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Original Article

Clinicohistopathological correlation of leprosy

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ABSTRACT

Background: Leprosy is a chronic infectious granulomatous disease caused by Mycobacterium leprae. It is a spectral disease which is classified into five groups according to Ridley and Jopling based on clinical, histological, microbiological and immunological criteria. Adequate clinical information combined with bacilloscopy and histopathology is helpful not only in classification of different types of leprosy but also useful for management of the cases.

Materials and Methods: 50 cases of leprosy were examined and clinical data was recorded. Slit skin smears were stained with Ziehl Neelsen stain. Skin biopsy was stained with Hematoxylin-Eosin stain and Fite Farraco stain was performed to demonstrate acid fast bacilli. All patients were classified according to Ridley & Jopling classification. Clinico-histopathological correlation was done. Statistical analysis was done using SPSS (Statistical Package for the Social Sciences) 16.0.

Results: Most common histological type of leprosy was tuberculoid leprosy seen in 19(38%) cases followed by indeterminate leprosy. Overall clinico-histopathological correlation was seen in 39.58%. The correlation was highest in indeterminate and histoid leprosy (100%) followed by lepromatous leprosy (66.66 %%) and tuberculoid leprosy (50%). Slit skin smear showed bacilli in 12 out of 48 cases (25%) while biopsy showed bacilli in 16 out of 48 cases (33.3%).

Conclusion: In the present study, clinical diagnosis did not correlate with histopathological diagnosis significantly (p value=0.04159). The study emphasizes the role of histopathological and bacilloscopic examination to aid the clinical diagnosis for accurate typing of leprosy cases then better management of the patient.

INTRODUCTION

Leprosy is a chronic granulomatous disease caused by Mycobacterium leprae. It is characterized by peripheral nerve damage and cutaneous lesion most of the time but eyes, mucosa of upper respiratory tract, muscle, bone, testes may be affected. The disease is often referred to as oldest disease known to mankind and Hansen in 1873 for the first time isolated mycobacterial as a cause of disease.[1]

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Leprosy is a major public health problem and worldwide prevalence has increased from 1 per 10000 population in 2002 to 2.3 cases per 10000 population in 2004.[1] Nepal, a known endemic country, has achieved elimination with prevalence rate of 0.89 per 10000 populations.[2]

Mycobacterial infection first causes a wide array of cellular immune responses. These immunological events elicit the second part of the disease as peripheral neuropathy with potentially long term consequences. The social and psychological effects of leprosy as well as its visible sequel

have resulted in historical stigma associated with leprosy.[3]

The disease is a spectral one and broadly manifests itself in two polar forms, namely, Lepromatous leprosy and tuberculoid leprosy, lying at two ends of a wide spectrum of the disease. Between these two polar forms lie the borderline and intermediate forms of disease.[4] The clinical presentation can vary from an insignificant skin lesion to extensive disease causing profound disability and disfigurement by damaging peripheral nerves, eyes and bones.[3] The occurrence of any one type of leprosy in any patient is dependent on the host immune response. Tuberculoid end of spectrum is result of an intense cellular response that results in localizing the infection.[4] Individuals with minimal cellular immune response have the lepromatous form of the disease, which is characterized by extensive skin involvement and disseminated disease. Skin lesions are infiltrated nodules and plaques, and nerve involvement tends to be symmetric in distribution in multibacillary leprosy.[5]

Clinical manifestation gives recognition only to gross appearances of the lesions, while the parameters used for the histopathological classification are well defined, precise and also take into account the immunological manifestations which enable it to successfully bridge the pitfalls in leprosy diagnosis.[6]

In 1966, Ridley and Jopling devised the classification of leprosy as a spectrum of disease based on combination of clinical, microbiological, histopathological and immunological indices: tuberculoid (TT), borderline tuberculoid (BT), mid borderline (BB), borderline lepromatous (BL) & lepromatous (LL).The term borderline is used to denote patterns that share some features of both tuberculoid and lepromatous leprosy. Indeterminate and pure neural forms fall outside this classification.[3] But Indian classification incorporates both indeterminate and neural forms of leprosy.[1] In 1982, WHO recommended an additional classification of Paucibacillary(PB) and multibacillary(MB) types of leprosy for operational purposes.[7]

Histopathology provides confirmatory information for suspected cases which can be helpful in clinical practice or epidemiological studies and helps in classification so do provide information of progression and regression of disease under treatment.[6]

Clinico histopathological examination of leprosy assumes a pivotal role for early diagnosis.[8] Early recognition and treatment limits the damage caused by the disease and renders the person non-infectious and remains the cornerstone of leprosy control.[9]

Present study was conducted for clinical and histopathological correlation of skin biopsy which is imperative for diagnosis and classification of disease.

MATERIALS AND METHODS

The present study is a descriptive study conducted at Department of Pathology, College of Medical Sciences, Bharatpur, Nepal from October 2010 to April 2012. Fifty clinically diagnosed cases of leprosy were included in the study irrespective of age and sex. All cases with newly clinically diagnosed leprosy regardless of age, sex, and socioeconomic status were included in the study. Cases showing features of reactional leprosy and who had received any specific therapy for leprosy in the past were excluded from the study.

An informed consent was taken from all patients enrolled in the study. A detail clinical history of the patient was recorded; nature of the lesion, hypoesthesia/anesthesia at the site of the lesion and cutaneous nerve thickening was recorded on a pre-designed proforma. The clinical classification was made under supervision of dermatologist.

The clinical diagnosis was based on finding at least one of the three cardinal signs of the disease: anesthetic skin lesion enlarged peripheral nerve trunks or acid fact bacilli in a slit skin smear.

• Slit skin smears were taken from 6 regions in all the cases as following[10]:

o 1 smear from each earlobe and each eyebrow

o 2 smears from the lesion

• Wade fite stain was done to detect Acid fast bacilli as per standard protocol.[11]

Excisional skin biopsy of 5 mm diameter was taken from the lesion and was kept in 10% buffered formalin solution and fixed for 12 hours. The tissue was processed as a routine in tissue processor.[12] The slides were stained with Hematoxylin and Eosin as per standard protocol.[13] The slides were also stained with Fite Farraco stain for detection of Acid fast bacilli. Then the slides were examined under microscope and histopathological findings were noted. Number of bacilli and it morphology were looked for and noted. Accuracy of clinical diagnosis was assessed by comparing the results with histopathological and bacilloscopic results.

Data analysis was done using SPSS 16.0 and MS Excel file. P value was calculated using chi-square test for clinical and histopathological correlation and to compare bacillary index and morphological index of slit skin smears with that of biopsy.

RESULTS

Fifty new cases of clinically diagnosed cases of leprosy

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Table 1: Clinico-histopathological correlation of leprosy

Clinical diagnosis	No leprosy	TT	BT	BB	BL	LL	HL	IL	Total
TT	2	10	2	1	1	0	0	6	22
BT	0	7	1	1	0	0	0	3	12
BB	0	1	1	1	0	0	0	0	3
BL	0	1	0	1	0	2	0	0	4
LL	0	0	0	0	1	4	1	0	6
HL	0	0	0	0	0	0	2	0	2
IL	0	0	0	0	0	0	0	1	1
Total	**2**	**19**	**4**	**4**	**2**	**6**	**3**	**10**	**50**
Parity %age		**45.4**	**8.3**	**33.3**	**0**	**66.6**	**100**	**100**	
P value= 0.04159									

TT-Tuberculoid, BT-Borderline Tuberculoid, BB-Mid Borderline, BL-Borderline Lepromatous, LL- Lepromatous, HL- Histoid, IL- Indeterminate

Table 2: Disagreement in Clinical and Histopathological Diagnosis

Clinical diagnosis	No. of cases	Total agreement	Minor disagreement	Major disagreement
TT	20(41.67%)	10(50%)	8(40%)	2(10%)
BT	12(25%)	1(8.33%)	8(66.66%)	3(25%)
BB	3(6.25%)	1(33.33%)	1(33.33%)	1(33.33%)
BL	4(8.33%)	0(0%)	3(75%)	1(25%)
LL	6(12.5%)	4(66.66%)	2((33.33%)	0(0%)
HL	2(4.17%)	2(100%)	0(0%)	0(0%)
IL	1(2.08%)	1(100%)	0(0%)	0(0%)
Total	**48(100%)**	**19(39.58%)**	**22(45.84%)**	**7(14.58%)**

TT-Tuberculoid, BT-Borderline Tuberculoid, BB-Mid Borderline, BL-Borderline Lepromatous, LL- Lepromatous, HL- Histoid, IL- Indeterminate

were included in the study during a period of October 2010 to March 2012. The age distribution of patients varied between 11-69 years. The mean age was 38.14 years (±16.35). Majority of the patients were between the age groups of 15-30 years followed by 46-60 years. There was slight mile preponderance with male to female ratio of 1.3:1. The most common histopathological diagnosis in both sex were TT (tuberculoid leprosy) with 11cases (22%) male and 8 cases(16%) female. Five (10%) male and 1(2%) female had LL (lepromatous leprosy). 1(2%) male and 1(2%) female, were diagnosed as chronic dermatitis and kept under unclassified category.

The most common pattern of skin lesion was plaque in 41(82%) cases followed by nodule in 4(8%) cases. 3(6%) cases showed macule/papule and 2(4%) cases had all three types of lesions. The lesion was common in the upper extremities consisting of 15(30%) cases followed by lesions all over body in 13(26%) cases. 10(20%) cases had lesions on lower extremities and 8(16%) had over head and neck area.

The commonest nerve involved was ulnar nerve in 13(26%) cases followed by radial and common peroneal nerve in 8% cases each. In 14% of cases, all the three nerves were involved, while in 12% of patients ulnar and radial nerves were involved. There was no nerve involvement in 10(20%) cases.

Thirty five (70%) cases had less than 5 lesions and 15(30%) cases had more than 5 lesions. Out of 35 cases with less than or equal to 5 lesions, 2(4%) had no leprosy, 17(34%) cases had tuberculoid leprosy, 10 (20%) cases had indeterminate leprosy, 3(6%) cases had borderline tuberculoid leprosy, 2(4%) cases had midborderline leprosy and 1(2%) had borderline lepromatous leprosy. Fifteen (30%) cases had more than 5 skin lesions. Out of these 15 cases, 6 (12%) cases had lepromatous leprosy, 3(6%) cases had histoid leprosy, 2(4%) cases had mid borderline leprosy, 2 (4%) cases had tuberculoid leprosy and 1(2%) case had borderline tuberculoid leprosy. Table 1 shows the clinic-histopathological correlation of leprosy.

Most common clinical type of leprosy was tuberculoid group of leprosy. Tuberculoid and borderline tuberculoid constituted 22(44%) and 12(24%) cases respectively followed by lepromatous leprosy constituting 6(12%) cases. Least number (2%) of cases was classified as indeterminate

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Table 3: Correlation on Bacillary index in tissue biopsy and in slit skin smear

Bacillary Index	No bacilli	1-10 bacilli/1-10HPF	1-10 bacilli/ HPF	10-100 bacilli/ HPF	100-1000 bacilli/HPF	>1000 bacilli/ HPF	Total
Biopsy	32	1	1	3	6	5	48
SSS	36	1	3	3	4	1	48
P value=0.506809							

leprosy. Most common histological type of leprosy was tuberculoid leprosy seen in 19(38%) cases followed by indeterminate leprosy constituting 10(20%) cases.

Histopathological features of leprosy were observed in 48 cases while other 2 cases showed histological features of non specific dermatitis. The distribution of cases on the clinical leprosy spectrum based on Ridley-Jopling scale revealed maximum cases of TT (n=19) followed by IL (n=10). In borderline group (BT+BB+BL), 4 cases belonged to BT, 4 to BB and 2 to Borderline lepromatous leprosy. Lepromatous leprosy consisted of 6 cases and HL consisted of 3 cases.

Maximum clinico-histopathological correlation was seen in IL (100%) and Histoid leprosy (100%) followed by LL (66.66 %%), TT (45.4%), BB (33.33%), BT (8.33%) and no agreement in Borderline lepromatous leprosy (0%).There was statistically significant correlation between clinical and histopathological diagnosis (P value <0.05).

Excluding 2 cases of chronic dermatitis, maximum clinico-histopathological correlation was seen in IL (100%) and Histoid leprosy (100%) followed by LL (66.66 %%), TT (50%), BB (33.33%), BT (8.33%) and no agreement in BL (0%) as shown in table-2. Overall concordance of diagnosis was seen in 39.58% cases.

On correlating clinical diagnosis with histological diagnosis, minor disagreement (difference of one group) was observed in BL cases with exception of one case of BL showing major disagreement (difference of two or more groups) while no disagreement in clinical and histological diagnosis was noted in clinically diagnosed cases of indeterminate leprosy and Histoid leprosy (Table 2). However major disagreement was seen in borderline spectrum ranging from 25% to 33.33%.

Thirty six out of 48 cases diagnosed histopathologically as leprosy showed no bacilli; none of the cases of IL, TT, BT and BB showed bacilli. 2 cases of BL and 1 case of HL showed 1-10 bacilli/HPF; 1 case of BB and 2 cases of LL showed 10-100 bacilli /HPF;3 cases of LL and 1 case of HL showed 100-1000 bacilli/HPF; 1 case of LL showed >1000 bacilli /HPF.

Thirty two out of 48 cases diagnosed histopathologically as leprosy showed no bacilli. 1case of TT showed 1-10 bacilli/HPF; 1 case of BB showed 1-10 bacilli/HPF and 3 case of BB showed 10-100 bacilli/HPF. 2 cases of BL and 4 cases of LL showed 100-1000 bacilli /HPF; 2 cases of LL and 3 case of HL showed >1000 bacilli /HPF. Correlation of bacillary index (BI) in tissue biopsy and in slit skin smear is shown in table 3. There was no statistically significant differences in the bacillary index of biopsy and slit skin smear (P value>0.05).

DISCUSSION

In the present study, cases were classified histopathologically according to Ridley-Jopling classification.[5] Additionally, indeterminate and histoid types were also included for analysis. Out of 50 cases, 48 (96%) cases showed histopathological evidence of leprosy and two cases had features of chronic dermatitis.

The age of patients varied between 11-69 years in our study. In our study, 4% of the cases were children; the youngest patient was 11 years old. Children below 9 years were reported to be least affected according to the study by Moorthy et al[14] while in a study by Sehgal et al, the incidence of leprosy among children was 10 percent.[15]

In the present study, male predilection was observed in both tuberculoid and lepromatous groups with M:F ratio of 1.4:1. Similarly, previous studies report increased prevalence of leprosy in male compared to female[6,14,16-20] but Varagas-Ocampo found females predominantly affected with tuberculoid leprosy while males were predominantly affected with lepromatous leprosy.[21]

The most common skin lesion seen in our study was plaques followed by nodules. Macules were found to be the most common skin lesions in studies done by Vargas-Ocampo and Mitttal et al[18,21]; but Sarkar et al[22] reported only 19 (12%) had macular lesion in their patients which is similar to our study. Nodules were seen in all the cases of histoid leprosy and in 66.6% cases of lepromatous leprosy.

The most commonly involved nerve was ulnar nerve in our study (26%) followed by radial and common peroneal nerve in 8% cases each. In 14% of cases, all the three nerves were involved, while in 12% of patients ulnar and radial nerves were involved. Studies by Kumar et al also had similar findings with involvement of radial nerve and common peroneal nerve and posterior tibial nerve in upper and lower

extremities respectively.[23] Karr et al found ulnar nerve to be the most commonly involved, followed by lateral popliteal nerve and posterior tibial nerve.[24]

In the present study,35 (70%) cases had less than 5 lesions of which 17 cases had tuberculoid leprosy, 10 cases had indeterminate leprosy, 3 cases had borderline tuberculoid leprosy, 2 cases had mid-borderline leprosy, 1 had borderline lepromatous leprosy and 2 had no leprosy. 15 (30%) cases had more than 5 lesions of which six had lepromatous leprosy, three had histoid leprosy, two cases had mid borderline and tuberculoid leprosy each and one had borderline tuberculoid leprosy.

WHO classified leprosy as paucibacillary to those having less than or equal to 5 skin lesions and as multibacillary to those having more than 5 skin lesions.[7] Skin examination alone may have missed out the cases and resulted in different treatment. A study by Norman et al (2004) reported that the sensitivity of WHO operational classification that classifies a patient with 6 or more lesions as multibacillary was 88.6% while the specificity was 86.7%.[25] Mehindiratta et al had only 74.6% cases correctly classified as multibacillary/ paucibacillary.[26]

Since 1966, the classification of leprosy by Ridley and Jopling into 5 subtypes (TT, BT, BB, BL, LL) based on clinical, histopathological and immunological features and bacteriological finding has been widely adopted by histopathologist and leprologist.[5] Despite having such an accurate classification, leprosy cases showed so many diversity between clinical and histopathological features.

The different clinical forms through which leprosy manifest, are accompanied by specific histopathological picture. Thus, towards TT end of spectrum, histopathology shows epitheloid cells, Langhans giant cells and lymphocytes while towards LL end of spectrum, there are more foamy macrophages.[5]

According to this classification, in the present study, the most common clinical subtype was tuberculoid leprosy followed by borderline tuberculoid leprosy consisting 22 (44%) cases and 12 (24%) cases respectively. Histopathologically, the most common classification made was tuberculoid leprosy constituting 19 (38%) cases. Clinically, only 1 (2%) case was classified as indeterminate leprosy while histopathologically, 10(20%) cases showed evidence of indeterminate leprosy. 2 out of 22 cases of clinically diagnosed tuberculoid leprosy showed no evidence of leprosy in histopathology.

Similar to the present study, Jha et al observed tuberculoid leprosy as the most common type of leprosy which constituted 57.5% cases.[20] Jindal et al had 90 (55.25%) patients in various spectrums of borderline disease followed by lepromatous and tuberculoid leprosy.[16] Bochud et al found borderline lepromatous (45.12%) cases followed by cases of borderline tuberculoid leprosy (29%).[19] The commonest histological type in a study by Sharma et al and Rao et al was borderline tuberculoid leprosy and that by Pandya et al was indeterminate leprosy.[6,8,27]

In our study, there was complete agreement between the clinical and histopathological diagnosis in 39.58% of the cases. Similar comparative studies by different authors showed complete agreement between clinical and histopathological diagnosis which ranged from 31.58% to 82%. Sarkar et al[22] showed 31.58% correlation in 150 cases; Sehgal et a1[5] had 33% correlation in 95 cases; Vargas-Ocampo[21] showed 42.9% correlation in 6000 cases. These findings were similar to our study. Sharma et al6 Mitra et al[28], Pandya et al[8], Moorthy et al[14] showed 53.44%, 57.16%, 58%, 62.63% correlation in their studies respectively. Similarly, Kalla et al[29], Ridley and Jopling[5], Jerath et al[30], Bhatia et al[31], Kar et al[32], Mittal et al[18] and Nadkarni et al[33] had clinico histopathological correlation in their studies ranging from 64.7% to 81.8 percent.

The disparity between clinical and histological observation is anticipated because the parameters used for the histopathological classification are well defined, precise and also take into account the immunologic response of the tissue, while the clinical classification gives recognition only to the gross appearances of the lesions which is due to the underlying pathological change.[6]

In the present study, clinico-histopathological correlation was better noted in indeterminate leprosy and histoid leprosy (100% each). Similarly highest percentage of agreement between clinical and histopathological diagnosis of indeterminate leprosy was observed by various authors.[6,22,30] However, in the present study, high percentage of agreement in indeterminate and histoid leprosy could be due to low sample size. After excluding indeterminate and histoid leprosy cases in the study, tuberculoid leprosy and lepromatous leprosy seemed to present the least problem for classification with 50% and 66.6% agreement respectively. Mathur et al, Moorthy et al, Bhatia et al and Nadkarni et al also found maximum correlation in lepromatous leprosy while Kar et al and Kalla et al found maximum correlation in tuberculoid group[14,29,31-34]

There was no complete correlation seen in borderline lepromatous cases while mid-borderline cases showed agreement in 1 out of 3 cases (33.33%) and borderline tuberculoid cases showed only 1 out of 12 cases (8.33%) diagnosed clinically. Bhatia et al, Kalla et al and Sharma et al found minimum correlation in mid-borderline leprosy.[6,29,31] Considering the data of present study and other comparative studies, we can say that maximum disparity is seen in borderline cases. Parity in polar group is maximum, because they are stable and shows fixed histopathology.[8]

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In the present study, maximum major disagreement was seen in mid borderline leprosy while minor disagreement was seen in borderline tuberculoid cases followed by tuberculoid cases. On correlating clinical diagnosis with histological diagnosis only minor disagreement was observed in 22 (45.84%) cases while major disagreement was observed in 7 (14.58%) cases. Ridley and Jopling had major disagreement in 25.6% cases and major disagreement in 6% cases.[5] Sharma et al had maximum minor disagreement in cases of tuberculoid leprosy and maximum major disagreement in mid borderline cases.[6]

Both tuberculoid and borderline tuberculoid leprosy overlap clinically, histologically and immunologically but differ only in degree and same is true for borderline lepromatous and lepromatous leprosy.[6] Clinically, both borderline tuberculoid and tuberculoid leprosy cases manifest with well defined lesions with partial or complete loss of sensation with or without thickened nerve and scanty acid fast bacilli. Histologically, they present with similar granulomatous reactions, so there is difficulty in differentiating the tuberculoid and borderline tuberculoid cases both clinically and histologically.[31]

Three cases diagnosed as borderline tuberculoid leprosy and 6 cases diagnosed as tuberculoid leprosy had features of indeterminate leprosy in histology. Mitra et al, Sehgal et al and Bhatia et al also found features of indeterminate leprosy in clinically diagnosed tuberculoid group of leprosy.[15,28,31] If a biopsy is taken at an early stage, more likely there can be discordance between clinical and histopathological observations.[6] There are also interobserver variation both clinically and histopathologically, so there could be overlap between different types of leprosy.[31]

The clinical and histopathological agreement of 39.58% obtained in the present study with p value=0.04159 (p value <0.05) is statically significant. This shows limitation of using a purely clinical system in the classification of leprosy patients without considering histopathological diagnosis. Correlation between clinical and histopathological classification has been the focus of permanent studies over the last few years. It has been emphasized to perform biopsies in all leprosy cases and to correlate biopsy results with those of the clinical diagnoses in order to improve classification and prognosis of patient. Confirmation of the leprosy diagnosis to determine the disease load in a given population and the correct clinical classification to determine the risk of patients developing incapacities are important motives for performing the histopathological examination.[35]

In slit skin smears, 36 out of 48 cases diagnosed histopathologically as leprosy showed no bacilli while in biopsy, 32 out of 48 cases diagnosed histopathologically as leprosy showed no bacilli. On correlating bacillary index (BI) in tissue biopsy and in slit skin smear, there is no statistically significant differences in the bacillary index of biopsy and slit skin smear with p value=0.506809 (P value>0.05).

More than 50% solid bacilli were seen in 12 cases in biopsy and only 9 cases in slit skin smear. Four cases showed <50% solid staining bacilli in biopsy and 3 cases in slit skin smear. On correlating morphological index (MI) in tissue biopsy and in slit skin smear, there is no statistically significant differences in the morphological index of biopsy and slit skin smear with p value=0.668071 (P value>0.05).

CONCLUSION

This study has demonstrated disparity in clinical and histopathological diagnosis of different types of leprosy. The highest parity was observed in indeterminate and histoid leprosy followed by lepromatous leprosy and tuberculoid leprosy and least parity in borderline tuberculoid leprosy. Lepra bacilli were better demonstrated in skin biopsy as compared to slit skin smears.

Histopathological examination of skin lesion is an important tool in the accurate classification of leprosy. Biopsies should be done in all cases of leprosy as clinical diagnosis alone may offer difficulty in accurate typing of leprosy leading to inappropriate treatment.

Correlation of clinical diagnosis with histopathological diagnosis and correlation of biopsy finding with bacillary index and morphological index helps to improve the classification, infectivity of patient, treatment with precision and prognosis of patient.

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