

# HISTOPATHOLOGIC STUDY OF HANSEN'S DISEASE

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## ABSTRACT

### Introduction

Hansen's disease is a chronic infectious disease caused by Mycobacterium leprae. Accurate clinical and histopathological diagnosis forms the backbone for appropriate treatment and preventing deformities and drug resistance. Several studies have been conducted on clinical presentation of leprosy however there is a paucity of leprosy related histopathological data from Nepal.

### Objectives

The objectives of this study were to evaluate histopathological features of leprosy in skin biopsies, categorize them into various types based on Ridley Jopling classification and to correlate them with clinical presentations.

### Methodology

Ninety six skin biopsies histologically diagnosed cases of leprosy from 16<sup>th</sup> October 2020 to 15th April 2021 were included in the study. Ethical consent was taken from the Institutional Review Committee of Kathmandu Medical College Public Limited (Ref.: 011020202005). Hematoxylin and Eosin stain was used to study histopathological details. Wade-Fite stain was used to evaluate Bacillary index. The lesions were classified as per the Ridley-Jopling classification. Histopathologic findings were correlated with clinical diagnosis.

### Result

Male to female ratio of patients was 2.4:1. Most of the cases were seen in the third decade of life (39.6%). Most of the cases presented clinically as papules, nodules and hypoaesthetic patches involving predominantly extremities of the body. Commonest histological diagnosis was Borderline Tuberculoid (BT) leprosy (31/96). All cases of Lepromatous leprosy (LL) showed Acid Fast Bacilli on Wade-Fite stain. Tuberculoid leprosy cases showed granulomas and perineural involvement.

### Conclusion

Histopathological examination remains the gold standard for definite diagnosis and categorization of Hansen's disease.

## KEYWORDS

Hansen's disease, bacillary index, histopathology



## INTRODUCTION

Hansen's disease or leprosy is one of the leading causes of physical disabilities, which contribute to intense social stigma resulting in discrimination of patients and their families, especially in low-economic communities. It is a chronic infectious disease caused by *Mycobacterium leprae*, principally affecting the cooler parts of the body, mainly skin and peripheral nerves; it also involves muscles, eyes, bones, testis and internal organs.<sup>1</sup> The causative agent of leprosy, *M. leprae*, was discovered in 1873 by Armauer Hansen. Even though it was discovered early, it has not been cultured as yet.<sup>2</sup> Leprosy is an important public health problem in most of the developing countries including Nepal. Prevalence of leprosy in Nepal was reported to be 0.99/10,000 population in 2017/18 according to statistics of Department of health services (DoHS) Nepal.<sup>3,4</sup> The clinical manifestations of leprosy are so diverse and can mimic a variety of unrelated diseases. Presentation may vary from an insignificant skin lesion to extensive disease.<sup>5</sup> Lack of accurate diagnosis and treatment of leprosy can cause permanent damage to skin, nerves, limbs and eyes leading to deformities.<sup>6</sup> In most of the cases, diagnosis of leprosy is based on different clinical parameters which involve detailed examination of skin lesion and peripheral nerve and skin smear examination.<sup>7</sup> In some early and borderline cases of leprosy, it is difficult to diagnose only on clinical basis, hence histopathological examination is a must for confirmation of diagnosis in doubtful cases of leprosy. Clinico-histopathological correlation of leprosy assumes a pivotal role for definite diagnosis.<sup>8-12</sup> Examination of a biopsy specimen for histopathology can also be valuable to evaluate prognosis of the disease and provide appropriate treatment. It may also help to assess regression of the disease in patients under treatment.<sup>13,14</sup>

In our institution, skin biopsy is commonly performed in order to confirm the diagnosis of leprosy. However, no study has been done regarding the diversity of histopathologic features. We aim to study the histopathological features of leprosy in skin biopsies and to categorize them into various types based on Ridley Jopling classification and to correlate with clinical presentations whenever possible.

## METHODOLOGY

This was a prospective study conducted among patients from 16<sup>th</sup> October 2020 to 15<sup>th</sup> April 2021. The institutional review committee of Kathmandu Medical College Public Limited has approved our research protocol. Using consecutive sampling techniques, clinically and histopathologically proven cases of leprosy were included in the study. Informed written consent was taken for the study. Relevant demographic data were obtained from the requisition form provided with the specimens. History and clinical examinations of patients regarding location of skin lesion and type of skin lesion was recorded. Clinical classification of leprosy done by dermatologist was noted. Skin biopsy samples submitted for histopathologic evaluation were stained by Hematoxylin-Eosin (HE) and Wade-Fite stain after routine histopathological processing.

Histopathological classification of leprosy was done according to Ridley and Jopling classification in H and E stained slides. Bacillary index was evaluated in Wade-Fite stained slides.

## RESULTS

Out of 96 cases submitted for histopathologic examination, borderline tuberculoid (BT) was the most frequently reported histologic type (31/96) followed by tuberculoid (TT: 21/96). Lepromatous leprosy (LL) accounted for (20/96) cases and borderline lepromatous (BL) accounted for 18/96 cases. Three cases were diagnosed as mid borderline (BB: 3/96) and three were assigned as indeterminate (IL: 3/96). There was a male preponderance with a male: female ratio of 2.3:1 (Fig. 1). Age of the patients ranged from 12 to 79 years with most of the cases falling in the third decade of life (39.6%). Skin lesions presented clinically as nodules and papules (31%) and hypoesthetic patches (69%). Most cases of Lepromatous leprosy presented clinically as nodular and papular lesions whereas tuberculoid spectrum of disease presented as hypoesthetic patches. (Fig. 2)

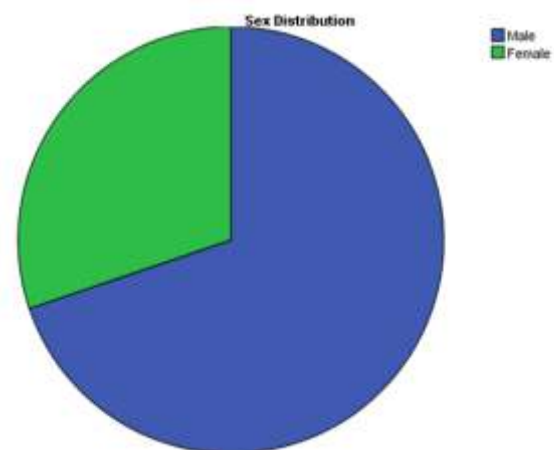


Figure 1: Sex distribution

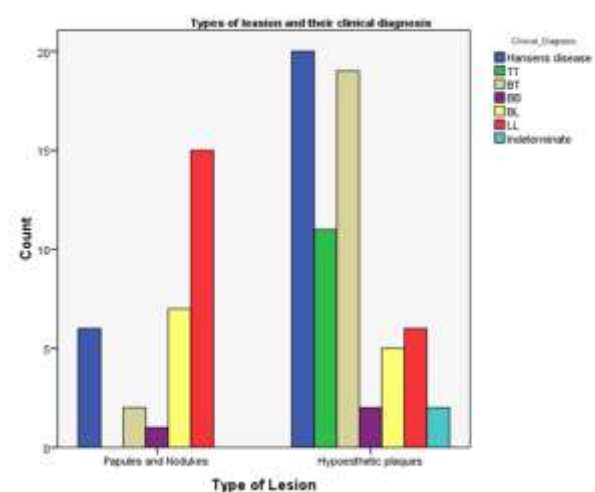


Figure 2: Type of lesion and the clinical diagnosis.

Histopathologic examination revealed epidermal and dermal changes in skin biopsies. Epidermal changes included presence of atrophy, hyperplasia, spongiosis and acanthosis. Dermal changes noted were presence or absence of Grenz zone, perineural and perivascular lymphocytic infiltrate, granulomas, aggregates of foamy macrophages and multinucleated giant cells. Perineural lymphocytic infiltrate and granulomas were noted in tuberculoid spectrum of disease whereas Grenz zone and foamy histiocytes were noted in lepromatous spectrum. (Fig. 3-5) Fite stain revealed Lepromatous bacilli in all cases of Lepromatous (LL), Borderline Lepromatous (BL) and Mid Borderline (BB) leprosy whereas bacilli could be demonstrated in only a single case of Tuberculoid leprosy (TT) and thirteen cases of Borderline Tuberculoid (BT) leprosy. (Fig.6) Bacillary index was also high in Lepromatous spectra of leprosy. No bacilli could be identified in indeterminate forms. (Table 1)

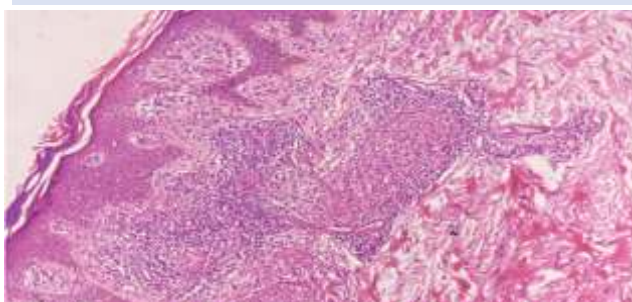
**Table 1:** Bacillary index in various histopathologic types of leprosy

Histopathologic Diagnosis	Bacillary_Index							Total
	0	1+	2+	3+	4+	5+	6+	
TT	20	1	0	0	0	0	0	21
BT	18	11	1	0	0	0	0	31
BB	0	1	1	1	0	0	0	3
BL	0	0	0	2	9	5	2	18
LL	0	0	0	0	3	8	9	20
Indeterminate	3	0	0	0	0	0	0	3
<b>Total</b>	<b>41</b>	<b>13</b>	<b>2</b>	<b>3</b>	<b>12</b>	<b>14</b>	<b>11</b>	<b>96</b>

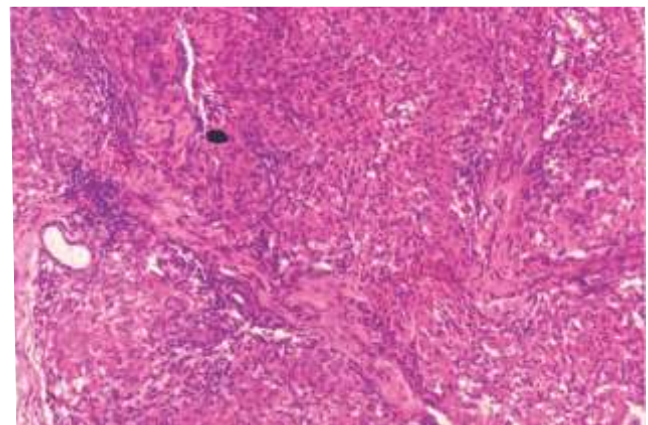
Overall clinicohistological correlation was 39.58% only and highest correlation was observed in LL (75%). Twenty six cases were clinically diagnosed as Hansen's disease only without any clinical classification and were not counted for statistical correlation. Table 2.

**Table 2:** Clinico-histopathological correlation of leprosy

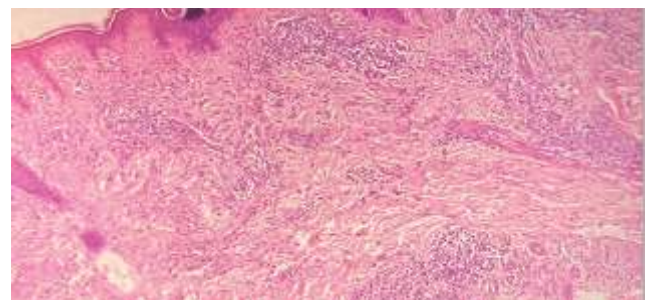
Clinical diagnosis	No of pt	Histopathologic diagnosis							Agreement	Percentage
		TT	BT	BB	BL	LL	IL			
Hansens disease	26	12	8	0	2	3	1	26	Not valid	
TT	11	6	3	1	0	1	0	6/11	28.57%	
BT	21	2	11	1	5	0	2	11/21	35.48%	
BB	3	0	1	1	1	0	0	1/3	33.33%	
BL	12	1	5	0	5	1	0	5/12	27.78%	
LL	21	0	1	0	5	15	0	15/21	75.00%	
IL	2	0	2	0	0	0	0	0/2	0%	
<b>TOTAL</b>	<b>96</b>	<b>21</b>	<b>31</b>	<b>3</b>	<b>18</b>	<b>20</b>	<b>3</b>	<b>38/96</b>	<b>39.58%</b>	



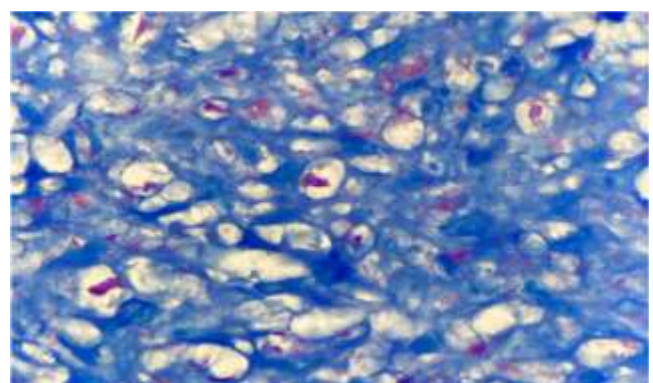
**Figure 3:** Tuberculoid leprosy with well defined granuloma in the dermis (100X). Multinucleated giant cells were also seen at places.



**Figure 4:** Perineural involvement in Tuberculoid leprosy (400X)



**Figure 5:** Lepromatous leprosy showing sub epidermal grenz zone and foamy histiocytes (100X).



**Figure 6:** Wade-Fite stain showing foamy histiocytes filled with lepra bacilli (1000X). BI 6

**DISCUSSION**

Hansen's disease is a chronic granulomatous disease caused by *M. leprae*. It can present with variable clinico-histopathologic features based on immune status of the host. Accurate diagnosis and classification of disease is necessary for the management of disease and prevention of disabilities. Ridley Jopling classification based on clinical, bacteriological, pathological and immunological parameters is the most widely used classification system for Leprosy.<sup>7</sup> Histopathologic diagnosis is considered the gold standard for diagnosis. Histomorphologic features considered for the diagnosis and classification of leprosy includes epidermal and dermal changes.<sup>8-12</sup>

We conducted a prospective study in 96 skin biopsies which

were clinically and histopathologically diagnosed as Hansen's disease and classified into various subtypes based on histopathologic features. Our study showed a male predominance with male to female ratio of 2.4:1. Other studies have also reported male preponderance.<sup>13-16</sup> Increased incidence of Hansen's disease in male could be due to increased chance of contact in males and occupational factors.<sup>14</sup> Vasaikar et al however found a higher number of female patients with male to female ratio being 0.8:1.<sup>17</sup>

Leprosy can occur at any age. Age of the patients in our study ranged from 12 to 79 years. Most of the cases were seen in the third decade (39.6%) followed by fourth (14.6%) and second decade (13.5%). Roy et al also reported maximum number of cases in third decade.<sup>16</sup> Kadam et al found most of their cases in 35-55 years age group.<sup>18</sup> Presence of Leprosy in a wide age range points towards the endemic nature of the disease in our community. Moreover increased incidence in a productive age group is a matter of concern for the nation.

Hypopigmented patches over skin surface with loss of temperature sense and numbness is a characteristic feature of leprosy.<sup>16</sup> We also observed hypoesthetic lesion as the most common presenting feature of leprosy (65/96) followed by papules and nodules (31/96). Similar findings were observed in studies done by Manandhar et al and Roy et al.<sup>13,16</sup> Hypoesthetic patches were more commonly noticed in tuberculoid spectrum of disease which is likely due to increased incidence of nerve damage.

The most common subtype of leprosy in our study was borderline tuberculoid BT (31/96) which is in contrast to the studies done by Sinha et al. who reported Borderline Lepromatous BL to be the most frequent type and Kaur et al who observed LL to be the commonest type.<sup>6,15</sup> Manandhar et al and Roy et al have however found BT to be the commonest sub type. This variation could be due to the regional differences, socioeconomic and immune status of the study population.<sup>19</sup>

Borderline tuberculoid BT and tuberculoid TT type leprosy typically show nerve obliteration and erosion with infiltration of neurovascular bundles and sweat glands. Granulomas and Langhan's giant cells are present.<sup>13,16</sup> Nerve involvement could be demonstrated in 27/31 cases of BT and 20/21 cases of TT in our study. Nerve involvement could not be identified in four cases of BT and one case of TT. However based on histomorphological features showing granulomas and Langhan's type of giant cells, diagnosis of BT and TT was possible. Granulomas and inflammatory cells might have destroyed the nerve structure causing difficulty in their identification on H and E sections. Dhakhwa et al have emphasized the role of S-100 immunostaining as an auxiliary diagnostic aid in demonstrating nerve remnants in which nerve involvement are not obvious on H and E stained slides.<sup>20</sup>

Diagnosis of Lepromatous spectrum of Leprosy is relatively easy. Lepromatous leprosy LL type showed typically presence of grenz zone and aggregates of foamy histiocytes in the dermis with high Bacillary Index (4+ to 6+). In our

study, poorly formed granulomas were observed in Borderline Leprosy (BL). Bacilli were readily demonstrable with Bacillary Index ranging from 3+ to 6+. Epidermal changes were variable ranging from atrophy, hypertrophy, spongiosis and non specific changes in both tuberculoid and lepromatous spectrum and were not of much help in classifying into subtypes.

In midborderline (BB) leprosy, macrophages are uniformly activated to epithelioid cells but are not localized in to distinct granulomas, and lymphocytes are scanty. There are no Langhan's giant cells. BI ranges from 3 to 4.<sup>21</sup> In our study also there were presence of ill defined granulomas in mid borderline (BB) leprosy. BI however ranged from 1 to 3.

The term indeterminate leprosy is used to describe patients presenting with very early leprosy lesions that cannot be categorized definitely along the immunopathologic spectrum (eg; cannot be determined as BT or LL).<sup>21</sup> In our study we came across three cases where there were mild lymphocytic and macrophage accumulation around neurovascular bundles. No well formed granulomas were seen. Bacilli could not be identified, however clinical features were suggestive of leprosy. Hence a presumptive diagnosis of IL was made.

Clinicohistopathologic correlation of Hansen's disease is challenging especially in early lesions.<sup>22</sup> In our study the overall clinicohistological correlation was 39.58% only and highest correlation was observed in LL (75%) and lowest in BL(27.78%). Twenty six cases were clinically diagnosed as Hansen's disease only without any clinical classification and were not counted for correlation. Clinicohistologic correlation showed a wide variation ranging from 33 to 81% in various studies (Table 3)

**Table 3: Clinico-histopathological correlation by different authors.**

Various studies	Number of cases	Clinicohistopathological correlation(%)
Present study, 2021	96	39.58
Manandhar U et al <sup>13</sup>	75	45.33
Sehgal VN et al <sup>23</sup>	95	33
Pandya AN et al <sup>9</sup>	50	58
Ridley DS et al <sup>7</sup>	82	68.3
Nadkarni NS et al <sup>24</sup>	2640	81.8
Kar PK et al <sup>25</sup>	120	70

This may be due to several factors like different criteria used to select the cases, number of cases of each type, age of the lesion, nature and depth of the biopsy, quality of the section, number of acid-fast stained sections examined, immunological and treatment status of the patient at the time of diagnosis, retrospective and prospective studies etc. There is also a possibility of inter observer bias both clinically and histopathologically.<sup>26</sup> Nadkarni et al found the highest clinicohistological correlation (81.8%) taking into consideration a larger sample size of 2640 cases.<sup>24</sup> Our study is limited by a small number of cases in a single institute for a



limited period of time and might not be representative of cases throughout the country. However findings of our study may provide a database regarding histologic profile of cases clinically suspected of leprosy. A larger study including cases from multiple centers could provide a more accurate clinico-histologic correlation.

## CONCLUSION

Histopathological examination remains the gold standard for definite diagnosis and categorization of leprosy into appropriate subtypes for effective treatment.

## LIMITATION OF THE STUDY

Our study is limited by a small number of cases in a single institute for a limited period of time and might not be representative of cases throughout the country.

## CONFLICT OF INTEREST

None

## FINANCIAL DISCLOSURE

None

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