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Original Article

Correlation between Clinical and Histopathological Diagnosis and Classification of Hansen's Disease - A Seven Year Retrospective Study from Himachal Pradesh, India

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Leprosy is a chronic granulomatous disease; its clinical presentation depends upon the immunologic responses of the host towards the pathogen. While histopathology is considered important to confirm the diagnosis in cases with vague clinical features, its correlation with clinical classification of disease has not always been found to be straightforward. This study has been done to correlate the histological picture in biopsy proven leprosy cases with the clinical findings in these cases to determine the usefulness of combining these two approaches. In this study, a retrospective analysis of 104 histopathologically confirmed leprosy cases has been done to correlate with the clinical diagnosis and classification of the leprosy cases who were attending the Dermatology Department of Dr Rajendra Prasad Government Medical College, Tanda, Kangra. Data analysis and histological review of all cases was done in the Department of Pathology in an anonymous manner. Hematoxylin and Eosin staining of tissue slides of all cases was done and all details recorded. Fite Faraco staining was also done for assessing the bacteriological index (BI) in the slides and recorded. These were compared with the clinical notes recorded at the time of taking biopsy. Among these histologically confirmed leprosy cases, Lepromatous Leprosy-LL (41.34%) was the most common leprosy type observed, followed by Borderline Lepromatous-BL (25%) and Borderline Tuberculoid-BT (18.26%) disease. However, Borderline Tuberculoid leprosy was the most common diagnosis in these 104 cases by clinical examination alone. Maximum concordance with clinical classification was seen with Lepromatous Leprosy (88.57%) and the least 28.5% for Tuberculoid (TT). One of three clinically diagnosed TT cases and 14/19 BT cases were found to be smear positive by Fite Faraco (FF) stain in their tissue slides. Furthermore, other clinically diagnosed MB cases were also found to be positive for acid fast bacilli (AFB) using the Fite Faraco stain. As this is a retrospective study the cases could not be followed up to know the outcome of treatment of cases who would have been treated with paucibacillary regimen but were found to have high bacteriological index (BI). With a decrease in the burden of cases, there is a need for closer follow-up of leprosy cases to see their response to treatment so that scope for improving the therapy may be determined out especially in cases with histopathology pointing to more extensive bacilliferous disease. Technical/Biological issues resulting in discordance even in polar

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cases like TT and also reactions like ENL also merit in-depth analysis. Thus, our study highlights the need for using both ZN staining and Fite Faraco staining for AFB of biopsies wherever possible and analyze them with treatment and follow-up.

Keywords : Hansen's Disease, Fite-Faraco Staining, Tuberculoid Leprosy, Histoid Leprosy, Bacteriological Index

Introduction

Gerhard Armauer Hansen identified the bacillus *Mycobacterium leprae* as the causative organism of leprosy in 1873. Since then, Leprosy or Hansen's disease has become a well-known chronic granulomatous disease, predominantly affecting the skin and peripheral nerves. Less commonly affected parts are the eye, testis, bones, lymph nodes etc. The involvement of internal organs is rarely manifested clinically and reported in leprosy. This may be due to a high core temperature not allowing the growth of *Mycobacterium Leprae* (Lastória & Abreu 2014). In endemic settings where almost the entire population is exposed to the agent, more than 90% of population does not develop the disease. Some of the cases who do develop the disease selfheal and do not have any clinical manifestations of the disease. In a very small percentage of exposed persons, develop the disease, The manifestations are mainly in the skin and nerves, varied and depends on the immunological host response to the bacterium.

Histological classification for leprosy was proposed by Ridley and Jopling in the year 1966 (Ridley & Jopling 1966) which is based primarily on immunological, clinical and histopathological assessment. According to this classification system, leprosy is classified as Tuberculoid (TT), Borderline Tuberculoid (BT), Mid-Borderline (BB), Borderline Lepromatous (BL), and Lepromatous leprosy (LL) (Arif et al 2018). The drawback of this classification is that Indeterminate leprosy (Ind) and pure Neuritic (N) have not adequately considered due to lack of such cases in their series and ill-defined distinguishing features. These two types have /were included in the five-group classification given by Indian Association of Leprologists (IAL 1982) which is followed in our country. Earlier, World Health Organization (1982) used the bacillary index (BI) for the operational classification of leprosy for treatment purposes, as multibacillary (MB) and paucibacillary (PB). In Paucibacillary leprosy, the BI index was <2 (on the Ridley Scale) and in Multibacillary leprosy, the BI index is >2 at any skin site. Broadly speaking, Indeterminate (Ind), Tuberculoid (TT), and Borderline Tuberculoid (BT) cases of leprosy were classified as paucibacillary, whereas Mid-Borderline (BB), Borderline Lepromatous (BL), Lepromatous leprosy (LL) and Polyneuritc leprosy were classified as multibacillary (MB). This classification is also used for deciding the treatment protocol (WHO 1982). However, smear examination had several drawbacks, and flaws and could not be undertaken in all places/ laboratories; There was a lot of inter observer differences in reading of the stained smears and it was time consuming. Therefore, for the universal implementation of Leprosy control programs and operational feasibility for providing treatment an operational classification system was proposed by WHO. This was based on clinical findings of the number of skin lesions and nerves involved (WHO 1994). According to this operational classification for treatment purposes, patient with more than 5 skin lesions and nerve involvement/thickening was classified as multibacillary (MB) Leprosy and given treatment with 3 drugs for 1 year; and those with less than five lesions (which included skin and nerve involvement) was considered as paucibacillary Leprosy and treated with 2 drugs

for 6 months (Parkash 2009).

Government of India in the year 1954-55 launched National Leprosy Control Program which was later in 1983 renamed as National Leprosy Eradication program. In the year 2005 India has achieved the National target of prevalence of leprosy less than 1 case per 10,000 population as per WHO criteria for elimination of leprosy as a public health problem. However, this could not be achieved at sub-national level. Some pockets still remain, and new cases continue to occur and are being treated. A targeted action is required to achieve zero leprosy goal of National Leprosy Eradication Program. One of the approaches could be using histopathology for diagnosis of new cases with the help of special stains like, suitably adapted Ziehl-Neelsen staining (ZN staining) / Fite-Faraco staining (FF staining) (Fite et al 1947) especially in tertiary care centers, so the patients are optimally treated and there is a break in the transmission of the disease. Among these 2-staining methods sensitivity, positive predictive value and negative predictive value is maximum with Fite-Faraco stain (Reja et al 2013). This analysis focuses on usefulness of Fite-Faraco staining of histopathological sections from leprosy cases for assessing the bacterial load in these cases.

Material and Methods

A seven-year retrospective data analysis and histopathology slide review of all skin biopsies with suspected leprosy submitted for histopathological evaluation in the Department of Pathology during 2013 to 2019 was carried out. One hundred and eleven untreated cases were submitted with a clinical diagnosis of leprosy of different types. Out of these, 104 cases were histopathologically confirmed as that of leprosy. All these cases were taken into consideration for the study purpose. Data about age, sex, and clinical presentation was analyzed, from the clinical details submitted, and a clinic-pathological correlation was investigated. The new Indian Association of Leprologists (IAL) classification which has been shown to correlate well with the Ridley Jopling Classification has been used in the study (IAL 1982). The clinical classification was made in the Dermatology Department, which was based on the number of lesions, type of lesion, symmetry of the lesions. degree of loss of sensation, number and consistency of nerves involved. These characteristics are described in detail by Kumar et al (2017).

Hematoxylin & Eosin (H & E) stained slides were examined. Fite-Faraco's staining was done after deparaffinizing each section with a mixture of xylene-peanut oil. The section is then stained into a carbol fuchsin solution for twenty minutes. Followed by counter staining with methylene blue (Fite et al 1947). The stained slides were viewed, and histopathological diagnosis was reached and recorded. The histological classification and diagnosis was made based on presence/absence of epidermal atrophy, presence of Grenz zone, presence/absence of granulomas, distribution of lymphocytes, histiocytes & foam cells, giant cell and their presence in the dermis, in and around nerves, blood vessels and adnexa and presence of acid fast bacilli (AFB).The Bacteriological index was assessed from the sections and histopathological classification of the type of leprosy was recorded based on the above findings.

Results

Out of 104 skin histopathological proven leprosy cases studied, 67 were male and 37 females. The male/female ratio was 1.8:1 (Table 1). Youngest as well as the oldest patient were males, of 15 years and 84 years of age respectively. The youngest female patient was 16 years, and the eldest female patient was 70 years old.

The maximum number of cases (25 out of 104) was in the 5th decade (41-50 years age group) of life. This was closely followed by the 31 to 40 year and 21 – 30 years age groups. Sixty-five percent

of cases were seen in the 21 to 50 years of age group. A small proportion (3.8%) of cases were seen in the 8th decade of life. There was no case seen under 10 years of age (Table 1).

The histopathological spectrum of the leprosy was Indeterminate 4, (3.84%); Tuberculoid 3, (2.88%); Borderline Tuberculoid 19, (18.26%)' Mid Borderline 2, (1.92%); Borderline Lepromatous 26, (25%); Lepromatous leprosy 43, (41.34%); Histoid leprosy 3, (2.88%); Neuritic 2, (1.92%); and Erythema nodosum leprosum 2, (1.92%); in the series. The Histo pathological diagnosis of indeterminate leprosy was made in 4 cases. In all these cases, there was mild lymphocytic infiltration around adnexal tissue with no epidermal atrophy, no granuloma was observed, and none of them had a Grenz zone, no AFB was seen using Fite Faraco stain. However, none of

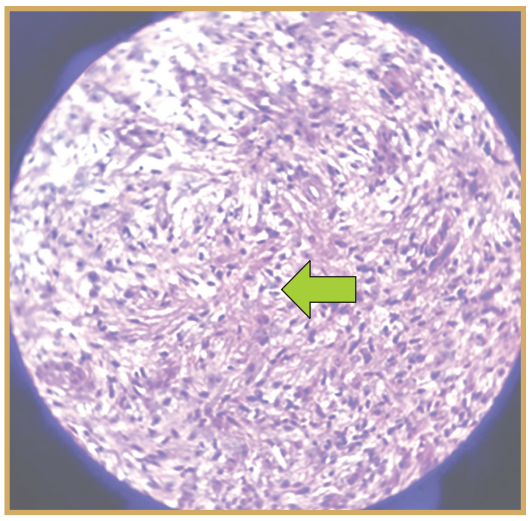

Fig. 1 : Skin biopsy showing histopathological features of Histoid leprosy. Spindled histiocytes in storiform pattern, 10X (H and E stain).

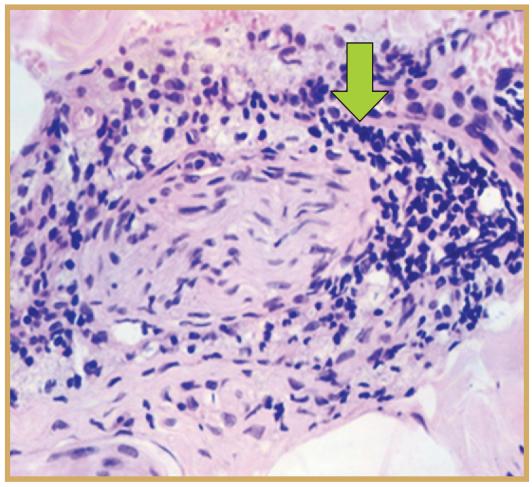

Fig. 2 : Skin biopsy showing histopathological features of Pure neuritic leprosy - lymphohistiocytic infiltrates around the nerve, 40X (H and E stain).

Table 1 : Age wise distribution of cases studied.

Age group in years	Total No. of patients (n=104)	Percentage	Male: Female ratio
11-20	5	4.80	4:1
21-30	19	18.26	1.1:1
31-40	24	23.07	2:1
41-50	25	24.03	1.3:1
51-60	14	13.36	1.8:1
61-70	12	11.53	3:1
71-80	4	3.84	4:0
81-90	1	0.96	1:0

them were clinically diagnosed as Indeterminate leprosy. There was 100 percent discordance between clinical and histopathological diagnosis in this group (Table 2). The mean age of presentation of Indeterminate leprosy was 40 years. The youngest patient was 28 years old female patient with having single lesion on her lips. The duration of symptoms was only 3 months, whereas in other cases it ranged from 2 to 6 years. Of the 7 TT cases diagnosed by clinical criteria 2 were confirmed histologically, whereas the other 5 had a different diagnosis as shown in Table 2. One case was histopathologically diagnosed as Lepromatous leprosy (Table 2). His lesion had ill-defined granuloma, and dense neurovascular lymphocytic infiltration around the pilosebaceous unit in the sections. There was no epidermal atrophy, and no Granz zone. The Bacillary Index was found 1+ on the Fite Faraco stain (Table 3).

Among the 19 clinically diagnosed BT cases, 13 cases were histologically confirmed as BT. In the discordant cases 2 were histologically Indeterminate, 1 BB and 3 BL. None of the cases in the series were mid borderline both clinically and histologically. Of the 31 clinically diagnosed BL cases 21 were confirmed as BL histologically, while the rest were classified differently histologically (1- Indeterminate; 2 – BT; 1- BB and 6 LL cases). Thirty-one cases out of 35

Table 2 : Clinico-Histopathological Correlation.

Clinical diagnosis	Histopathological diagnosis										
	IL 4/104 3.8 %	TT 3/104 2.88%	BT 19/104 18.26%	BB 2/104 1.92%	BL 26/104 25%	LL 3/104 2.88%	Histoid 26/104 25%	Neuritic 2/104 1.92%	ENL 2/104 1.92%	Concor-dance	Discor-dance
IL (0/104)	-	-	-	-	-	-	-	-	-	0%	100%
TT (7/104)	1	2	3	-	-	1	-	-	-	28.57%	71.42%
BT (19/104)	2	-	13	1	3	-	-	-	-	68.42%	31.57%
BB (0/104)	-	-	-	-	-	-	-	-	-	0%	100%
BL (31/104)	1	-	2	1	21	6	-	-	-	67.74%	32.25%
LL (35/104)	-	1	1	-	-	31	2	-	-	88.57%	11.42%
Histoid (2/104)	-	-	-	-	-	1	1	-	-	50%	50%
Primary Neuritic (3/104)	-	-	-	-	1	-	-	2	-	66.66%	33.33%
Leprosy reaction (7/104)	-	-	-	-	1	4	-	-	2	28.57%	71.42%

Table 3 : Bacteriological index (BI) in histopathology slides by Fite- Faraco staining.

Histopathological diagnosis	Bacteriological index (BI)						
	0	1+	2+	3+	4+	5+	6+
IL = 4/104	4	0	0	0	0	0	0
TT= 3 /104	2	1	0	0	0	0	0
BT=19/104	5	5	9	0	0	0	0
BB= 2/104	1	0	0	1	0	0	0
BL=26/104	4	0	10	6	6	0	0
LL=43/104	0	0	1	1	16	14	11
Histoid=3/104	0	0	0	0	1	1	1
Neuritic = 2/104	1	0	0	0	0	0	1
ENL=2/104	1	0	1	0	0	0	0
Total	17.30%	5.8%	20.19%	7.69%	22.11%	14.42%	12.5%

clinically diagnosed LL cases were confirmed as LL cases while 4 cases were classified differently histologically (1 as TT; 1 as BT and 2 as Histoid leprosy). One of the 2 cases of clinically diagnosed Histoid leprosy was confirmed histologically (Fig. 1) while the other showed only LL features histologically. Two of the three Neuritic leprosy cases were confirmed as Neuritic leprosy (Fig. 2) while the remaining third case had BL features histologically. Although 7 cases were diagnosed clinically as ENL cases, only 2 could be confirmed as having histological features of ENL while, 1 as that of BL and 4 of LL type. It may be noted that ENL reactions occur in borderline and LL cases only and maybe the biopsy specimen was taken from the non-inflammatory skin tissue and not from the ENL nodules.

Using the Fite-Faraco staining of tissue sections for detecting Acid fast bacilli (AFB) the details of BI are shown in Table 3. None of the histologically proven Indeterminate cases showed presence of AFB, while 1 case of TT leprosy and 5 cases of BT leprosy were also 1+ BI positive in the tissue sections. Nine cases of clinically diagnosed BT leprosy showed 2+ positivity for AFB in their tissue sections and ,5 showed 1+ in the series (Table 3). Similarly, One out of 2 BB patient and 4/26 BL patients; one of the two Neuritic and one out of 2 ENL patients were also AFB negative in their tissue sections (Table 3).

Discussion

Male predominance has been observed in many studies as in the present study where the M: F is 1.8:1. Atram et al (2020) study had a similar finding with a M: F of 1.5:1. Semwal et al (2018) had similar observations. This trend can be attributed to the higher chances of contracting infection due to higher outdoor activity of males and frequent meetings with several persons. Another reason could be fewer numbers of females are brought to tertiary care centers for treatment.

Most of patients in our study were in their 4th and 5th decades of life accounting for 47.11% which is similar to that reported by Kaur et al (2003) and Suri et al (2014) in their respective studies. As the studies have been conducted in Tertiary care center and Medical College it is not surprising. Lesser cases have been reported in

the younger age group as well as those over 80 years of age.

The most common type of leprosy observed in the present study was lepromatous leprosy which accounted for 41.34% of total cases. This observation was similar to studies conducted at Himachal Pradesh by Tegta et al (2019), Rattan et al (2017) and Jindal et al (2009). However, in a study reported by Sharma et al (2008) from Jammu; Bhanusree et al (2016) from Puducherry; study from Rajasthan by Kumar et al (2014), reported BT as the commonest form of leprosy in their series. This observation of Lepromatous leprosy being the commonest type at Himachal Pradesh may be due to the late reporting of cases in this hilly region. In the present study, clinical-histopathological concordance was highest in LL (88.57%) similar to the result seen by Banushree et al (2016) and the least concordance was in Indeterminate leprosy (0%). While taking the biopsy for histopathological diagnosis it is important to collect the specimen from the right place as it will represent the disease in the body. There was no case of Indeterminate clinical leprosy in the series but histologically Indeterminate leprosy (which does not fall in the known groups, no AFB was seen even by Fite-Faraco staining) was seen in four cases, probably due to inappropriate sample collection in the present study.

Another important observation was that several TT, BT cases were AFB positive by Fite- Faraco staining. This shows that although these patients are grouped as PB cases they habour bacilli and need to be treated more carefully and perhaps extensively. There is a need to follow up these cases to see how they behave after completion of treatment. Unfortunately, even ZN staining and examination of smears is not done routinely and needs to be re-instituted and observed specially in tertiary care and referral settings. All the Histoid cases, 41/43 LL cases and one of the 2 Neurtic cases were between 4 to 6+ AFB positive as observed by Fite Faraco staining. These cases need to be followed up and treated carefully, preferably till AFB negativity or as determined by proper trials is attained to prevent relapses, disabilities and reduce the transmission risk in the community.

Conclusions and future perspective

Our study shows major discordance among clinical and histopathological diagnosis in several cases whose biopsies were sent to Pathology. Reasons for several well-defined clinical types being identified as Indeterminate by histopathology, TT diagnosed as BT and their implications on prognosis should be investigated. BT cases with high BI by Fite-Faraco staining may also have therapeutic relevance which should be studied prospectively in relation to outcomes and comparative usefulness of other techniques including molecular assays (Reza et al 2013).

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