Journal of Interdisciplinary Histopathology
www.scopmed.org
DOI: 10.5455/jihp.20161208123939

Original Research

Clinicopathological correlation in diagnosis of Hansen's disease: A histopathologist's perspective

Reshma Gopal Kini, Hemangini Choudhury

Department of Pathology, Father Muller Medical College, Mangalore, Karnataka, India

Address for correspondence:
Dr. Reshma Gopal Kini, Department of Pathology, Father Muller Medical College, Kankanady, Mangalore - 575 002, Karnataka, India.
Phone: +91-9986287395. E-mail: drreshmakini@gmail.com

Received: July 17, 2016
Accepted: October 14, 2016
Published: December 31, 2016

ABSTRACT

Objectives: Hansen's disease follows a chronic course and though curable causes considerable degree of disability and deformity. Key to managing leprosy is its early diagnosis and treatment with multidrug regimen. Histopathological evaluation of skin biopsies plays crucial role in the correct diagnosis of clinically ambiguous cases. Moreover, classifying lesions by the Ridley-Jopling (RJ) system gives personalized information about the immunological status of the individual and also aids in placing the patient in the correct treatment category. **Materials and Methods:** Skin biopsies obtained from newly diagnosed cases of leprosy were included. Paraffin-embedded sections stained with hematoxylin-eosin and Fite-Faraco were evaluated for features confirming leprosy and further categorized as per the RJ system. Sensitivity, specificity, and concordance rates were studied. **Results:** A total of 93 cases were studied after excluding those which had a component of reaction. Among the clinically suspected cases, 93% of the biopsies were positive for leprosy. Sensitivity of clinical diagnosis ranged from 60% for borderline (BB) to 100% for histoid leprosy. Specificity ranged from 84.5% for borderline tuberculoid (BT) to 100% for neuritic leprosy. The agreement between histopathological and clinical diagnosis was more than 90% in all the subclasses except for BT which showed agreement in about 82% of the cases. Two of the cases were categorized into multibacillary type of leprosy-based histopathological evaluation. **Conclusion:** Confirmation of leprosy by the examination of skin biopsy before starting the patient on long-term multidrug therapy is invaluable. Experience of the leprologists and adherence to histopathological criteria as per the RJ classification yield excellent concordance rates.

KEY WORDS: Histopathology, leprosy, Ridley-Jopling classification

INTRODUCTION

Hansen's disease is a chronic infectious condition affecting principally the skin and peripheral nerves [1]. In the absence of the classic involvement of the peripheral nerves, the clinical manifestations of leprosy are diverse and can mimic a host of other skin disorders. With decreasing prevalence of the disease in the current post-elimination era, the opportunities to study this enigmatic disease are fewer whereas the need to sustain a high level of diagnostic expertise is absolutely necessary. The consequence of untreated or undertreated leprosy is not only the permanent and debilitating deformity suffered by these patients but also the risk posed by these individuals who act as reservoir for infection in the community. At this juncture, the histopathological examination of skin biopsies for diagnosis of leprosy and for the categorization of clinically suspected cases plays a pivotal role [2,3].

Hence, we aimed to evaluate the histopathological features of cases diagnosed as leprosy on clinical examination and also to assess the applicability of the Ridley-Jopling (RJ) system of classification in the current era of decreasing disease prevalence by correlating the clinical and the histopathological features [4,5].

MATERIALS AND METHODS

Settings and Design

This study is a descriptive, hospital-based retrospective study.

Skin biopsies obtained from patients clinically diagnosed as leprosy in the OPD and leprosy clinic of our institute between January 2012 and November 2015 were included in the study. The study was initiated after obtaining ethical clearance from the Ethics Committee of our institution.

Slides stained with hematoxylin and eosin and Fite-Faraco were evaluated for features representing/indicative of leprosy. Cases positive for Hansen's disease were evaluated for the presence or absence of granulomas, type of cells comprising the granulomas, nature of the histiocytes - whether foamy/epithelioid, presence of epidermal involvement, evidence of neural involvement/destruction, presence location and density of lymphocytes, type

and number of giant cells, and bacillary index. Based on these, the biopsies were categorized into five classes of RJ classification system as tuberculoid (TT) leprosy, borderline tuberculoid (BT) leprosy, mid-borderline leprosy (BB), borderline lepromatous (BL), and lepromatous leprosy (LL) [4,5].

Data were analyzed by:

i. Comparing the histopathological diagnoses with the clinical impression.
ii. Calculating the accuracy, sensitivity, specificity, and positive and negative predicted values of clinical categorization for individual subclasses.
iii. Evaluating the concordance of histopathological and clinical diagnosis for each of the classes.

Concordance in cases of indeterminate, histoid leprosy, and neuritic leprosy were also studied.

RESULT

A total of 93 cases were included in the study. The majority of the patients were males (60.2%).

The age of the patients ranged from 7 to 72 years. Of the 93 cases diagnosed clinically, 7 were negative for features of leprosy. The distribution of cases into individual subclasses by clinical and histopathological criteria is presented in Table 1 and Figures1 and 2.

BT cases were the largest in number. The borderline groups together constituted more than 50% of the cases. The histopathological diagnosis of the clinically categorized cases with the sensitivity, specificity, and concordance is shown in Tables 2 and 3.

Clinical diagnosis of TT was based on the presence of one or very few well-demarcated hypoanesthetic patches of slightly raised plaques in asymmetrical distribution with neural thickening adjacent to the skin abnormalities. We identified classic tuberculoid granulomas composed of epithelioid histiocytes with numerous well-developed Langhans' type of giant cells and dense lymphocytic infiltrate in 11 of the 18 cases [Figure 3a and b]. Bacillary index was uniformly 0 in all the cases of TT. Dermal fibrinoid necrosis, periadnexal, and perineural lymphocytes were additional points.

Cases classified as BT type differed from cases of TT by the presence of greater number of lesions slightly ill-defined though with equal or more loss of sensations [Figure 4a and b]. Histopathologically BT lesions showed significantly less number of giant cells as well as lymphocytes in comparison with TT [Figure 4c and d]. Three cases had bacillary index of 1 and one had surprisingly high load 4. Neural involvement by granulomas considered a classic feature of BT was seen in 57.1% of the cases. Rest of the cases showed either absence of dermal nerves in the biopsy or only lymphocytic infiltrate around the nerve bundles of which two cases showed no granulomas.

Table 1: Distribution of cases in individual categories based on clinical and histopathologic criteria

Type of leprosy	Clinical diagnosis	Histopathological diagnosis
TT	18	16
BT	33	30
BB	3	5
BL	12	9
LL	5	7
Histoid	8	6
Neuritic	1	1
IL	13	12
Not leprosy	-	7
Total	93	93

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

Table 2: Histopathological diagnosis of clinically classified lesions

Clinical diagnosis	Histopathological diagnoses								
Clinical (*n*-number of cases)	TT	BT	BB	BL	LL	Neuritic	Histoid	Indeterminate	Negative
TT-18	11	3	1						3
BT-33	4	22	1	2				2	2
BB-3			3						
BL-12		5		7					
LL-5					4				1
Neuritic1						1			
Histioid-8					2		6		
IL13		1	1					10	1
Total-93	16	30	5	9	7	1	6	12	7

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

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

Type of leprosy	Sn (%)	Sp (%)	PPV (%)	NPV (%)	Agreement
TT	68.75	91.46	61.11	93.75	92.4
BT	73.3	84.51	66.67	88.24	82
BB	60	100	100	97.83	97.8
BL	77.78	94.19	58.33	97.59	92.6
LL	66.67	98.88	80	97.78	96.8
Histoid	100	97.7	75	100	93.8
IL	83.33	96.39	76.9	97.5	94.7
Neuritic	100	100	100	100	100

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

Cases that showed several ill-defined skin lesions with mild loss of sensation and involvement of several nerves were classified into BB of mid-borderline type. There was 100% concordance between the clinical and histopathological diagnosis in BB.

Histopathological hallmark of BB lesions was the total absence of the Langhans' type of giant cells and scant number of

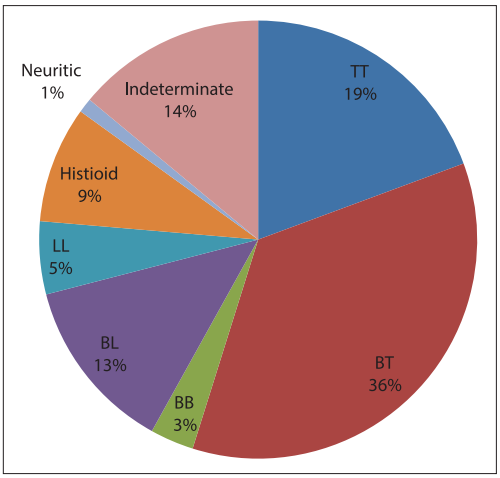

Figure 1: Distribution of cases by clinical criteria

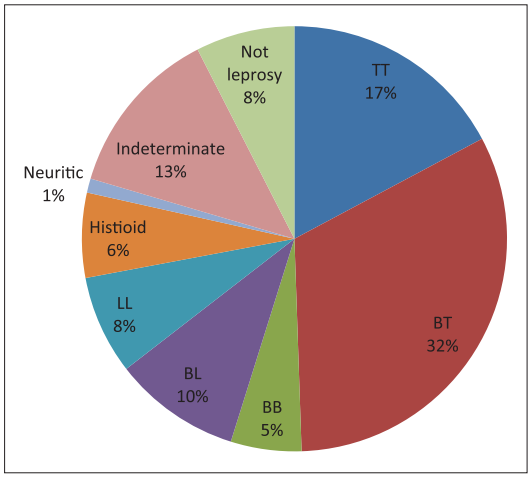

Figure 2: Distribution of cases by histopathological criteria

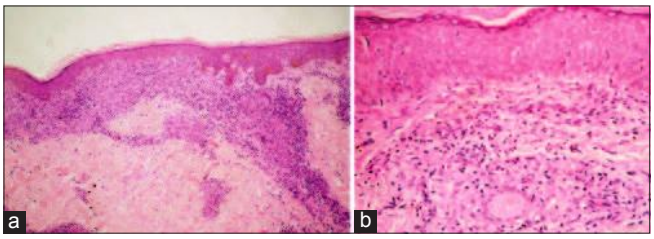

Figure 3: (a) Histopathology of 3a showing well-formed granulomas with many Langhans' giant cells eroding into the epidermis from below. Note the loss of melanocytes at the site of erosion in comparison with the adjacent uninvolved epidermis representing the clinically perceivable hypopigmentation. Hematoxylin and eosin. Original magnification ×100, (b) histopathology of tuberculoid showing granuloma composed of epithelioid histiocytes, lymphocytes, and well-developed Langhans' type of giant cell. Hematoxylin and eosin original magnification ×400

lymphocytes [Figure 5a]. The proportion of epithelioid cells within the granulomas was less as compared to BT, the cells being replaced by foamy macrophages [Figure 5b].

BL cases were diagnosed based on the presence of several asymmetrically distributed lesions ranging from mere macules

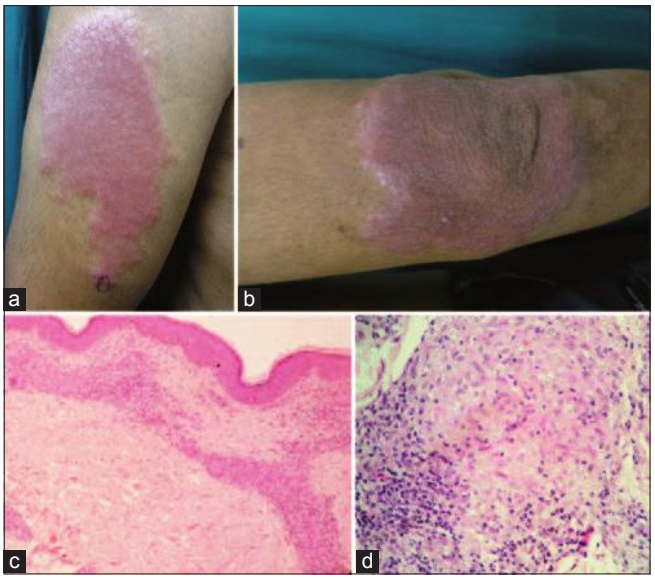

Figure 4: (a and b) A patient with clinical diagnosis of borderline tuberculoid showing two well-defined erythematous dry scaly plaques over the left arm and right elbow (a and b, respectively). The mark over the lesion on the left arm represents the site from which the biopsy was later taken, (c) histopathology revealed well-developed granulomas not involving the epidermis. A few Langhans' type of histiocytic giant cells and lymphocytes can be discerned. Hematoxylin and eosin Original magnification ×100, (d) classic tuberculoid granulomas comprised exclusively of well-developed epithelioid histiocytes with lymphocytes not forming a mantle. Hematoxylin and eosin. Original magnification ×400

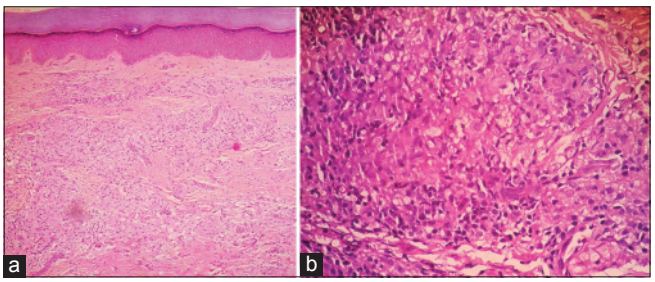

Figure 5: (a) Skin biopsy in borderline showing periadnexal granulomas with scant lymphoid cells. Note the absence of giant cells which helps in distinguishing it from a borderline tuberculoid lesion H and E (Hematoxylin and eosin). Original magnification ×40, (b) granulomas composed of the so-called immature epithelioid cells, histiocytes, and scant lymphocytes. H and E original magnification ×400

to patches to plaques to nodules [Figure 6a] cases with similar lesions, but more shiny and distributed in symmetrical pattern were categorized into LL [Figure 7]. Cases of LL showed classic morphology with very high bacillary index [Figure 8].

Seven out of twelve cases of clinically diagnosed cases of BB revealed the presence of granulomas comprised predominantly of foamy macrophages with scattered epithelioid cells. Granulomas were present in 66% of the cases. One case showed epidermal involvement by granulomas. However, the nature of the histiocytes and bacillary index of 2 helped in classifying it into BB as opposed to TT which classically shows epidermal involvement. The lymphoid infiltrate was rather more dense

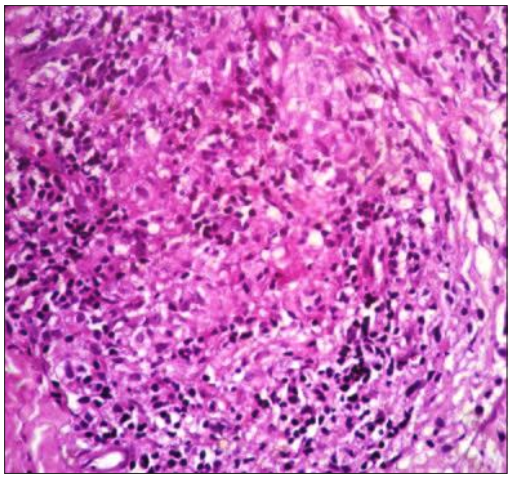

Figure 6: Patient clinically diagnosed as borderline lepromatous showing asymmetrically distributed papules and nodules over the left flank, (b) granulomas composed of macrophages and showing only occasional epithelioid cells. There is a denser infiltrate of lymphoid cells throughout the granuloma as compared to borderline (Figure 5b) hematoxylin and eosin original magnification ×400

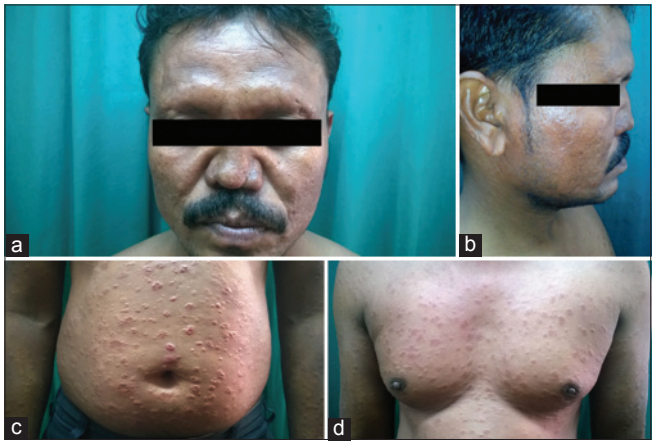

Figure 7: (a) Classical case of lepromatous leprosy leprosy showing infiltration of skin of forehead with madarosis, (b) patient had depressed nasal bridge and mild ear lobe infiltration, (c and d) numerous plaques and papules distributed symmetrically over the trunk and both upper limbs

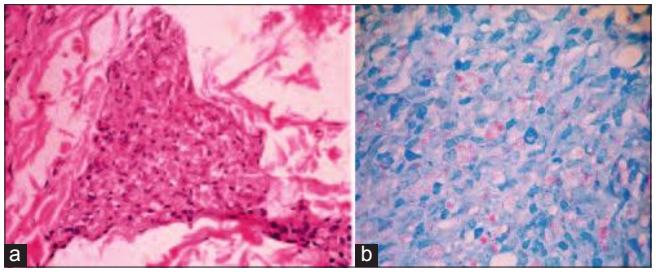

Figure 8: (a) Lepromatous leprosy granuloma composed of histiocytes, many of them showing vacuolated cytoplasm. Granulomas lack lymphoid infiltrate representing the second trough after borderline in the degree of lymphoid population. Hematoxylin and eosin original magnification ×400, (b) Fite stain revealed a bacillary index of 6. Original magnification ×1000

than in BB [Figure 6b]. The rest of the five cases showed features consistent with those of BT.

Indeterminate cases numbered 11, of which 9 were clinically diagnosed as IL and 2 as BT.

The definitive diagnosis of IL depended on the presence of acid-fast bacilli with nerve lesion. Histopathologically, a diagnosis of leprosy was also even in the absence of bacilli when perineural/periadnexal lymphocytic infiltrates were present in the biopsy, especially in patients from endemic regions [Figure 9].

We encountered 7 cases of clinically diagnosed histoid leprosy, of which 5 were LL and 3 were histoid histopathologically. Histopathology of histoid leprosy showed spindle cell proliferation of macrophages resembling a storiform tumor. The stain for leprae organisms showed huge clumps of bacilli arranged like sheaves of wheat [Figure 10].

The patient diagnosed as pure neuritic leprosy had no skin lesions as the definition demands. He had involvement of multiple nerves in both upper and lower limbs. Histopathology revealed the presence of foamy histiocytes and a high bacillary load within the substance of the nerve [Figure 11].

Discussion

RJ in their seminal paper classified leprosy based on combination of clinical and histopathological features into five categories as TT, BT, BB, BL, and LL. The outcome of this classification system was the categorization of the patients based on their immunological response to leprosy. In 1982, the World Health Organization advocated the use of two separate regimens for the treatment of leprosy based on the RJ classification system into paucibacillary (PB) group (including TT and BT) and multibacillary (MB) group including (BB, BL, and LL) with treatment being longer in the latter. The current treatment protocol, however, depends on counting of the lesions (Less than or equal to five lesions-PB, more than five-MB).[4-6]

It has been estimated that following of the latter protocol has resulted in risk of undertreatment of 38-51% of the leprosy cases, specifically in those with lesions numbering <5. A histopathological evaluation of skin lesions in a suspected case of leprosy is therefore very much desirable. This entails a high level of diagnostic proficiency in the reporting pathologist on whom the treatment might ultimately depend [6].

In our series, the accuracy of clinical diagnosis of leprosy was 92.4%. The rest of the cases were negative for leprosy. The evidentiary information obtained which helps in ruling out leprosy and consequently its social stigma and prolonged treatment is in fact one of the most important indications for performing a biopsy in a clinically suspected case of leprosy [Table 4].

The polar forms of tuberculoid and LL comprised 25% of total number of cases where the borderline types were the majority and the indeterminate leprosy (IL) the least common category of leprosy. This finding is similar to those observed by Nadkarni and Rege [11].

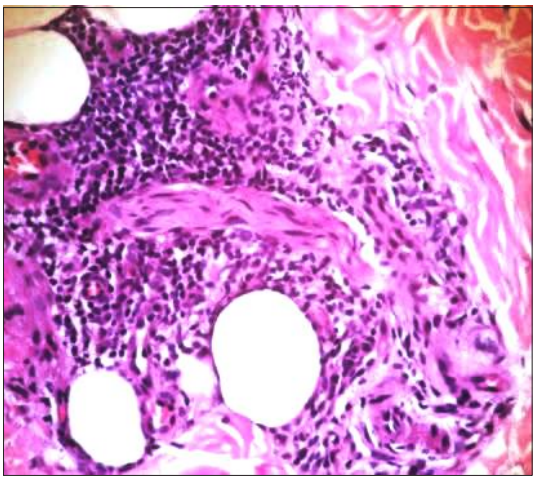

Figure 9: Perineural lymphocytic infiltrate is a clue to leprosy in otherwise indeterminate cases. Hematoxylin and eosin. Original magnification ×400

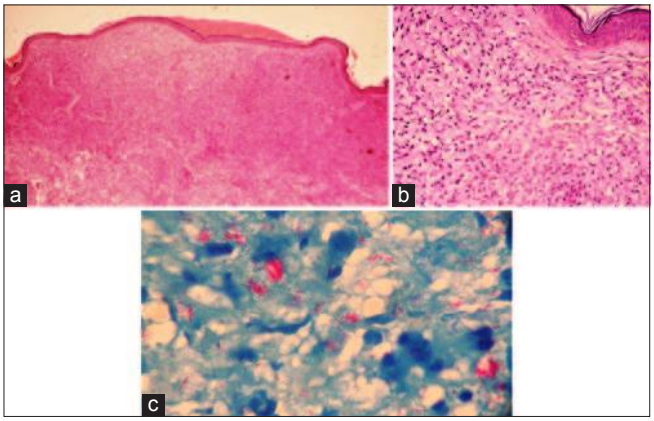

Figure 10: (a) Skin biopsy from one of the nodules from a case of histoid leprosy reveals a well-defined Grenz zone beneath which there are sheets of histiocytes the spindle shape of which can just be discerned. Hematoxylin and eosin (H and E) original magnification ×40, (b) section showing aggregates of spindle-shaped histiocytes H and E original magnification ×400, (c) Fite stain reveals acid-fast bacilli in classical sheaves of wheat arrangement. Original magnification ×1000

Tuberculoid Leprosy

The concordance between clinical and histopathological diagnosis for TT (92.4%) was on the higher side as compared to other similar studies where the concordance rates ranged from around 24% to nearly 95% [Table 5]. The histopathological diagnosis of TT is rather more straightforward than the other categories owing to being one of the polar forms.

Three of the cases diagnosed clinically as TT were categorized histopathologically into the BT. This shift of one group is understandable as the clinical and histopathological features of TT and BT overlap. The majority of TT and BT have <5 lesion, and since treatment would depend on the status of the slit skin smears, this was considered to be a minor discrepancy. The advantage of distinguishing TT and BT histopathologically is in the fact that it alerts the treating clinician to possibility of a Type 1 reaction that can occur once treatment is initiated in the latter category of patients [18,19].

When in doubt, we have observed the presence of epidermal erosion to be a very useful characteristic in distinguishing TT from BT as this feature excludes the latter [Figure 3].

Table 4: Comparison of agreement in our study as compared to similar studies

Present study	Ridley *et al*. [4]	Santos *et al*. [7]	Suri *et al*. [8]	Sharma *et al*. [9]	Shivaswamy *et al*. [10]
91.7%	68.3%	84.8%	75.5%	53.5%	74.7%

BT

As in other studies, BT constituted a major chunk in our study [16]. Concordance for BT in our study was the least when compared to that in other categories. This is a unique feature as other similar studies have obtained the better concordance rates in BT than in other categories [11,12,17].

We observed minor discrepancy (shift of one group on either side) in 4 cases (3 TT and 1 BB) and major discrepancy in six cases (2 LL, 2 IL, and 2 negative).

Histopathological examination in these discrepant cases was invaluable. It helped in ruling out leprosy in two suspected cases. Two of the cases with histopathological features of LL had lesions of only the plaque type and were <5 in number. These patients would under the current protocol be categorized under the PB regimen. Histopathological findings, however, aided in the correct classification of these patients both of whom are currently undergoing the MB regimen.

The concordance rate for the mid-borderline leprosy (BB) in our study was the highest (97.8%). This is in contrast to the other studies which quote either the least concordance in this category [9] or a concordance among the lowest [14,11]. This could be explained by the fact that we received only three cases clinically suspected and histologically conforming to the diagnosis of BB whereas the others had substantially more number.

The concordance rates of BL (92.6%) are comparable with those of Nadkarni and Rege [11]. However, when compared to other studies, it is significantly higher [12,16].

When compared to the rates in other categories, however, concordance rate is lower. It is known the borderline categories (BT, BB, and BL) are immunologically unstable. Among the three, BB is the least stable. Shifting of the cases from one category to another is common. It does not follow, however, that the histopathological findings will correspond exactly to the category at a given point of time as the morphology can precede or succeed the clinically observable changes so much so that the features of each of these classes can be present in different biopsies in a single patient and also in serial sections of biopsies of the same lesion. Hence, discrepancy in the borderline categories is not only observed but also to be expected [18,19].

Table 5: Concordance rates for TT, BT BB, BL, LL, and IL in our study in comparison with other studies

Leprosy class	Present study	Jerath and Desai [12]	Bhatia *et al*. [13]	Nadkarni and Rege [11]	Kar *et al*. [14]	Kalla *et al*. [15]	Moorthy *et al*. [16]	Manandhar *et al*. [17]	Shivaswamy et al. [10]
TT (%)	92.4	74.5	50	97	87.5	76.7	46.15	24	56
BT (%)	82	64.7	77	95	60.9	44.2	66.6	63.15	64.1
BB (%)	97.8	53.8	25	89	54.5	37	50	0	50
BL (%)	92.6	28.5	43	87	53.8	43.7	70	57.4	73.3
LL (%)	96.8	61.5	91	98	71.4	75.6	80	57.1	84.2
IL (%)	93.8	88.8	35	-	81.2		20	0	50

BB: Borderline, BL: Borderline lepromatous, LL: Lepromatous leprosy, IL: Indeterminate leprosy

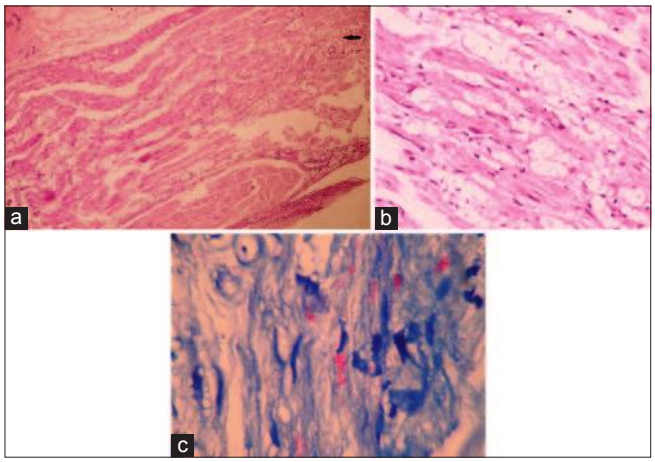

Figure 11: (a) Nerve biopsy from a case of neuritic leprosy showing mildly edematous nerve. With infiltration of foamy histiocytes within the nerve (arrow), (b) high power view of the nerve with collection of histiocytes having vacuolated cytoplasm. Hematoxylin and eosin original magnification ×400, (c) globi of lepra bacilli seen within the foamy cells. Original magnification ×1000

IL was identified by RJ as those cases in which the histopathological and clinical features are sufficient for diagnosis of leprosy but not for classification of the type as it was an early and transitory stage of leprosy found in persons, whose immunological status was yet to be determined [5,20,21].

We received 13 clinically diagnosed cases of IL, of which 12 were confirmed to be leprosy with 10 of them categorized into IL and one each into BT and BB. The proportion of cases diagnosed is similar to those observed by Nadkarni and Rege and Sharma *et al*. [9,11]. In two of the cases of BT, we failed to find granulomas, but histopathological features suggestive of leprosy were present. This further emphasizes the asynchrony of the temporal relationship between the clinical and the histopathological features of leprosy which requires a careful clinical and histopathological correlation to avoid overlooking the subtle features indicative of leprosy.

The original definition of pure neuritic leprosy required the absence of skin lesions along with involvement is of single or multiple nerves with sensory loss in the areas of distribution of the nerves. Studies on the histopathology of leprosy have demonstrated features suggestive of all the categories as defined in the RJ classification. With the exclusive presence of foamy histiocytes and a high bacillary load, our case would belong to the LL group [22].

Histopathological examination of skin biopsy is recommended in all clinically suspected cases of leprosy for accurate diagnosis as well as to avoid undertreatment of cases of MB especially in the current post-elimination era. Borderline cases represent majority of the lesions of leprosy and must receive special consideration due to their unstable immunologic status. The high rates of concordance in our study are indicative of the continuing expertise of our clinical colleagues and a good clinicohistological correlation with strict adherence to diagnostic criteria.

ACKNOWLEDGMENTS

We would like to acknowledge with gratitude Dr. Ramesh M. Bhat, Professor, Department of Dermatology, Father Muller Medical College for providing us with the clinical photographs.

REFERENCES

1. World Health Organization. Leprosy, 2016. Available from: http://www.who.int/mediacentre/factsheets/fs101/en/. [Last cited on 2016 Feb 09].
2. National Leprosy Eradication Programme, 2013. Available from: http://www.nlep.nic.in/about.html. [Last cited on 2016 Mar 22].
3. National Leprosy Eradication Programme, 2013. Available from: http://www.nlep.nic.in/pdf/MO%20training%20Manual.pdf. [Last cited on 2016 Mar 22].
4. Ridley DS, Jopling WH. Classification of leprosy according to immunity. A five-group system. Int J Lepr Other Mycobact Dis 1966;34:255-73.
5. Ridley DS, Jopling WH. A classification of leprosy for research purposes. Lepr Rev 1962;33:119-28.
6. Pardillo FE, Fajardo TT, Abalos RM, Scollard D, Gelber RH. Methods for the classification of leprosy for treatment purposes. Clin Infect Dis 2007;44:1096-9.
7. Santos S, Teles P, Neto M, Oscar F. Evaluation of agreement between clinical and histopathological data for classifying leprosy. Int J Infect Dis 2012;17:189-92.
8. Suri SK, Iyer RR, Patel DU, Bandil S, Baxi S. Histopathology and clinico-histopathological correlation in Hansen's disease. J Res Med Den Sci 2014;2:37-44.
9. Sharma R, Sharma A, Goswsami K, Bardwaj S. Clinico-histopathological correlation in leprosy. J K Sci 2008;10:120-3.
10. Shivaswamy KN, Shyamprasad AL, Sumathy TK, Ranganathan C, Vidushi A. Clinico histopathological correlation in leprosy. Dermatol Online J 2012;18. Available from: http://www.escholarship.org/uc/item/. [Last accessed on 2016 Mar 24].
11. Nadkarni NS, Rege VL. Significance of histopathological classification in leprosy. Indian J Lepr 1999;71:325-32.
12. Jerath VP, Desai SR. Diversities in clinical and histopathological classification of leprosy. Lepr India 1982;54:130-4.
13. Bhatia AS, Katoch K, Narayanan RB, Ramu G, Mukherjee A, Lavania RK. Clinical and histopathological correlation in the classification of leprosy. Int J Lepr Other Mycobact Dis 1993;61:433-8.
14. Kar PK, Arora PN, Ramasastry CV, Sayal SK, Dhaka RS.

Clinicopathologica study of macular lesions in leprosy. Indian J Lepr 1994;66:435-42.
15. Kalla G, Salodkar A, Kachhawa D. Clinical and histopathological correlation in leprosy. Int J Lepr Other Mycobact Dis 2000;68:184-5.
16. Moorthy BN, Kumar P, Chatura KR, Chandrasekhar HR, Basavaraja PK. Histopathological correlation of skin biopsies in leprosy. Indian J Dermatol Venereol Leprol 2001;67:299-301.
17. Manandhar U, Adhikari RC, Sayami G. Clinico-histopathological correlation of skin biopsies in leprosy. JPN 2013;3:452-8.
18. Parakh R, Mulchandani V, Parakh KK. Clinico-histopathological correlation in leprosy - A tertiary care hospital based study at Udaipur. Int J Sci Res 2015;4:56-8.
19. Sampaio EP, Sarno EN. Expression and cytokine secretion in the states of immune reactivation in leprosy. Braz J Med Biol Res 1998;31:69-76.
20. Jopling WH, McDougall AC. The disease. In: Handbook of Leprosy. 5th ed. New Delhi: CBS Publishers and Distributors; 1996. p. 10-53.
21. Job CK, Baskaran B, Jayakumar J, Aschhoff M. Histopathologic evidence to show that indeterminate leprosy may be a primary lesion of the disease. Int J Lepr Other Mycobact Dis 1997;65:443-9.
22. Rao PN, Suneetha S. Pure neuritic leprosy: Current status and relevance. Indian J Dermatol Venereol Leprol 2016;82:252-61.

Source of Support: Nil, Conflict of Interest: None declared.