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Histopathological Evaluation of Multibacillary Leprosy Patients after Fixed Duration Multidrug Therapy (Fd-Mdt) of One Year: A Hospital Based Study

Gh Mohi Ud Din Wani[1], Shabir Ud Din Lone[2], Bilques Khursheed[3], Hilal Ahmad Wani[4*]

[1]Medical Officer Dermatology, Directorate of Health Services, Kashmir, J & K, India.
[2]Assistant Professor, Department of Physiology, Government Medical College, Srinagar, J & K, India.
[3]Medical Officer, Directorate of Health Services, Kashmir, J & K, India.
[4*]Research Scientist-II, Multidisciplinary Research Unit, Government Medical College, Srinagar, J & K, India.

ABSTRACT

A Hospital based study regarding histopathological evaluation of 100 multibacillary leprosy patients attending the urban leprosy centre of SMGS Hospital/Govt. Medical College, Jammu has been conducted to assess the impact of fixed duration multidrug therapy of 1 year in multi-bacillary leprosy in terms of histopathological upgrading (improvement). The histopathological evaluation was done by follow-up skin biopsy. Biopsy results were compared with respect to clearance of dermal granulomas consisting of lymphocytes, epithelioid cells, giant cells, macrophages and foam cells in variable proportions depending upon the type of leprosy and measured by estimating the reduction in granuloma fraction and clearance of acid fast bacilli. The mean granuloma fraction (G.F) of 100 patients before treatment was 59.2 % while as, after treatment, it was 21.3%. The average reduction in G.F. was 37.9% at the completion of 12 months MDT which was found to be statistically significant (p=0.005). The results of our study indicate that shortened FD-MDT of 12 months for multibacillary patients is effective and safe.

Key words: Mycobacterium Leprae, Acid Fast bacilli, Granuloma Fraction.

***Correspondence to:**

Dr. Hilal Ahmad Wani,
Research Scientist-II,
Multidisciplinary Research Unit,
Government Medical College Srinagar, J & K, India.

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INTRODUCTION

Leprosy, also called Hansen's disease is a chronic infection. The disease was widespread during the middle age in almost all countries of the world and has indeed left a horrifying legacy of a highly stigmatized disease responsible for human misery due to mutilation, rejection and exclusion from the society. Mycobacterium leprae is an acid and alcohol fast, rod shaped, intracellular bacillus belonging to the family Mycobacteriaceae. Although it has not been cultivated in artificial media or tissue culture, the organism can be propagated in nine banded armadillos and in the footpads of mice. After the entry of M. leprae into the body, there is an early bacillemia and seedling of the microbes into different tissues of the body. The resultant host response results in the formation of leprous granulomas consisting of epithelioid cells, giant cells and other types of chronic inflammatory cells. Some non-immunological factors like genetic, nutritional, environmental etc. has also been proposed as the probable causes of susceptibility or resistance.[1]

Histopathologically, at the tuberculoid pole, cell mediated immunity prevails and epithelioid granulomas with scarce or no bacilli predominate. At the lepromatous pole, a specific inflammation represented by lepromatous granuloma or virchowcytic granulomas containing modified macrophages called lepra cells or virchowcytes is seen. In the borderline leprosy, both types of granulomas may coexist, not infrequently with epithelioid cells and lepra cells. Indeterminate leprosy reveals lymphocytic infiltrates, perhaps related to the immune mechanism that precedes the development of tuberculoid granulomas and epidermal lichenoid reaction, or the appearance of few lepra cells.[2] For the purpose of therapy, leprosy is classified into paucibacillary and multibacillary.[3] Paucibacillary leprosy includes only smear negative indeterminate, TT and BT leprosy. Multibicillary leprosy includes: (a) all cases of LL, BL and BB leprosy (b) smear positive indeterminate, TT and BT leprosy. In 1981, a WHO study group recommended that duration of multidrug therapy for multibacillary leprosy should be given for at least two years and preferably continued, whenever possible, up to skin smear negativity.[3] In 1997,[4] the WHO expert committee on leprosy, at its seventh meeting, considered the possibility of further shortening the duration of multidrug therapy for multibacillary patients to 12 months.[5]

The recommendation was based on the claim that more than 99.999% viable organisms are killed by the administration of 3 monthly doses of rifampcin. The fixed duration multidrug therapy of one year and relapses in multi-bacillary cases raise a few basic issues regarding the clinical activity and the histopathological changes which occur in patients on multibacillary-multidrug therapy. The present study was carried out to elucidate such changes.

AIMS AND OBJECTIVES

To assess the impact of fixed duration multidrug therapy of 1 year in multibacillary leprosy in terms of histopathological upgrading and to find out the patients who are at risk of relapse and therefore need prolonged follow up.

MATERIALS AND METHODS

A Hospital based study regarding the histopathological evaluation of 100 multibacillary leprosy patients attending the urban leprosy centre of SMGS Hospital/Govt. Medical College, Jammu has been conducted. A detailed history and a thorough clinical, bacteriological[6] and histopathological evaluation was done.

Histological

The histopathological evaluation was done by follow-up skin biopsy, taken preferably from the site of initial biopsy in as many cases as possible.

A detailed histopathological examination was done by senior pathologist of the department of Pathology Govt. Medical College, Jammu and the findings were recorded and compared with the histological findings of the sections retrieved from the paraffin blocks of the earlier biopsies. Biopsy results were compared with respect to clearance of dermal granulomas consisting of lymphocytes, epithelioid cells, giant cells, macrophages and foam cells in variable proportions and measured by estimating the reduction in granuloma fraction and clearance of acid fast bacilli. The granuloma fraction (G.F.) is the fraction of dermis occupied by the granuloma in a low power section and may range from 0-100%. Granuloma fraction is zero when there is no granuloma and it is 100% when the whole thickness of dermis is occupied by the granuloma.[7]

Statistical Analysis

The reduction in granuloma fraction was analysed by applying Wilcoxon signed test.

Table 1: Frequent chief complaints at presentation

S.No.	Chief Complaints	No. (%)
1	**Peripheral anesthesia in glove and stocking distribution**	36%
2	**Multiple nodules**	30%
3	**Multiple erythematous plaques**	26%
4	**Multiple wide spread symmetrical hypo-pigmented macules or patches**	20%
5	**Annular lesions**	15%
6	**Diffuse infiltration**	12%
7	**Reactions**	6%

*Majority of the patients had more than one complaint.

Table 2: Distribution of granuloma fractions before and after treatment

GF (%)	Before therapy Number (%) of patients	After therapy Number (%) of patients
<15	0	27
15-29	3	37
30-44	26	33
45-59	20	0
60-74	15	3
=75	36	0
Total	100	100

Table 3: Mean±SD of granuloma fractions before and after treatment

Before Treatment	After treatment	Reduction
59.2±19.10	21.3±14.20	37.9%±4.90

Table 4: Upgradation of histopathological diagnosis in patients after treatment

Before treatment histopathological Diagonosis (n%)	After Treatment histopathological Diagnosis (n%)					
	BL		BT		NSI	
	Number	%	Number	%	Number	%
LL+ Histoid(44)	8	(19%)	Nil		3	(5%)
BL (48)	Nil		5	10%	10	(20%)
BB (7)	NIL		2	(29%)	3	(42.8)
BT (1)	NIL		Nil		1	(100%)
Total	8		7		17	

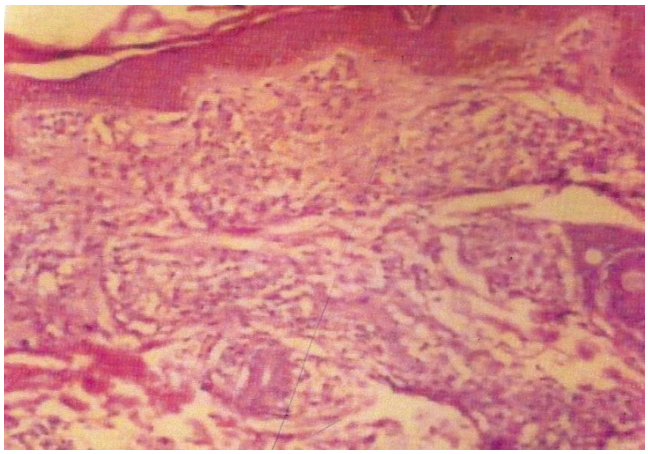

Fig 1: Pre-treatment skin biopsy of a patient showing extensive dermal granulomatous infiltration GF 70% H&E x 140.

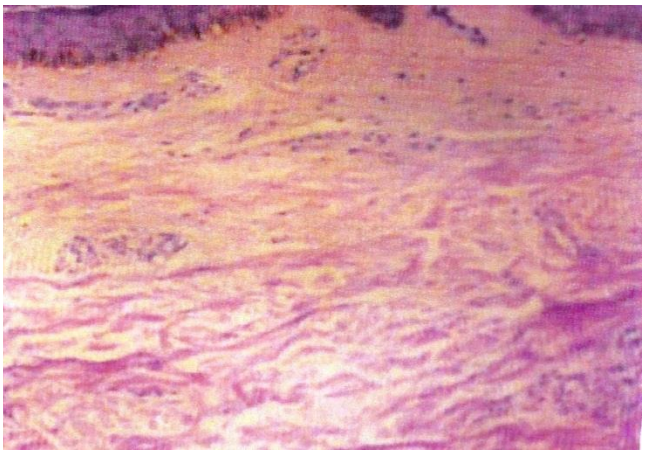

Fig 2: Post-treatment skin biopspy of the same patient showing reduction in granuloma after 12 months GF 30% (H&E x 140)

OBSERVATIONS

100 patients including 15 females and 85 males with multibacillary leprosy were selected for the study with age ranging between 16 and 65 years. The mean age of the patients was 36.5 years and the maximum patients were in the range of 21-50 years. Most frequent chief complaints at presentation are given in Table 1. Duration of the disease in the patients ranged from 2 months to 10 years. The mean duration of the disease was 1.41±1.55.

Out of 100 patients, 48% had BL type of leprosy followed by LL (42%), BB (7%), Histoid (2%) and BT (1%). Distribution of granuloma fractions before and after treatment is given in Table 2.

Histopathological changes were observed by noting the reduction in granuloma fraction (GF). The granuloma fraction (GF) before treatment ranged from 20—90%. Out of 100 patients, 26 had GF between 30-34%, 20 had GF between 45-59%, 15 had GF between 60-74% and 36 had GF of more than 74%. Only 3 patients showed GF of less than 30%. In majority (97%) of patients, GF was between 30%-80%. The mean granuloma fraction of 100 patients was 59.2%.

After treatment, granuloma fraction ranged from 0-60%. Out of 100 patients, 27 had GF less than 15%, 37 had GF between 15-29%, 33 had GF between 30-44%. Only 3 patients had GF of more than 44%. The mean granuloma fraction of 100 patients was 21.3% (Fig: 1 & 2).

While analyzing the data by Wilcoxon Singed Test, Z value was found to be 8.4268, which is highly significant at p=0.005. While analyzing the mean, a reduction of 37.9% has been recorded in granuloma fraction after therapy. Mean ± SD of granuloma fractions before and after treatment is given in Table 3.

Histopathological Upgrading

The histopathological changes were also evaluated to see changes suggestive of upgrading (LL to BL), like reduction in the number of foam cells and macrophages, reappearance of epithelioid cells and increase in the number of lymphocytes and plasma cells in granulomas. Similarly the sections were labelled as BT when the infiltrate became well circumscribed, comprising of epithelioid cells, occasional langhans type giant cells and lymphocytes. In some patients the histological improvement was more marked; no definite granulomas or AFB were identified and the sections showed mild to moderate degree of lymphohistiocytic infiltration in the dermis which was either randomly scattered or periadnexal in location, this was labelled as NSI i.e. non-specific inflammation. Upgradation of histopathological diagnosis in patients after treatment is given in Table 4.

Out of 44 cases of LL and histoid, 8 (19%) coverted into BL type and 3(5%) coverted into NSI after therapy. The remaining 33 (76%) patients did not convert. Out of 48 cases of BL, 5 (10%) cases converted into BT and 10 (20%) cases into NSI. The remaining 33 (70%) patients did not convert. Out of 7 cases of BB, 2 (29%) cases converted into BT and 3 (42.8%) case into NSI. The remaining 2 (28.2) patients did not convert. One case of BT (100%) converted into NSI.

DISCUSSION

Fixed duration multi drug therapy (FD-MDT) for MB cases is effective, acceptable and safe, and histopathological activity and smear positivity have no bearing on the efficacy of FD-MDT, and relapses are low.[8] By shortening the duration of MDT, the national leprosy elimination programme (NLEP) will be more effective.[9]

The present study was carried out to find out the effectiveness of 12 months FD-MDT in case of multibacillary leprosy by analyzing histopathological improvement. The findings at the time of completion of treatment were compared with the findings at the start of treatment. The duration of the disease ranged from 2 months to 10 years, however in majority of the patients, it ranged from 6 month to 2 years. The mean duration of disease was 1.41 years. The findings are in agreement with other studies.[10,11]

After MDT, patients showed rapid bacillary clearance and there by marked reduction in the size of granulomas. Before treatment 97% of our patients had granuloma fraction (GF) ranging from 30-80% with a mean granuloma fraction of 59.25% while as after treatment, 97% of patients had granuloma fraction ranging from 0-44% with mean G.F of 21.3%. The granuloma fraction (G.F.) at 12 months was significantly reduced with a mean reduction of 37.9%. Our results are comparable to De Sarkar et al[10], who found a mean reduction of 38.55% in the G.F. of patients of MDT group at 12 months of treatment. Narang et al[11], found a mean reduction of 32.50% in the G.F of patietns of MDT group at 12 months of treatments: Mean reduction in G.F at 12 months of MDT in different studies are given in Table 5.

In 17 patients, granulomas and AFB cleared completely with histopathological picture suggestive of nonspecific lympho histocytic infiltrate (NSI) that was either randomly scattered or periadnexal in location. They included 3(5%) LL, 10 (20%) BL, 3

(42.8%) BB and 1 (100%) BT patients. After treatment all the patients showed change in the composition of granulomas. There was reduction in the number of foam cells and macrophages, reappearance of few epithelioid cells with increase in the number of lymphocytes.

The bacillary load was markedly reduced and the remaining bacilli were in granular or fragmented form. The number of patients showed conversion of granuloma to a higher spectrum e.g., granulomas in 8 (19%) LL patients changed to BL type and granulomas in 5 (10%) BL patients changed to BT type. Similarly granulomas in 2 (29%) BB patients changed to BT type. Similar histopathological changes (i.e. conversion of BL/BB to BT type, LL to BL type, total disappearance of granuloma and replacement by NSI) has been reported by Mukherjee et al.[12] Up gradation of CMI following MDT has possibly led to the change of granulomas from lower to higher spectrum. From the data it is clear that NSI after treatment (which is the marker of histopathological inactivity) is mostly seen in BT, BB, some case of BL and occasionally seen in LL. In other words patients of LL and BL with high initial Bacteriological load showed persistence of granuloma after treatment (which is the marker of histopathological activity) hence are high risk cases and may show relapse.

Table 5: Mean reduction in G.F at 12 months of MDT in different studies

Mean G.F			
Study	**Before Treatment**	**After treatment**	**Reduction**
DeSarkar et al (2001)	64.25	25.7	38.55
Narang et al (2005)	55.25	22.75	32.50
Present study (2008)	59.20	21.30	37.90

SUMMARY

100 MD leprosy patients (all smear positive) who have taken FD-MDT of 12 months were taken for the study to find out the effectiveness of FD-MDT in terms of histopathological upgradation at the end of treatment.

- Majority of the patients were males (85%).
- Mean age of the patients was 36.5 year and maximum number of patients was in the age group of 21-50 years.
- Duration of the disease ranged from 2 months to 10 years and the mean duration of disease was 1.41 years.
- The clinical spectrum of the disease was 2 histoid, 42 LL, 48 BL, 7 BB and 1 BT type of leprosy.
- Histopathological improvement (reduction in granuloma fraction) was evaluated by skin biopsies taken before and after treatment .The mean granuloma fraction (G.F.) of 100 patients before treatment was 59.2 % while as, after treatment , it was 21.3%. The average reduction in G.F. was 37.9% at the completion of 12 months MDT which was found to be statistically significant (p=-0.0005).
- Conversion of granuloma to higher spectrum was seen in 15% patients. In another 17% patients, there was total clearance of granuloma and replacement by nonspecific lympho-histiocytic infiltrate (NSI) that was either randomly scattered or peri-adnexal in distribution.

The results of our study indicate that shortened FD-MDT of 12 months for multibacillary patients is effective and safe and seemingly it has tremendous operational advantage and we should be prepared to treat few relapses in post elimination period as they occur. However, a long term follow up in large number of patients especially highly bacilliferous cases is the best option to settle issue of safety & efficacy of shortened Fd-Mdt of 12 months.

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