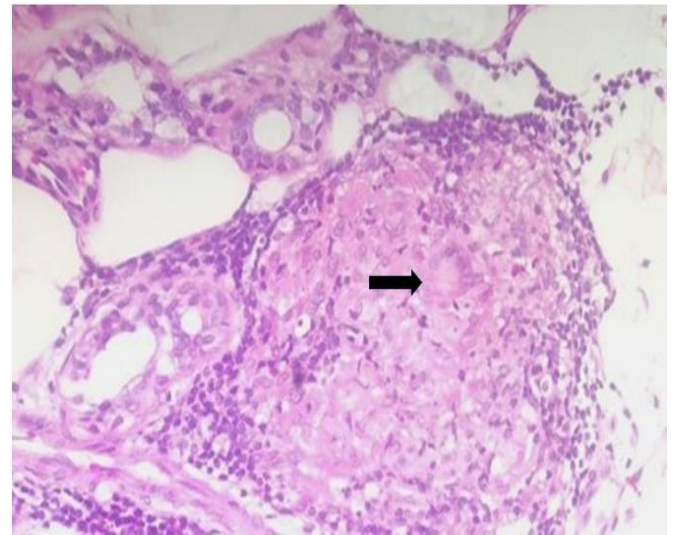


Fig. 2. A well-formed epithelioid cell granuloma containing Langhans type of giant cell (black arrow) in Tuberculoid (TT) leprosy (H & E; 40x).

Special staining with Fite-Faraco was done to detect the acid-fast bacilli (AFB) in all the cases. It was found to be positive in 37 cases (74%). BI was zero in the single case (2%) of TT, 15 cases (8%) of BT, 6 cases (12%) of indeterminate Leprosy, and 1 case (2%) each of BB and lepra reaction. All

the cases of BL and LL were positive for AFB, with the BI being 4+ (6 cases [12%] of BL and 5 cases [10%] of LL and 5+ (4 cases [8%] each of BL and LL). (Fig. 1). (Table 2. Bacillary Index Correlation with histopathological diagnosis).

Table 2. Bacillary Index correlation with histopathological diagnosis.

BI	TT N(%)	BT N(%)	BB N(%)	BL N(%)	LL N(%)	I N(%)	Lepra Reactions N(%)	Total N(%)
0	1(2)	15(30)	1(2)	0	0	6(12)	1(2)	24(48)
1+	0	1(2)	0	0	0	2(4)	2(4)	5(10)
2+	0	0	0	0	0	0	0	0
3+	0	0	2(4)	0	0	0	0	2(4)
4+	0	0	0	6(12)	5(10)	0	0	11(22)
5+	0	0	0	4(8)	4(8)	0	0	8(16)
6+	0	0	0	0	0	0	0	0
Total	1(2)	16(32)	3(6)	10(20)	9(18)	8(16)	3(6)	50(100)

TT: Tuberculoid, BT: Borderline Tuberculoid, BB: Mid Borderline, BL: Borderline Lepromatous, LL: Lepromatous Leprosy, I: Indeterminate.

Of all the cases studied, maximum concordance was seen in LL and Indeterminate (100%), followed by BT (80%) and lepra reactions (75%). A good clinical-histopathological correlation was observed between the

lepromatous and tuberculoid poles of the leprosy spectrum. (Table 3. Histopathological correlation with clinical diagnosis).

Table 3. Histopathological correlation with clinical diagnosis.

Clinical Diagnosis (N)	Histopathological Diagnosis							Agreement	Percentage (%)
	TT (N)	BT (N)	BB (N)	BL (N)	LL (N)	I (N)	Lepra Reactions (N)		
TT	3	0	2	0	1	0	0	0/3	0
BT	15	1	12	0	0	0	2	12.0/15.0	80
BB	4	0	1	2	1	0	0	2.0/4.0	50
BL	17	0	1	1	8	4	3	8.0/17.0	47.1
LL	5	0	0	0	0	5	0	5.0/5.0	100
I	2	0	0	0	0	0	2	2.0/2.0	100
Lepra Reactions	4	0	0	0	0	0	1	3.0/4.0	75
Total	50	1	16	3	10	9	8	32/50	64

TT: Tuberculoid, BT: Borderline Tuberculoid, BB: Mid Borderline, BL: Borderline Lepromatous, LL: Lepromatous Leprosy, I: Indeterminate.

#### 4. Discussion

Leprosy comes across as a major health problem in some of the countries of Asia, Africa, and Latin America. Even though India achieved the elimination of Leprosy as a public health problem in 2006, it continues to pose a major health problem in some of the districts of developing India. The highest prevalence rate is in Vidarbha, Amravati, Gondhia, and Wardha districts.<sup>[9]</sup> Numerous factors affect the prevalence rate, such as population migration from rural to urban areas, overcrowding, malnutrition, poverty, and inadequate or lack of treatment.<sup>[10]</sup> Leprosy is solely a disease of humans; the source of infection is a Leprosy patient.<sup>[11]</sup> Often, there is a disparity between the clinical and the pathological diagnosis, which affects the treatment course. Another source of disparity is the varied clinical and histopathological presentation. The morphology can vary from compact granulomas with giant cells at one end of the spectrum to diffuse dermal infiltration with foamy macrophages at the other, which is caused by variation in immunologic response between the individuals to the causative agent.<sup>[3]</sup> The histopathological examination is the gold standard for accurate diagnosis and subtyping of the lesions.<sup>[1]</sup> Our study included the age range from 11-73 years. The most commonly affected age group was 21-30 years, with 18 cases (36%). This concurred with similar studies conducted by Mukherjee et al., Mathur et al., Bijjaragi et al., and Manandhar et al.<sup>[11-14]</sup> The reason for infection in this particular age group has been postulated to be the difference in exposure and immune response, leading to varied infection opportunities in children and adults.<sup>[14]</sup> In the present study, male predominance was observed with 33 cases (66%), and the M: F ratio was found to be 1.9:1. This was similar to the findings of Mukherjee et al. and Manandhar et al.<sup>[11, 14]</sup> Only 1 study by Suri et al. showed slight female preponderance.<sup>[15]</sup> This male preponderance has been attributed to more exposure of males to urbanization and industrialization, leading to more opportunities for contact with Leprosy patients. Females are less numerous as many are confined to household activities, and the social stigma may lead to less reporting.<sup>[3]</sup> The most significant factor for this sex difference is the opportunity for contact, and it has been observed that there is practically no sex predilection when the opportunity for contact remains the same.<sup>[16]</sup> Most patients presented with multiple hypopigmented patches 19(38%), followed by a single hypopigmented patch 11(22%). A few presented with erythematous nodules,

patches, and plaques. Similar findings were noted in studies by Shivamurthy et al., Khamankar et al., and Giridhar M et al.<sup>[17-19]</sup> In the present study, clinically and histopathologically, most cases were in the borderline spectrum of Leprosy. The most common clinical subtype was borderline lepromatous 17 (34%), followed by borderline tuberculoid 15 (30%). Histologically, the most common subtype was borderline tuberculoid, with 16 cases (32%), which was in concordance with Shivamurthy et al., Tiwari et al., Bal et al., Semwal et al., Sharma and Hazarika D et al.<sup>[17, 20-24]</sup> The spectrum of the histopathological lesions of Leprosy, along with the Bacteriological Index (BI), is given by the Ridley Jopling classification.<sup>[2]</sup> This classification does not include indeterminate Leprosy as it has no distinguishing features. This is the earliest detectable skin lesion comprising one or few hypopigmented macules with variable loss of sensation. Histologically, mild lymphocytic and macrophage accumulation is seen around the neurovascular bundles, dermal vessels, and sweat glands.<sup>[25]</sup> Our study noted 8 cases (16%) of indeterminate Leprosy. Our study's incidence rate was higher than the previous studies reported.<sup>[20, 25, 26]</sup> This higher incidence could be attributed to the increased awareness of Leprosy among people. In our study, Fite Faraco stain for AFB bacilli was found to be positive in 26 cases (52%), in 1 case of BT, 2 in BB, 10 in BL, 9 in LL, and two each in Indeterminate and lepra reactions. None of the TT cases showed any bacilli. However, the stain was positive for all the cases of BL and LL cases. Studies by Shivamurthy et al., Sharma et al., and Banushree et al. showed similar results.<sup>[17, 23, 26]</sup> Our study observed a clinicopathological correlation in 32 skin biopsies (64%). Even though the literature mentions specific histopathological findings of the different forms of Leprosy, numerous overlapping features are observed in practice. This makes categorization of the lesions into one specific entity challenging. The biopsy site selection also plays an important role as clinically dissimilar lesions biopsied from the same patient can display different histopathology types.<sup>[27]</sup> Thus, the correlation between clinical histopathological findings and BI is considered pertinent for precisely typing Leprosy.<sup>[23]</sup>

#### Limitations

As the study was conducted in a tertiary care center, it cannot be generalized to the population, as only the severe cases with comorbidities are more likely to come to the center.

## 5. Conclusion

Even though India eliminated Leprosy as a Public Health problem in 2006, it is still prevalent in many regions. A better understanding of its occurrence, transmission, and prevention is needed to eradicate the disease. Diagnosis of early lesions is quite challenging. So, it is recommended that a histological examination of skin lesions be done in all cases and correlated with clinical findings. Clinico-histopathological correlation, along with the Bacteriological Index, aids in accurately typing Leprosy compared to any single parameter alone. This further helps better manage the patients and thus helps reduce the disease burden.

## Conflict of Interest

The authors declared that there is no conflict of interest.

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