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A STUDY OF CONCORDANCE BETWEEN CLINICAL AND HISTOPATHOLOGICAL DIAGNOSIS IN CASES OF LEPROSY WITH RELEVANCE TO THERAPY

Pathology

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ABSTRACT

AIMS AND OBJECTIVES: To achieve the goal of WHO new global strategy of 2016-20 to decrease the case load, early and proper diagnosis for treatment and avoiding disability. Examination of a biopsy specimen of skin or nerve biopsies for histopathology can be a valuable aid for reaching confirmatory diagnosis of leprosy and its subtypes, differential diagnosis, prognosis of the disease and assessment or regression of the disease in patient under treatment and also for research, especially in early and borderline cases. The aim of this study was to correlate histopathological diagnosis of skin biopsies with clinical diagnosis of leprosy. This study was conducted to seek out and highlight the efficacy of the test and therefore its importance in current diagnostic scenario. **MATERIALS AND METHODS:** The retrospective study was carried out on the skin biopsies from untreated cases of leprosy seen in the Department of Dermatology and reported in the histopathology section of the Department of Pathology, School of Tropical Medicine, Calcutta between August 2016 to June 2019. HE sections of skin biopsies of all the cases of leprosy were examined for Epidermal atrophy, epithelioid granulomas, number & distribution of lymphocytes, histiocytes & foam cells; Infiltration of nerves, blood vessels and adnexa; Grenz zone. Sections stained with ZN were examined for lepra bacilli in all cases. Histopathological findings were graded into (TT), (BT), (BB), (BL) and (LL) according to Ridley and Jopling scale. Clinical diagnosis of the leprosy cases (as provided by department of Dermatology) using Ridley & Jopling scale was correlated with the results of histopathologic examinaton of their respective biopsies. **RESULTS:** Out of total cases in the OPD over Aug 2016 to June 2019,115 were sent for biopsy with conclusive clinical diagnosis of Leprosy out of which 45 cases came with the positive diagnosis of leprosy out of which TT(12) , BT(12), BB(3), BL(2),LL(8), Histoid(8). In 2016-17 the accuracy of clinic-histopathological correlation was 35.4% ,41.3%in 2018 ,36.36% till mid 2019 . The discrepancy with the HPE refuting clinical diagnosis was 48.38% in 2017 ,58.62% in 2018 ,63.63% in mid 2019}. Histoid leprosy and ENL were 10 out of 31 cases in 2018-19 while 2cases were histopathologically diagnosed as leprosy despite having Sarcoidosis / Gr. Annulare clinically. **CONCLUSION:** Although the clinico-histopathological agreement in this study leaves much to be desired for prompt diagnosis, the disparity in correlation does decrease the chances of false positives and helps in better finalising the diagnosis for better treatment, Prognosis, follow-up and monitoring of the diseases are also aided by correct histopathological diagnosis especially in case of early and borderline cases of leprosy.

KEYWORDS

Leprosy, Histopathology, Fite Farraco stain,Cilinical diagnosis

INTRODUCTION

Leprosy , also known as Hansen's disease is a chronic granulomatous infectious disease caused by Mycobacterium leprae that primarily affects skin and peripheral nerves. It is a very slowly progressive disease and clinicopathological manifestations depends on the immune status of the host.[1]

Leprosy is a very ancient disease and its references are found in Indian, Chinese and Egyptian literature. Leprosy was named as "Kushtha" in Manu smriti in ancient Vedic writings. Leprosy is a major public health problem in India and in spite of available simple and effective treatment it is still difficult to identify early cases as it is related with a social stigma and complications like deformities associated with it.[2]

National leprosy control programme was launched in India in 1955 with single drug dapsone. It was switched to multidrug therapy in 1982 following recommendation of WHO and there was remarkable decline in disease burden. In 1993 the National Leprosy Elimination programme (NLEP) was initiated by WHO with a goal to decrease prevalence rate of leprosy below 1 case/10000 population. India achieved the goal in 2005 with prevalence rate of 0.95/10000 population except2 states/UT Chhattisgarh and Dadra& Nagar Havelli.[3,4] Epidemiological situation as on March 2015 show prevalence rate at national level 0.69/10000 population and annual new case detection rate (ANCDR) of 9.74/one lakh population. India contribute 58.8% of new cases detected globally.[5] Current data from WHO (2019)show WHO's South East Asia region reported 71% of all global cases by 2 countries- India and Indonesia. Detection of leprosy cases in children is considered as an indication of recent transmission of infection in community. In 2018 WHO's South East Asia region accounted for 74% of all new paediatric cases globally.[6,7]

In 2016 WHO has launched a global strategy '2016-2020' to accelerate towards a leprosy free world and to avoid disability especially in children in endemic area. [8,9]

To achieve WHO new global strategy to reduce case load it is essential for early and proper diagnosis by clinico histopathological correlation of leprosy cases.

Histopathological examination of skin or nerve biopsies and demonstration of acid fast bacilli in histopathological section and in slit skin smear aid in diagnosis of leprosy.

Examination of a biopsy specimen for histopathology can be valuable aid to reach confirmatory diagnosis and its subtypes, differential diagnosis and prognosis of the disease and assessment or regression of the disease in patient under treatment and also for research.[3]

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 early diagnosis.[10]

Ridley and Jopling in 1974 suggested a classification system which employed correlation of clinical & histopathological status.[11]

Present study had been conducted for clinical and histopathological correlation of skin biopsy to arrive at a definitive diagnosis of leprosy and to classify the types of disease. The aim of this study was to correlate histopathological diagnosis of skin biopsies with clinical diagnosis of leprosy or suspicious for leprosy with negative skin slit smears.

MATERIALS AND METHODS

The retrospective study was carried out on the skin biopsies sent from Department of Dermatology to the Department of Pathology with clinical diagnosis specially slit skin smear negative and untreated cases of leprosy or with differential diagnosis of leprosy along with other skin diseases like sarcoidosis, tuberculosis etc. All the biopsies are examined and reported in the histopathology section of the Department of Pathology, CSTM between August 2016 to June 2019.

Skin biopsy was performed on OPD basis and tissue obtained was immediately fixed in 10% neutral buffered formalin. Then the skin biopsies were processed routinely , stained with Haematoxylin and eosin stain and modified Fite Farraco stain in all cases.

Stained sections of skin biopsies of all the cases of leprosy were examined for:

a) Epidermal atrophy, epithelioid granulomas, number & distribution of lymphocytes, histiocytes & foam cells.
b) Infiltration of nerves, blood vessels and adnexae.
c) Grenz zone.

Sections stained with modified Ziehl Neelsen's stain were examined for lepra bacilli in all cases. Histopathological findings were graded into (TT), (BT), (BB), (BL) and (LL) according to Ridley and Jopling scale.

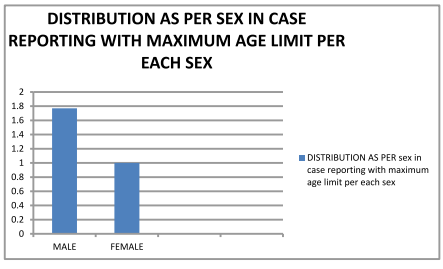
Clinical diagnosis of the leprosy cases (as provided by department of Dermatology) using Ridley & Jopling scale was correlated with the results of histopathological examination of their respective biopsies. Clinical examination was thoroughly done and one or more of the following cardinal features of different type of lesions like hypopigmented patches, plaque, papules, nodules, nerve infiltration noted. Partial or total loss of cutaneous sensation in affected area.

and Presence of thickened peripheral nerves.

RESULTS

This study was conducted on skin biopsies of 115 clinically diagnosed untreated cases of leprosy in the Department of Pathology. The study show 74 (64.34%)males and 41(35.65%) females and male: female ratio was 1.77:1.The majority of male patient belonged to the average age of 39yrs with maximum of 72 yrs. Average age of female patients was 31 yrs with maximum of 66 yrs. Age group of all patient ranged from 19yrs to 72 yrs.[Table-1]

Table 1: Age and sex distribution



Out of total 686 cases in the OPD over Aug 2016 to June 2019, (311 in 2016-17, 201 in 2017-18 and 174 in 2018-19June) a total of 115 cases (29 in 2016-17, 55 in 2017-18, and 31 in 2018-19 June) were sent for biopsy with conclusive clinical diagnosis of Leprosy (without Ridley-Jopling classification).

Table-2: Year wise distribution of clinically diagnosed cases

TOTAL CACSES CLINICALLY DIADNOSES AS LEPROSY &SENT FOR BIOPSY	NUMBERS(n)
2016-17	29
2017-18	55
2018-19 up to June'19	31

Atypical cases namely Histoid leprosy and ENL reactions were 10 out of 31 cases in 2018-19. While Incidentally 3cases were histopathologically diagnosed as leprosy despite having clinical diagnosis as Sarcoidosis / Granuloma Annulare /Lupus vulgaris . Cases with no parity in clinico-HPE correlation like out of 67 cases over 3 years with no parity in clinical and histopathological correlations. 32 were histologically diagnosed as Sarcoidosis , 21 were histologically diagnosed as lupus vulgaris, 4 were histologically diagnosed as Granuloma Annulare , 5 were histologically diagnosed as chronic granulomatous inflammatory reactions and 5 were descriptive.

Table-3 Distribution of cases of leprosy & other skin diseases

Histological type	Number of cases	%age
TT	12	10.43%
BT	12	10.43%
BB	3	2.60%
BL	2	1.73%
LL	8	6.95%
Histoid	8	6.95%
ENL	3	2.60%
Sarcoidosis	32	27.82%
Lupus Vulgaris	21	18.26%
Granuloma Annulare	4	3.47%
Granulomatous lesion	5	4.34%
Descriptive	5	4.34%
Total	115	100%

It has been observed that 45 cases (39.13%) was correlated with clinical diagnosis where 67 cases(58.26%) was discordant. In the present study TT and BT was the most common type of leprosy.

In 2016-17 the accuracy of clinico- histopathological correlation was 35.4% which rose to 41.3%in 2018 and descended to 36.36% till mid 2019 . But the discrepancy in the histopathological findings and the clinical diagnosis with the HPE refuting clinical diagnosis was 48.38% in 2017 which rose to 58.62% in 2018 and steadily climbed to 63.63% in mid 2019.

Table 4

CASES SENT FOR BIOPSY	CASES WHERE CLINICAL DD MATCHED WITH HPE AND DIAGNOSED WITH SPECTRUM OF LEPROSY	CASES WITH CLINICAL DD PREDICTED LEPROSY BUT WAS REFUTED BY HPE
2016-17 29	12 OUT OF 29 = 41.3%	17 OUT OF 29 = 58.62%
2017-18 55	20 OUT OF 55 = 36.36%	35 OUT OF 55 = 63.63%
2018-19(JUNE) 31	11 OUT OF 31 = 35.4%	15 OUT OF 31 = 48.38%

Out of the 115 cases sent for HPE over 3years, 48 cases came with the positive diagnosis of leprosy out of which TT(12) , BT(12), BB(3), BL(2),LL(8), Histoid(8),ENL(3).

Table 5 -cases Divided In Ridley- Jopling Scale

YEAR	TUBERCULOID	BORDERLINE TUBERCULOID	BORDERLINE BORDERLINE	BORDERLINE LEPROMATOUS	LEPROMATOUS	HISTOID LEPROSY
2016-17	5	4	2	2	4	1
2017-18	4	5	-	-	2	3
2018-19 (JUNE)	3	3	1	2	2	4
TOTAL	12	12	3	2	8	8

Three cases were incidentally diagnosed as ENL which were clinically diagnosed as sarcoidosis and lupus vulgaris.The discrepancy is explained due to misinterpretation and sometimes over diagnosis of hypopigmented patches as leprosy specially in children with lesion on face.

The present study has been compared with other studies to show the % of agreement and disagrrement between clinical diagnosis of leprosy and histomorphological diagnosis.

Journals and published studies with authors referenced	Agreement of HPE and clinical diagnosis	Disagreement of HPE and clinical diagnosis
Clinico-histopathological correlation of leprosy Ghodke, Valand, Bhubaneswar Deka*, Ramraje and Z Ali ,Dep Of Pathology, Grant Government Medical College and Sir JJ group of Hospitals, Mumbai . DOI: 10.21276/APALM.1645	56.33 % (over 2 years)	43.83% (over 2 yrs)

2. Clinico-Histopathological Correlation in Leprosy Anuja Sharma, Rajesh Kumar Sharma*, K C Goswsami, Subash Bardwaj JK science Journal	53.4% (over 2 years)	46.56% (over 2 years)
3. A study of histological types of leprosy along with clinic-histopathological correlation in a tertiary centre from North Maharashtra region ; Vasikar, Patil, Thakur, Sri Bhausaheb Hire Govt Medical college , Dhule, Maharashtra, 10.21276/APALM.1174	47.8% (over 4yrs)	52.2% (over 4 years)
4. Current study done at CSTM 2019.	39.13% (over 3 years)	56.87%(over 3 years)

DISCUSSION:

Environmental presence of Mycobacterial species are commonly known ,Mycobacterium leprae as the first such organism which was associated with leprosy in humans, was stated by A B G Hansen in 1873.[12,13,14]. India contribute to have high share of 58.8%of world leprosy population[5]It is known that the disease has a long incubation period which may range from few weeks to 30 yrs.[15,16]

It is known that a chronic disease like leprosy may infect contacts in the population who are incubating the disease will emerge later as leprosy cases and in post elimination era appearance of new cases will delay the progress towards elimination ,so surveillance is necessary.[17]

Significant number of cases of treatment drop out from multidrug regimen , patients lost to follow up would have transmitted the disease in community. In endemic areas basic hygiene and sanitisation if not improved there will be shedding of bacilli from infected caseswill provide continuous source of infection. Mycobacterium leprae has been shown to remain in soil and water for long time.[18,19] There is immediate need for education of the community regarding the early signs and symptoms of leprosy for awareness of the disease .BCG has already been found to provide increased protection to control population from 50% in Malawi and to 90% in Sao Paulo, Brazil .India can not afford to be complacent about leprosy but Ayushman Bharat can be a true initiative of the end ofthis disease as a curse in India.[20]

An attempt was made to correlate the clinical and histopathological diagnosis of the leprosy cases available at leprosy clinic of Calcutta School of Tropical Medicine.

Out of total 686 cases in the OPD over Aug 2016 to June 2019, (311 in 2016-17, 201 in 2017-18 and 174 in 2018-19June) a total of 115 cases (29 in 2016-17, 55 in 2017-18, and 31 in 2018-19 June) were sent for biopsy with conclusive clinical diagnosis of Leprosy (without Ridley-Jopling classification).

In 2016-17 the accuracy of clinico- histopathological correlation was 35.4% which rose to 41.3%in 2018 and descended to 36.36% till mid 2019 . But the discrepancy in the histopathological findings and the clinical diagnosis with the HPE refuting clinical diagnosis was 48.38% in 2017 which rose to 58.62% in 2018 and steadily climbed to 63.63% in mid 2019.

Atypical cases namely Histoid leprosy and ENL reactions were 10 out of 31 cases in 2018-19. While Incidentally 3cases were histopathologically diagnosed as leprosy despite having clinical diagnosis as Sarcoidosis / Granuloma Annulare /Lupus vulgaris Out of the 115 cases sent for HPE over 3years, 48 cases came with the positive diagnosis of leprosy out of which TT(12) , BT(12), BB(3), BL(2), LL(8), Histoid(8),ENL(3)

TT showed well defined epithelioid granulomas with giant cells involving neurovascular bundles but ZN stain was negative.(Fig.1)

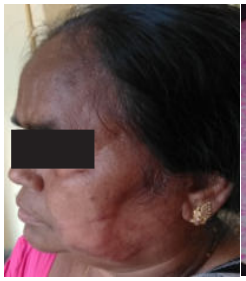
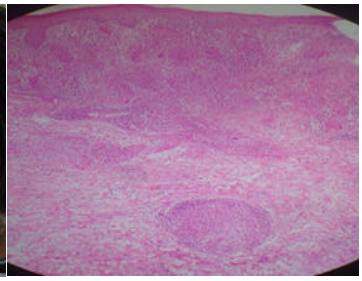


Fig.1Hypopigmented patches over cheek



Tuberculoid Leprosy TT (H&E X100)

BT showed few ill defined granulomas with larger number of giant cells, ZN stain was negative. (Fig.2)

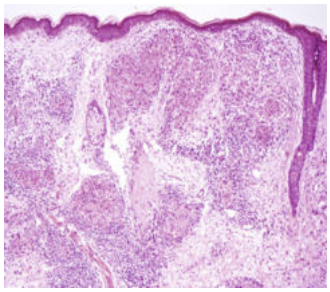


Fig.2-Borderline Tuberculoid(BT)H&EX100

Borderlines(BB+BL) started showing presence of foamy macrophages with prominent lymphocytes. Number of ZN stain positive bacilli increased over the spectrum.

LL showed presence of Grenz zone, foamy macrophages and positive Lepra bacilli in the form of globi (+3 to +4) in all cases. (Fig.3)

Histoid leprosy showed Grenz zone but mass of polyhedral to spindle shaped histiocytes in storiform pattern. ZN stain showed plenty of Lepra bacilli (positivity+++)(Fig.4)

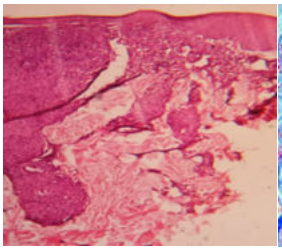
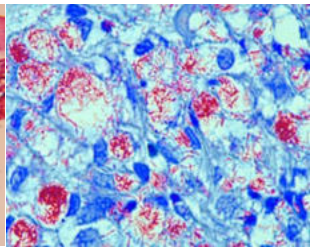


Fig.4Histoid leprosy(H&EX100)



Fite Farraco stain showing numerous bacilli

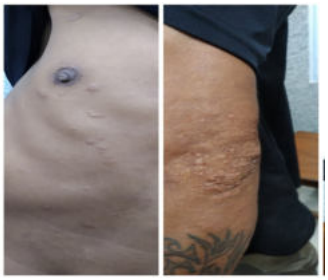
Histiod Leprosy is avariant of LL with better CMI. Usually seen in patients with incomplete chemotherapy or acquired drug resistance specially with Dapsone mono therapy.It usually present with clinical features of cutaneous and subcutaneous nodules.Hispathologically Characterized by presence of spindle shaped histiocytes in tissue section with atrophic epidermis and sub epidermal Grenz zone.Fite stain shows numerous acid fast bacilli.

Pattern of arrangement is storiform or whorls or interlacing bands or tight curlicues.Histoid leprosy usually represents probable resistant bacilli and highly active lepromatous process. In our study one case of histoid leprosy was clinically diagnosed as molluscum contagiosum.

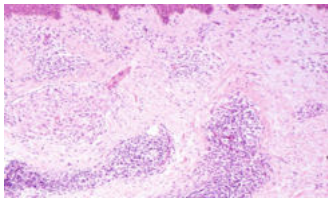
In some early and borderline cases of leprosy, it is difficult to diagnose only on clinical basis, hence histopathological examination is a must for confirmation of diagnosis in doubtful cases of leprosy. Clinico-histopathological correlation of leprosy assumes a pivotal role for early diagnosis.[10]

The histopathological classification has advantage over clinical diagnosis and it indicates better in case of shift of patient's condition in a spectrum. Histopathological classification is essential for treatment .[21] Many studies has been done for clinic histopathological correlation and disparities between these two have been observed. If a biopsy is taken at an early stage chance of discordance between clinical and histopathological diagnosis is high. As disparity depends upon the lesion of biopsy taken at the time of study it should be taken from the lesion which is morphologically suggestive of clinical diagnosis /serial

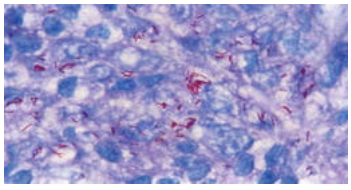
biopsies from same lesion or from paired lesions for a good clinicopathological correlation.[1]



Skin lesions in Histoid leprosy



Lepromatous leprosy LL (H&EX100)



Fite Farraco stain showing multiple Lepra bacilli

CONCLUSION

The present study conducted on CSTM premises from 2016-2019 on SSS negative cases , although the clinico-histopathological positive agreement leaves much to be desired, the disparity in correlation does decrease the chances of false positives and helps in better finalising the diagnosis for better treatment.

Prognosis, follow-up and monitoring of the diseases are also aided by correct histopathological diagnosis especially in case of early and borderline cases of leprosy.

Thereby histopathological examination remains quite relevant in diagnosis of leprosy , thus a definitive diagnosis for proper treatment will help us to achieve the goal of WHO global leprosy strategy 2016-2020 towards a leprosy free world.

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