Original Article

A Clinicohistopathological Correlation of Hansen's Disease in a Rural Tertiary Care Hospital of Central India

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Abstract

Background: Leprosy is an ancient, chronic granulomatous infectious disease caused by *Mycobacterium leprae,* principally affecting the skin and peripheral nerves. The clinical manifestations of leprosy are variable and can mimic a variety of other skin diseases. Thus, histopathological examination plays an important role in early diagnosis and management. **Aim:** The aim was to study the clinicohistopathological correlation of all suspected cases of Hansen's disease. **Materials and Methods:** A retrospective study was conducted on 207 skin biopsies obtained from patients clinically diagnosed as new lesion of leprosy in the department of pathology from 2016 to 2019. Demographic, clinical details of the patients were retrieved from hospital information system. Hematoxylin–eosin- and Fite–Faraco-stained sections were evaluated for features confirming leprosy and further categorized as per Ridley–Jopling system. Sensitivity, specificity, and concordance rates were studied. **Results:** The male-to-female ratio was 1.5:1. The agreement between histopathological and clinical diagnoses was more than 90% in all the subclasses except for borderline tuberculoid leprosy (BT) and tuberculoid leprosy (TT) which showed an agreement of 86.5% and 88.4%, respectively. The sensitivity of clinical diagnosis ranged from 69.70% for indeterminate to 100% for histoid and neuritic types. The specificity ranged from 90% for BT and TT to 100% for neuritic leprosy. **Conclusion:** Clinical diagnosis of early leprosy lesions offers difficulties even to experienced dermatologists as a patient presents in different clinicopathological forms, depending on host immune status. Thus, the correlation between clinical, histopathological, and bacteriological features is required for diagnosis and classification of leprosy. Nerve damage is irreversible; therefore, early detection and treatment is important to prevent Grade 2 disabilities.

Keywords: Clinicohistopathological correlation, leprosy, morbidity

Introduction

Leprosy is a chronic granulomatous infectious disease caused by noncultivable *Mycobacterium leprae*.[1] Although there has been a significant reduction in the prevalence of Hansen's disease (HD) worldwide since the mid-1980 to the elimination levels, new cases continue to arise in several Southeast Asian countries, particularly India and Indonesia, indicating continuous transmission.[2,3]

Due to its clinical diversity and ability to mimic other skin diseases, it is difficult to diagnose leprosy clinically in early stages.[4] Thus, histopathological examination of skin biopsies plays a pivotal role in early diagnosis, categorization, and treatment to prevent permanent nerve damage and Grade 2 deformities.

Materials and Methods

This study is a retrospective study carried out in the Department of Pathology of a tertiary care rural hospital. The study was approved by the institutional ethical committee. Skin biopsies from patients clinically diagnosed as new lesion of leprosy from 2016 to 2019 were included. Demographic, clinical details, histopathology, and treatment reports were retrieved from patient records in hospital information system and pathology records. Clinical details such as age, sex, site, type of lesion, and deformity were noted. A Ridley–Jopling criterion was used to classify the disease clinically and histopathologically.

Hematoxylin and Eosin- and modified Fite–Faraco (FF)-stained slides were examined by two investigators for changes in the

Access this article online

Quick Response Code:

Website: www.jgid.org

DOI: 10.4103/jgid.jgid_58_20

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How to cite this article: Atram MA, Ghongade PV, Gangane NM. A clinicohistopathological correlation of Hansen's disease in a rural tertiary care hospital of Central India. J Global Infect Dis 2020;12:191-6.

Received: 05 April 2020 **Accepted in Revised Form:** 11 June 2020
Published: 30 November 2020

epidermis, dermis, presence of granulomas, lymphohistiocytic infiltrate, epithelioid cells, Langhans giant cells, nerve involvement, and presence of acid-fast bacilli (AFB). Cases classified as indeterminate, histoid, and neuritic leprosy were also included in the study. Clinicohistopathological correlation was done for all cases. Slit-skin smear (SSS) findings were also reviewed, whenever possible.

Results

Two hundred and seven skin biopsies diagnosed clinically as leprosy were included in this study. Of these, 189 cases were confirmed on histopathology as leprosy and 18 were negative. Of the 189 cases, 113 (59.78%) were male and 76 (42.21%) were female, with a ratio of 1.5:1. The youngest patient was 12 years old and the oldest was 84 years old. Majority of the cases were found in the age group of 21–40 years. Eleven cases had a positive family/contact history in neighborhood, and most of them were children.

The most common clinical presentation was hypoanesthetic patches found in 153 (80.95%). Nine patients (4.34%) had limb deformities, and 7 (1.5%) of them had tropical ulcer, whereas five patients came to the outpatient department for sudden-onset fever, erythematous eruptive lesion, and arthralgia.

The most common site of lesion was upper limb (107), followed by lower limb, trunk, and face. Clinically, borderline leprosy cases were in the largest number, together constituted nearly 50% of the cases (borderline tuberculoid leprosy [BT] – 64 and borderline lepromatous leprosy [BL] – 27), and followed by tuberculoid leprosy (TT) and indeterminate leprosy (IL). The distribution of cases in individual categories based on clinical and histopathological criteria is summarized in Table 1.

Clinical and histopathological findings

The patients of TT were diagnosed clinically by the presence of <5 asymmetrical, hypopigmented, hypoanesthetic patches. Microscopically, the dermis showed well-defined granulomas and lymphocytic infiltrate seen in 24/29 cases [Figure 1a and b].

BT cases differed clinically from TT by a greater number of elevated lesions with altered sensation. Histopathological examination showed granulomas along superficial vascular plexus with variable number of Langhans giant cells. The bacillary index (BI) was 1 in 21 and 2 in 4 cases.

Clinically, mid borderline leprosy (BB) cases were diagnosed by the presence of irregularly dispersed ill-defined hypopigmented plaques and multiple nerve involvement. Histopathological hallmark of BB was the absence of Langhans giant cells and few lymphocytes and activated macrophages with prominent dermal edema. BI was three in most of the BB cases.

Cases with multiple asymmetrical nodular lesions and those with symmetrical shiny nodular lesions were categorized into BL and lepromatous leprosy (LL), respectively. Microscopically, BL cases showed dense lymphocytic infiltrates and foamy macrophages, whereas LL cases showed the presence of Grenz zone and Virchow cells [Figure 2a and b]. The BI index was 5 in 12 of LL.

Five of the seven cases were confirmed as histoid leprosy (HL) showed proliferation of spindle-shaped histiocytes oriented in storiform pattern with BI of six in all five cases [Figure 3a, b1 and b2]. IL on histopathology revealed mild lymphohistiocytic infiltration around dermal appendages and nerves. No epithelioid granuloma was seen.

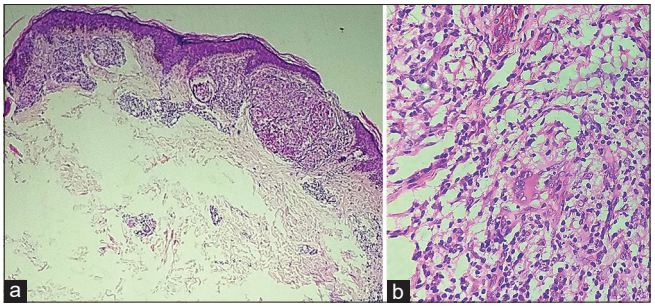

Figure 1: (a) Photomicrograph shows well developed epithelioid granuloma eroding the epidermis in tuberculoid leprosy (H and E, ×10). (b) Photomicrograph of tuberculoid leprosy shows classic tuberculoid granulomas comprised of epithelioid cells and giant cells surrounded by lymphocytes (H and E, ×40)

Table 1: Histopathological diagnosis of clinically classified cases in individual categories

Clinical diagnosis (*n*=207)	Histopathological diagnosis (*n*=189)									Total
	TT (*n*=29)	BT (*n*=64)	BB (*n*=11)	BL (*n*=27)	LL (*n*=17)	Histoid (*n*=5)	Neuritic (*n*=3)	IL (*n*=33)	Negative	
TT	23	7						5	6	41
BT	4	51		5				5	1	66
BB	2	2	10						3	17
BL			1	22	03				1	27
LL		1			14				2	17
Histoid		2				5			2	9
Neuritic							3		0	3
Indeterminate		1						23	3	27
Total	29	64	11	27	17	5	3	33	18	207

TT: Tuberculoid leprosy, BT: Borderline tuberculoid leprosy, BB: Borderline leprosy, BL: Borderline lepromatous leprosy, LL: Lepromatous leprosy

Three patients with pure neuritic leprosy had multiple nerve involvement in both limbs without skin lesions. Biopsies showed the presence of foamy histiocytes and lepra bacilli within the substance of nerve [Figure 4]. The histomorphological findings are shown in Table 2.

Clinical evidence of lepra reaction was found in five patients. Three patients had type I and two had type II reaction. All three patients of type I lepra reaction were in the age group of 20–40 years and from BT spectrum. Sections showed edema and fibrinoid necrosis within granulomas in the lower epidermis. Patients on multidrug treatment (MDT) with type II reaction were admitted to the emergency department with fever, tender eruptive lesions, and arthralgia. Multiple skin biopsies showed neutrophilic abscesses, vasculitis, and macrophages with fragmented bacilli.

Discussion

Leprosy is an ancient disease of mankind that affects mainly peripheral nerves and skin but also affects other sites such as reticuloendothelial system, eyes, bone, joints, muscles, testes, and adrenals. It has varied clinical manifestations, which are associated with host immune responses.[1,4,5]

Leprosy can occur at all age groups.[6] In the present study, majority of the patients were in the age group of 21–40 years (51.1%), similar to a study conducted by Kumar *et al*. (62%).[7] Leprosy has a variable and long incubation period which is responsible for this age distribution.[6]

Leprosy is common in males, with a male-to-female ratio of 1.5:1 in this study. Male preponderance might be attributed to increased chances of exposure due to increased job-related mobility.[8] Social customs and taboos may also account for the smaller number of females reporting to the hospital. Male preponderance of leprosy was seen in a study by Semwal *et al*.[9]

A hypoanesthetic patch was the most common clinical presentation in our study.[6] Since skin and nerves are the most common sites of *M. leprae* infection, signs and symptoms related to the skin and nerves were common.[6]

Of the 207 patients diagnosed clinically as leprosy, biopsies showed evidence of leprosy in 189 cases with overall agreement 92.4% in the present study. Ridley and Jopling[10] found agreement between clinical and histological types in 68.3%, similarly Kini and Choudhary, 92.4%;[4] Mathur *et al*., 80.4%;[11] Sharma and Rai, 85.8%;[12] and Murunantham *et al*., 62.85%.[13]

The BT and BL comprised majority of the cases, followed by polar type. Our findings show a similar dominance of cases in the borderline group, as noted by Bijjaragi *et al*.[14]

In the present study, the most common clinical and histological subtype was BT, followed by TT similar to various studies in the literature.[4,6,15]

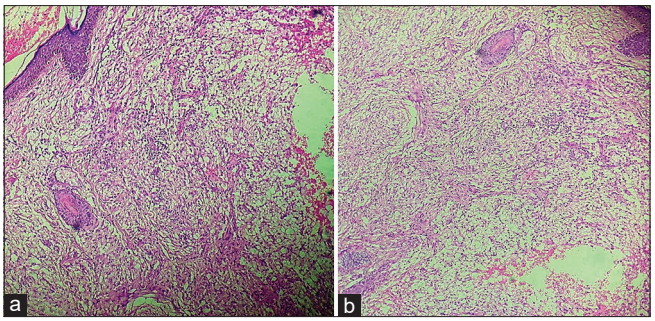

Figure 2: (a and b) Photomicrograph of lepromatous leprosy shows atrophic epidermis, grenz zone, and diffuse macrophage infiltration (H and E, ×10 and × 40)

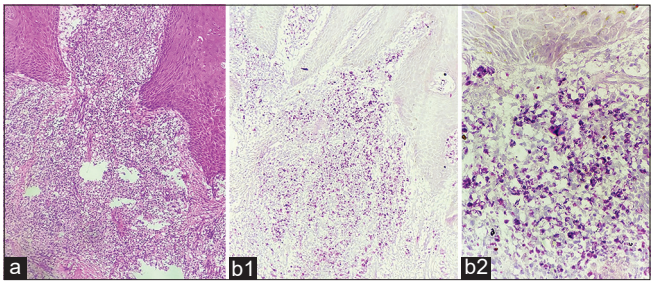

Figure 3: (a)Photomicrograph of histoid leprosy shows sheets of spindled shape histiocytes (H and E, ×10). (b1 and b2) Fite–Faraco stain reveals acid fast bacilli in classical sheaves of wheat arrangement (b1 ×10 and b2 ×40)

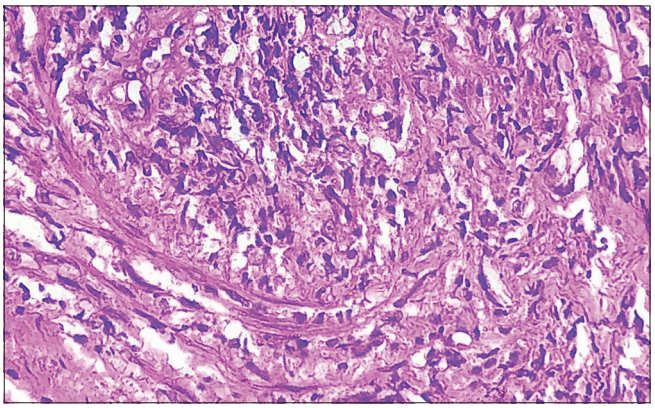

Figure 4: Photomicrograph of nerve abscess (H and E, ×10) showing infiltration of nerve by inflammatory cells

In our study, the highest clinicohistopathological agreement was noted for LL (97.1%). It was on the higher side in our study as the histopathological diagnosis of LL is rather more straightforward than other categories owing to being polar form. The least agreement was noted for BT (86.5%) and TT (88.4%). As some of the cases diagnosed clinically, TT was categorized histopathologically into BT and vice versa. This shift of one group is understandable as clinical and histopathological features of TT and BT were overlapping. However, it is important to categorize TT and BT histopathologically as it alerts the treating clinician to the possibility of a type 1 reaction that is common patients

of BT on treatment.[15,16] We observed minor discrepancy (shift of one group on polar tuberculoid side) in four cases (4 – TT) and major discrepancy in nine cases (5 – BL and 4 – IL). The clinicohistopathological agreement in each category is summarized in Table 3.

IL is an early and transitory stage of leprosy seen in persons whose immunological status is yet to be determined. It has nonspecific histology, so it becomes difficult to diagnose.[6] The definitive diagnosis of IL depends on demonstration of nerve lesions and AFB, but can diagnosed even without finding a single bacillus, if clinical and histopathological features are suggestive, especially in endemic areas.[6] We found IL more on histopathology (33 cases) than clinically (23) similar to Kini and Chaudhary[4] [Table 4].

HL is bacillary-rich leproma composed of spindle-shaped histiocytes with fibromatoid tendency in chronic form.[17] Its incidence is estimated to be 2.79%–3.60% in India.[18] In the present study, it constitutes around 2.64% of all leprosy cases. HL was described in patients on inadequate dapsone therapy; however, occasional cases of HL can occur *de novo*.[17]

In our study, three patients presented with primary neuritic leprosy without cutaneous lesion. In Indian studies, pure neuritic leprosy constitutes about 4%–18% of leprosy patients.[19] In study by Jacob M and Arunthathi S[20], 67% of primary neuritic leprosy patients developed skin lesions on long-term follow-up. This suggests that neuritic symptoms probably are the earliest symptoms of leprosy before the development of skin lesions, so patients of pure neuritic leprosy

Table 2: Histopathological findings observed in the epidermis and dermis along with bacillary index in leprosy cases

Histopathology	TT (*n*=29)	BT (*n*=64)	BB (*n*=11)	BL (*n*=27)	LL (*n*=17)	Histoid (*n*=5)	Neuritic (*n*=3)	IL (*n*=33)	Total (*n*=189), *n* (%)
Epidermal changes									
Unremarkable	28	35	7	4		1	1	30	106 (56.06)
Thinning/atrophic	0	19	3	18	17	4	-	-	61 (32.27)
Erosion/ulceration	1	10	1	05	02	-	2	3	24 (12.69)
Dermal changes									
Granulomas	24	51	-	-	-	-	-	-	75 (40)
Giant cells	1	49		-	-	-	-	-	50 (26.45)
Periappendgeal lymphocytes	28	51	6	25	10	-	-	-	120 (66.66)
Perineural lymphocytes	27	43	5	27	5	-	-	-	108 (57.14)
Plasma cells	-				16				16 (8.4)
Virchow cells	-	-	-	20	17				37 (19.57)
Dermal edema			7						7 (3.70)
Grenze zone	-	-	1	24	17	-	-	-	42 (22.22)
Bacterial index (*n*=51.85)									
BI-0	29	39	-	-	-	-	1	22	91 (48.14)
BI-1	0	21	-	-	-	-	2	11	34 (17.98)
BI-2	-	4	1	-	-	-	-	0	5 (2.64)
BI-3	-	-	7	-		-	-	-	7 (3.7)
BI-4	-	-	3	19	5	-	-	-	26 (13.75)
BI-5	-	-	-	8	12	-	-	-	20 (10.58)
BI-6	-	-	-	-	-	5	-	-	5 (2.64)

BI: Bacillary index, TT: Tuberculoid leprosy, BT: Borderline tuberculoid leprosy, BB: Borderline leprosy, BL: Borderline lepromatous leprosy, LL: Lepromatous leprosy

Table 3: Sensitivity, specificity, positive predictive value, negative predictive value, and agreement of clinical diagnosis for individual categories

Leprosy subclass	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Agreement (%)
TT	79.3	89.9	56.1	96.4	88.4
BT	79.6	89.5	77.2	90.8	86.5
BB	90.9	96.4	58.8	99.4	96.1
BL	81.4	97.2	81.4	97.2	95.1
LL	82.3	98.4	82.3	98.4	97.1
Histoid	100	98	55.6	100	98
Neuritic	100	100	100	100	100
Indeterminate	69.7	97.7	85.1	94.5	93.2

TT: Tuberculoid leprosy, BT: Borderline tuberculoid leprosy, BB: Borderline leprosy, BL: Borderline lepromatous leprosy, LL: Lepromatous leprosy, PPV: Positive predictive value, NPV: Negative predictive value

Table 4: Comparison of concordance rates for tuberculoid leprosy, borderline tuberculoid leprosy, borderline leprosy, borderline lepromatous leprosy, lepromatous leprosy, and indeterminate leprosy in our study with other studies

Leprosy subclass	Present study	Shivswamy *et al*.	Bajjragi *et al*.	Suri *et al*.	Kumar *et al*.[7]	Kini and Chaudhary[4]	Sharma *et al*.
TT	88.4	56	75	33.3	81.8	92.4	80.0
BT	86.4	64.1	57.3	94.1	34.5	82	56.0
BB	96.1	50	16.7	100	54.1	97.8	50
BL	95.1	73.3	40	62.5	21.3	92.6	86.2
LL	97.1	84.2	76.9	50	64.3	96.8	77.4
IL	93.2	50	66.7	100	93.6	94.7	68.4
HL	98		57.3	50	87.5	93.8	85.7
Neuritic	100					100	

TT: Tuberculoid leprosy, BT: Borderline tuberculoid leprosy, BB: Borderline leprosy, BL: Borderline lepromatous leprosy, LL: Lepromatous leprosy, IL: Indeterminate leprosy

must be followed up for long term.[20] Clinicopathological agreement of neuritic leprosy was 100% in our study similar to Kini and Choudhary.[4]

Histopathological examination with FF stain of 189 cases showed the presence of lepra bacilli in 98 (51.85%), whereas no bacilli in 91 (48.14%) cases. All 100% cases of TT showed no lepra bacilli, whereas mid-borderline, BL, LL, and HL showed the presence of bacilli in 100% of cases. Our findings were similar to a study conducted by Bhushan *et al*.[21]

The results of SSS correlated with FF-stained sections in LL spectrum. Although SSS test has high sensitivity and helps in establishing an early diagnosis, it has low specificity as 70% of the cases are smear negative.[9] Furthermore, BI in granulomas was found to be higher on FF than that of SSS by Ridley and Jopling who opined that SSS reflected density at particular foci while sections took into account the size of the lesion along with density.[9,10]

Lepra reactions are an important cause of morbidity in leprosy patients. Erythema nodosum leprosum (ENL) (type II reaction) is an immunological complication affecting approximately 50% of the patients with LL and 10% of BB.[22] In the present study, two patients of LL presented with ENL after successful completion of MDT. Awareness of the diverse clinical features of ENL is useful for the accurate diagnosis successful management and prevention of permanent disabilities.[22]

The reasons for emergence of new cases in post elimination era, is the long incubation period of leprosy which range from few weeks to 30 years. Thus, the cases appear "hidden" and the numbers cannot go up or down suddenly.[23] Furthermore, social stigma prevents most patients from seeking medical treatment until it is too late.[6]

Nerve damage is irreversible, and once disabilities set in, social rehabilitation becomes very challenging. Although the global disability rate reduced from 4.5% to 3.8%,[2] in India, the percentage of Grade 2 disability (G2D) among new cases detected has increased from 3.10% by 2010–2011 to 4.61% in 2014–2015. The high G2D rate among new cases indicates that leprosy is being detected late, and there may be hidden cases in the community.[24] Therefore, early detection and treatment of HD is important.

Clinical diagnosis of early leprosy lesions is often difficult even to experienced dermatologists because of the varied clinical manifestations. Thus, we emphasized the importance of histopathological examination in all clinically suspected cases of HD for early diagnosis and treatment before any disability sets in.

Conclusion

There is significant reduction in prevalence rate of leprosy to 0.23 / 10,000 population worldwide in 2020. Despite this India had more than 50% of leprosy patients of the world, which necessities identifying the reasons for transmission and to adopt preventive measures to control the disease. A leprosy patient presents in different clinicopathological forms, depending on the host immune status. Borderline cases represent majority of the lesions of leprosy and must receive special attention due to their unstable immunological status. Since the impact of finding one new case of leprosy is huge, histopathological examination of skin biopsy is recommended in all clinically suspected cases of leprosy for accurate diagnosis and treatment and to prevent nerve damage and permanent disabilities.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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