



# Histopathological Correlation in Different Types of Leprosy in a Tertiary Health Care Centre

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## **Authors' contributions**

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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## **ABSTRACT**

Hansen's disease or Leprosy, is a chronic infectious disease that is contagious and has a slow evolution. It affects mainly skin and schwann cells in the peripheral nerves and causes peripheral neuropathy which contributes to the permanent functional impairments [1]. It is caused by a rod shaped, acid fast staining bacteria known as Mycobacterium Leprae which has parallel sides, round ends and a characteristic bundle of cigar appearance due to the presence of a glial substance which is a surface lipid that makes the bacilli to be arranged side by side in parallel arrays [2]. It has a distinctive empathy towards the peripheral nerves where it establishes originally therefore it is the site where the pathological processes start mainly with the principal target being Schwann cell [3,4]. Amidst the communicable diseases, Leprosy is the most common cause of physical disabilities which is permanent. When the bacterium enters a person with good cell-mediated immunity against it, it gets destroyed. If there is a slight impairment in the cell-mediated immunity against it, some bacilli will multiply and a lesion develops. Depending upon the immune status of a host, it expresses itself in different clinico-histopathological forms [5]. Ridley and Jopling suggested a five-group classification of leprosy known as immunological classification based upon the immunological status of the patient as (a) tuberculoid (TT), (b) borderline tuberculoid (BT), (c) mid-borderline (BB), (d) borderline lepromatous (BL) and (e) lepromatous (LL) [6]. Bacteriological, immunological, clinical and histopathological features exhibit continuous but slow changes from

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one pole to another pole. The main disadvantage of this classification is that there is no specific position for pure neuritic as well as indeterminate leprosy in the spectrum [7].

**Keywords:** Leprosy; clinical; histopathology.

## 1. INTRODUCTION

Hansen's disease or Leprosy, is a chronic infectious disease that is contagious and has a slow evolution. It affects mainly skin and schwann cells in the peripheral nerves and causes peripheral neuropathy which contributes to the permanent functional impairments [1]. It is caused by a rod shaped, acid fast staining bacteria known as *Mycobacterium leprae* which has parallel sides, round ends and a characteristic bundle of cigar appearance due to the presence of a glial substance which is a surface lipid that makes the bacilli to be arranged side by side in parallel arrays [2]. It has a distinctive empathy towards the peripheral nerves where it establishes originally therefore it is the site where the pathological processes start mainly with the principal target being Schwann cell [3,4]. Amidst the communicable diseases, Leprosy is the most common cause of physical disabilities which is permanent. When the bacterium enters a person with good cell-mediated immunity against it, it gets destroyed. If there is a slight impairment in the cell-mediated immunity against it, some bacilli will multiply and a lesion develops. Depending upon the immune status of a host, it expresses itself in different clinico-histopathological forms [5]. Ridley and Jopling suggested a five-group classification of leprosy known as immunological classification based upon the immunological status of the patient as (a) tuberculoid (TT), (b) borderline tuberculoid (BT), (c) mid-borderline (BB), (d) borderline lepromatous (BL) and (e) lepromatous (LL) [6]. Bacteriological, immunological, clinical and histopathological features exhibit continuous but slow changes from one pole to another pole. The main disadvantage of this classification is that there is no specific position for pure neuritic as well as indeterminate leprosy in the spectrum [7].

### 1.1 Aim and Objective

To conduct clinical and histopathological correlation of skin lesions displaying clinical doubt of Hansen's disease.

### 1.2 Justification of Study

Depending upon the immune status of a host, leprosy expresses itself in different clinical and

histopathological forms. Clinical assortment provides awareness only to the obvious finding of the lesions whereas histopathological examination forms the "gold standard" technique by providing a definite, clear cut and accurate diagnosis. It provides a confirmatory guidance for all the cases with suspicion of leprosy which can be overlooked in medical practice and also takes into consideration the immunological demonstration of the patient which enables us to assist in the diagnosis. This justifies the significance of clinical and histopathological correlation in providing a better diagnosis thereby preventing development of deformity and disability by early commencement of treatment. It also helps in getting control of the disease.

## 2. MATERIALS AND METHODOLOGY

This is a cross-sectional comparative study of 30 patients who were selected on a random basis coming to the outpatient department of dermatology of our hospital. The study was executed by conducting punch biopsies from untreated patients with clinical suspicion of leprosy and then examining the sections after staining with Hematoxylin and Eosin which were noticed in the Department of Dermatology, venereology and leprosy and were communicated in the cytology section of the Department of Pathology, Chettinad hospital and research institute, Tamil Nadu between July 2020 to July 2021. Information regarding the age, sex, history, clinical inspection of patients concerning the site and type of lesion, slit skin smear stained with Ziehl-Neelsen stain were noted. Particular focus was given to the following findings while examining the histopathological sections : 1) Invasion of the epidermis with or without atrophy, Grenz zone involvement 2) Epithelioid granuloma, epithelioid cells and density of lymphohistiocytic infiltrate 3) infiltration of nerves. Histopathological categorization was made based on Ridley and Jopling classification.

## 3. RESULT OF THE STUDY

This study was performed by conducting punch biopsies of 30 newly diagnosed untreated cases with clinical suspicion of Hansen's disease. There were 21 males and 9 females among the

study group and their age varied between 13 to 45 years with most of them ranging in between 20 to 40 years of age. Among the study group of 30 cases, three cases exhibited no evidence of leprosy which was identified by performing histopathology and were corresponding to histopathology of lepra reaction (1), non specific dermatitis (NSD) (1) and another case was found to have insufficient biopsy (1) therefore diagnosis of Hansen’s disease was excluded in them and were not included in the study. So, the total cases with confirmation of diagnosis of leprosy made with histopathology that are included in the study were 27 out of 30 as conveyed in Table-1. The remaining 27 cases which are confirmed as leprosy were classified depending upon the histopathological features into the 5 group classification by Ridley-Jopling showing the

largest number of cases (70.38%) in the BT,BB,BL group commonly termed as borderline group. Two cases (7.40%) pertained to the TT polar group whereas five cases (18.51%) pertained to the LL polar group. Lowest number of cases (3.70%) were labelled as indeterminate leprosy commonly abbreviated as IL. Altogether agreement of diagnosis was spotted in 62.97% of the cases. Paramount correlation clinically and histopathologically was found in Indeterminate leprosy (100%) subsequently by BT (66.67%), BB (66.67%), LL (60%) and least in TT (50%) and BL (50%) as conveyed in the Table-2. Indeterminate leprosy cases which were clinically identified were found to have no dispute in clinical and histological diagnosis after correlating them as conveyed in the Table-3.

**Table 1. Type of leprosy based on histopathology**

Histopathological type	No	%
TT	3	10%
BT	10	33.34%
BB	5	16.67%
BL	2	6.67%
LL	5	16.67%
Indeterminate leprosy	2	6.67%
Lepra reaction	1	3.34%
NSD	1	3.34%
Insufficient	1	3.34%
Total	30	100%

**Table 2. Clinical and Histopathological correlation**

Clinical diagnosis	Histopathological diagnosis						consistency%
	TT	BT	BB	BL	LL	IL	
TT(2)	1	1					50%
BT(9)	1	6	1			1	66.67%
BB(6)	1	1	4				66.67%
BL(4)			1	2	1		50%
LL(5)			1	1	3		60%
IL(1)						1	100%
Total (27)	3	10	5	2	4	3	40%

**Table 3. Dispute in Clinical and Histopathological Diagnosis**

Clinical cases		Complete consistency	inconsiderable dispute	maximum dispute
Type	No.	No.%	No.%	No.%
TT	2	1 (50%)	1 (50%)	
BT	9	6 (66.67%)	2 (22.23%)	1 (11.12%)
BB	6	4 (66.67%)	1 (16.67%)	1 (16.67%)
BL	4	2 (50%)	1 (25%)	1 (25%)
LL	5	3 (60%)	1 (20%)	1 (20%)
IL	1	1 (100%)		
Total	27	17 (62.97%)	6 (22.22%)	4 (14.82%)

On connecting the clinical as well as histopathological diagnosis only inconsiderable dispute was found with variation in two or more groups in LL and BB cases except one case of LL which revealed maximum dispute with variation of two or more groups which was a deviation. Maximum disparity was found in LL and BB cases varying between 20-25%.

#### 4. DISCUSSION

Hansen's disease caused by *Mycobacterium lepra* bacilli does not own any toxin so the changes in histopathology are mainly because of the presence or absence of the host immune reaction against the antigen or bacilli itself. Leprosy itself is considered as an immunologic disease as most of the tissue damage which occurs in the host is a result of delayed hypersensitivity reaction [8]. The spectrum of the disease presentation is one of the striking examples of the same organism causing different clinicopathological features in man. More proof for the varied response of the immunological system came out by performing histopathological examination of the skin lesions. Even though the tissue pathology of the skin lesions from the patients with leprosy was narrated meticulously by Indian and American pathologists, Ridley and Jopling highlighted it in great detail based upon the lymphocyte and macrophage infiltrates in the skin lesions which reflect the immunological features of a person [9]. Thereafter, Ridley and Jopling five group classification, also known as immunological classification, became popular after these cells were discovered to play a crucial role in the immune response. It is a classification which depends upon the correlation of bacteriological, immunological, clinical features and histopathology of leprosy. The main remarkable feature of this classification is the steadiness of clinical manifestations in polar forms of TT and LL type of leprosy, while BT, BB and BL commonly termed as borderline forms are unstable and express a great tendency to progress into leprosy reactions. In spite of having a precise classification, cases exhibit heterogeneity among clinical and histopathological characteristics [10].

Variation in clinical and histopathological diagnosis relies upon the time at which the lesion is biopsied. If an early stage lesion is biopsied, there is likely to be discordance between the clinical and histopathologic observations so to get the recommended clinical and histopathological correlation for a case to be

studied, periodical skin biopsies should be performed from the same lesion which has an appearance indicative of clinical diagnosis. In a few early cases, distinctive histopathological features may occur before the classical clinical findings or the classical clinical findings may occur before the currently known distinctive histopathological features [11].

The histopathological features characteristic for different forms of leprosy are :

##### 4.1 Indeterminate Leprosy

It is classified histopathologically into two stages - early and late stages. In the early stage, acid fast bacilli can be seen occasionally in the zone below the epidermis, hair follicles, arrector pili muscle, normal nerve and/or perivascular infiltrate. In the late stage of indeterminate leprosy, characteristic features are proliferation of Schwann cells of normal nerve thereby resulting in baton shape of the involved nerve or infiltration with lymphocytes which are seen in the perineural sheath not involving the parenchyma of nerve as shown in Fig. 1. There will be no granuloma formation which excludes indeterminate leprosy [12,13,14].

##### 4.2 Tuberculoid Leprosy

In this type of leprosy, acid fast bacilli will not be seen. The features which will be seen usually are compact clusters of one or two granuloma within lymphocytes which will be copious in number as seen in figure-2. In the deeper dermis, there will be more evident findings of abundant lymphocytes proportionate to granuloma which form around it a concentrated peripheral mantle [12,13,14].

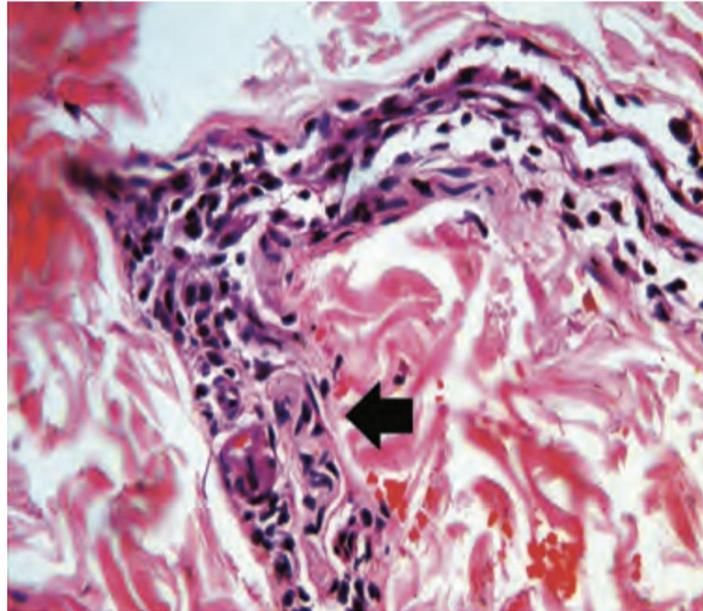
##### 4.3 Borderline Tuberculoid

Feature that will not be seen in this spectrum is necrosis and feature which is characteristic is the existence of foreign body giant cells as seen in figure -3. Subepidermal zone will be involved variably. In the advanced phase, there will be absolute destruction of all the AFB and nerve fibres [12,13,14].

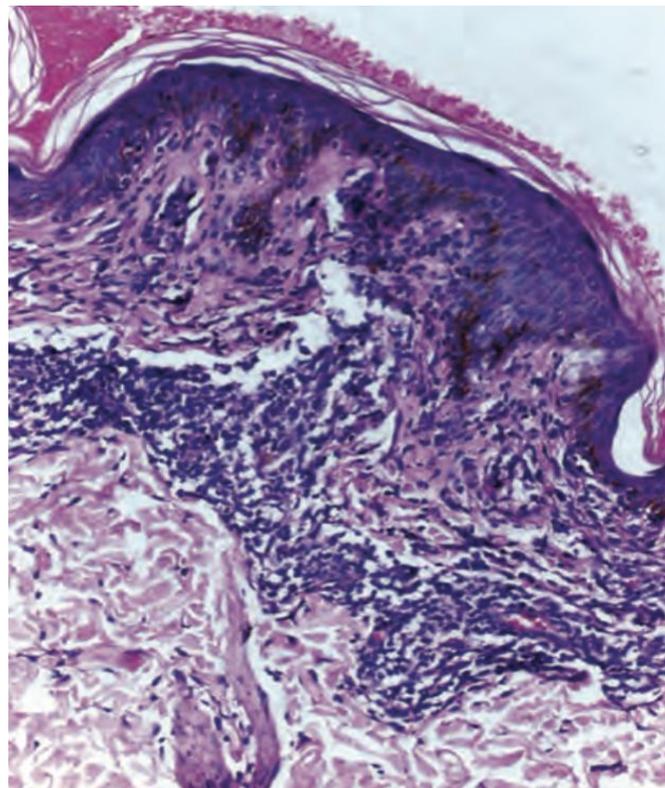
##### 4.4 Borderline Borderline

The characteristic features are the presence of numerous AFB and translucent grenz zone. Edema frequently conceals the histological features which indicate reactional instability. The

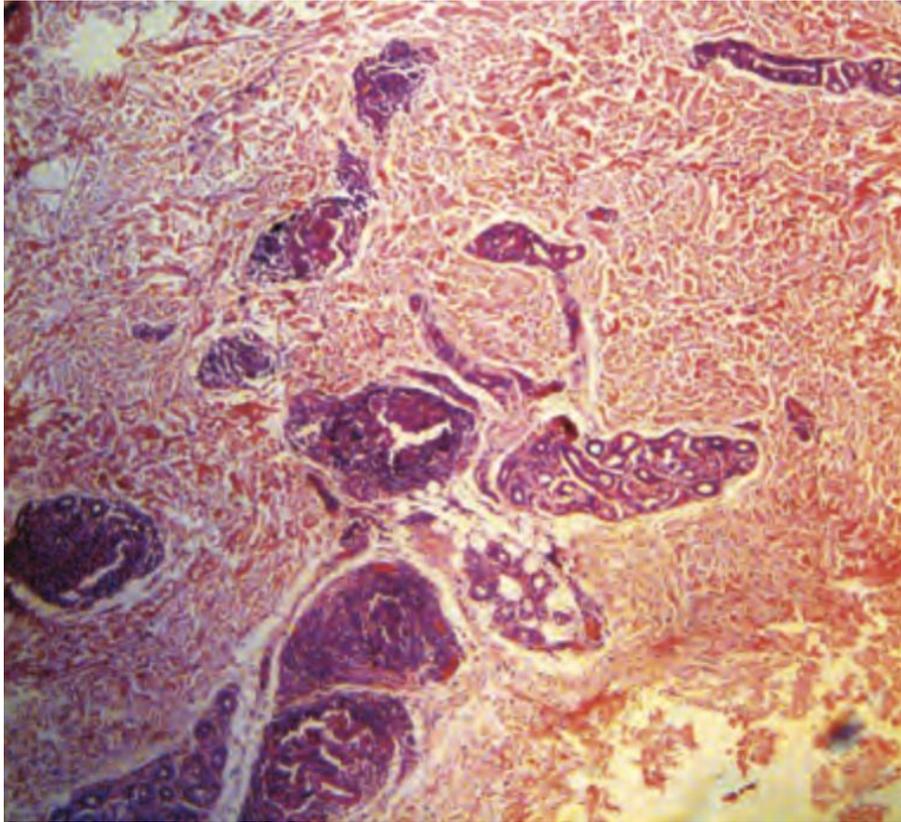
other features of BB are few inflammatory cells and absence of cuff of lymphocytes around which include lymphocytes, missing giant cells granuloma [12,13,14] as shown in Fig. 4.



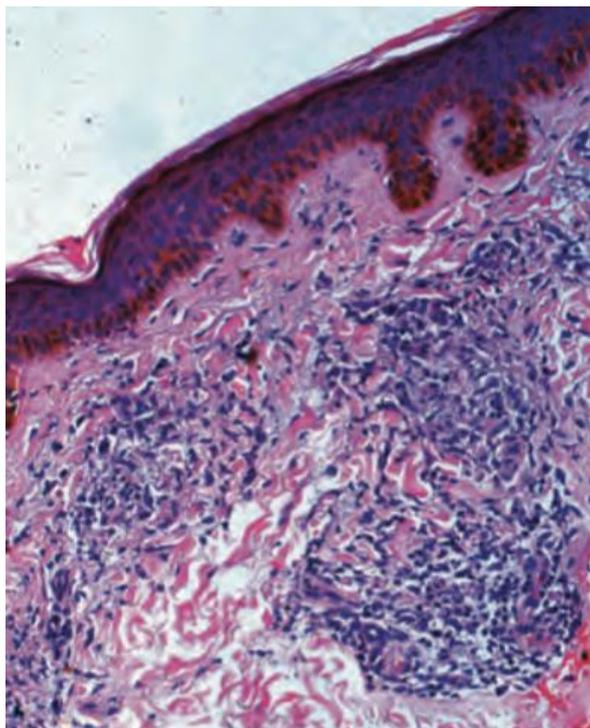
**Fig. 1. Skin biopsy showing infiltration with lymphocytes around a twig of nerve seen under higher magnification**



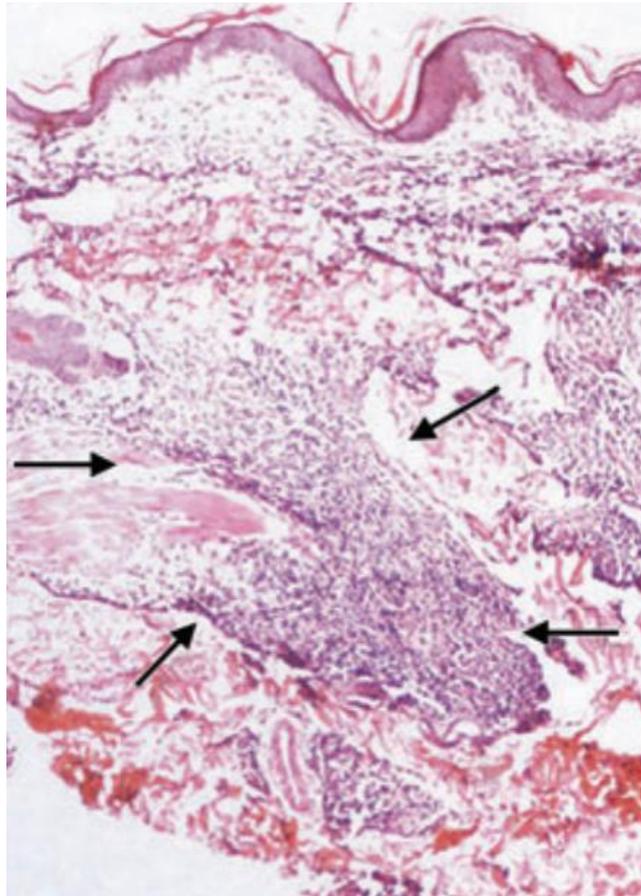
**Fig. 2. skin biopsy features which are suggestive of tuberculoid leprosy are no clear subepidermal zone with copious lymphocytes within which compact epithelioid cell granuloma are seen**



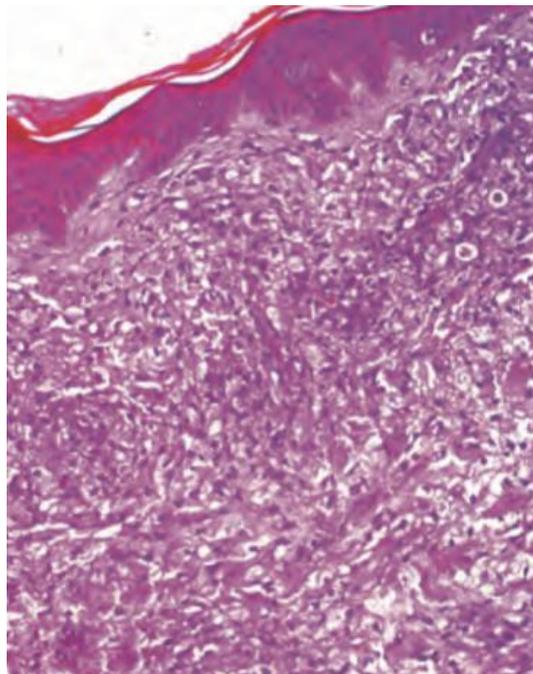
**Fig. 3. Numerous epithelioid foreign body giant cells are seen**



**Fig. 4. Features suggestive of BB are absent giant cells or lymphocyte mantle with disseminate epithelioid cell granuloma**



**Fig. 5. Macrophage granuloma suggestive of borderline lepromatous leprosy is seen**



**Fig. 6. Macrophage granuloma with foamy macrophages with clear grenz zone is seen**

#### 4.5 Borderline Lepromatous

AFB are seen similarly as seen in LL. Feature suggestive of BL is presence of macrophage granuloma which contains mildly foamy cytoplasm as shown in figure -5 within which there is a thick cuff of lymphocytes located peripherally surrounding a nerve bundle. Granuloma is separated from epidermis by a free grenz zone. The feature which is not seen here is the giant cell. Plasma cells can also be present [12,13,14].

#### 4.6 Lepromatous Leprosy

Thin and atrophic epidermis with rete ridges which are flattened completely are seen in conventional lesions. There is a visible free subepidermal zone between cellular infiltrate and epidermis. As the lesions become mature, cytoplasm of macrophages becomes foamy as shown in Fig. 6. Focal plasma cells will be present. Nerve swelling is not a finding in LL [12,13,14].

Among the 30 cases studied, three cases did not show evidence of leprosy upon histopathological examination among which one case had insufficient biopsy for making a diagnosis whereas other two cases showed histopathological findings corresponding to non specific dermatitis and lepra reaction thereby ruling out diagnosis of leprosy in them and were excluded from the study. Because of the absence of differentiating characteristics on histopathological examination which fail to observe a granuloma, Indeterminate leprosy cannot be allocated in the spectrum of Ridley-Jopling scale. In the current study, 3.70% cases were identified to have indeterminate leprosy based on the clinical examination whereas 6.67% cases are identified after performing a histopathological examination. For an accurate diagnosis of indeterminate leprosy, examination of the nerve lesions is required [15]. After removing the cases of indeterminate leprosy, the lowest difficulty for categorisation is found with BB cases as depicted in the Table-2.

In the current study, clinical identification was compatible with distinctive histopathological features in 17 out of 27(62.96%) cases and among the clinical scale of Ridley-Jopling spectrum, most of the cases were observed in borderline group (70.38%) subsequently by LL(18.51%), TT(7.40%) and least in IL group

(3.70%) and 2 predominance of cases in borderline group was also observed by Shivasamy et al [16] and Nadkarni & Rege [17]. BL and TT cases showed the lowest agreement in the current study.

In the current study, around 6.67% cases were identified histopathologically as indeterminate leprosy in opposition to 3.70% clinical cases. Sharma et al [18] identified 20% of cases as indeterminate leprosy based upon the histopathology which were assorted clinically as BT, BB and LL cases of leprosy. In the current study, indeterminate leprosy cases which were found histopathologically were clinically identified as BT cases and none were found in the BL category because of different immunological responses by different hosts. This type of leprosy because of the lack of characteristic finding of granuloma histologically rather than clinically, cannot be categorised within the leprosy spectrum.

A greater correlation was observed when BL and LL patients are combined in one lepromatous group and BT and TT patients in one tuberculoid group for the basis of research. Analogous increase in agreement of lepromatous as well as tuberculoid groups was found by Sharma et al [18]. There is often an overlap immunologically, clinically and histopathologically among borderline tuberculoid and tuberculoid cases of leprosy as well as among lepromatous and borderline lepromatous cases of leprosy but they vary only in degree making them unaffected to the treatment and also in the result of the disease when combined into two groups as BL-LL and BT-TT [18]. Even after the presence of histopathological findings which are specific for different forms, an overlap among various types of leprosy occurs. Least stable form immunologically is the mid borderline leprosy and also in the same patient there can be different forms of clinical feature making it important to correlate clinical and histopathological findings [18]. It is a familiar fact that even after treatment, bacilli which are not active may remain in nerves of indeterminate or borderline patients [19]. This also makes clinico histopathological correlation important to evaluate reactivation or relapse of the disease and also to track the response of a person to the treatment given.

Lowest stability immunologically is observed with mid borderline histopathological type of leprosy and the same patient can exhibit numerous lesions clinically which have an unrelated

appearance. In the current study, mid borderline cases showed the highest dispute (25.3%) linking the clinical and histopathological identification and such similar observation was also observed by Singhi et al [20]. Hence, it is necessary to relate the clinical findings with the histopathological characteristics of a lesion to attain a finer correlation.

## 5. CONCLUSION

Leprosy presents itself in various clinical presentations, hence an accurate diagnosis for it can be made by performing a histopathological examination and correlating it with the clinical features. Therefore, dermatologists and pathologists should put a careful and persistent effort in correlating the clinical findings and histopathological findings to make an appropriate diagnosis thereby aiding in early detection and treatment of leprosy and also reducing the disabilities occurring secondary to it which cause an impact to the person's day to day activities.

## CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

## ETHICAL ISSUES

The study was performed after getting clearance from the Ethical Committee.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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