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Original Article

Clinicohistopathologic and Bacteriological Outcomes in Leprosy Patients after 6 months of Adult MB-MDT : A Prospective Study

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Multi drug therapy (MDT) is a crucial approach for leprosy control programmes introduced by WHO in 1981. Inadequacy of 1 year MDT in eliminating lepra bacilli is being increasingly reported across India. This study attempts to understand the changes in clinical features, bacteriological Index (BI) and histologic features after commencing MDT, giving us a window to make appropriate changes when needed. Sixty patients diagnosed as leprosy included 46 newly diagnosed cases and 14 were partially treated cases but the past records were unavailable to verify the months of treatment taken. All underwent clinical, histological and bacteriological examination, before and after taking 6 months of adult multibacillary (MB)-MDT. Patients were subjected to slit skin smear (SSS) and skin biopsy at 1st visit and 6 months of starting MDT. Of these 60 patients 41 were males and 19 females. These were diagnosed as lepromatous (LL) = (29) 43%, borderline lepromatous (BL) = (20) 33.3%, borderline tuberculoid l(BT) = (5) 8.3%, histoid (HL) = (3) 5%, tuberculoid (TT) = (2) 3.3% and mid borderline leprosy (BB) = (1) 1.67%). After 6 months of MDT, 7 patients showed clinical improvement while 7 presented with new skin lesions, worsening of neurological impairment. Mean BI done at 1st visit and after 6 months of MDT showed decrease in BL, LL, HL while it remained negative in TT, BT, BB types of leprosy. Histopathological changes evaluated were epidermal changes like atrophy, hyperkeratosis, rete pegs shortening, flattened basal layer, and dermal changes like epithelioid granuloma, histiocytic granuloma, giant cells, grenz zone, superficial and deep dermal infiltrate, periappendageal infiltrate, foamy macrophages, foamy histiocytes. However, no potential marker for monitoring could be identified. Clinicohistopathological correlation showed 73.3% concordance (p value < 0.05) at the 1st visit and 71.6% concordance (p value <0.05) at 6th month post treatment. There was no uniform improvement in bacteriological index, clinical features and histopathological changes. Doing an early biopsy may help in understanding markers/ patterns of clinical responsiveness. Larger studies are required for the same.

Keywords: Leprosy, Clinicohistopathology, Bacteriological Index, Multi Drug Therapy

Introduction

Leprosy is a chronic granulomatous infectious disease caused by *Mycobacterium leprae* and is known to affect mainly the cooler parts of the body – the skin, upper respiratory tract, anterior part of the eye, peripheral nerves and testes (Binford 1985).

Leprosy was classified by Ridley and Jopling

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based on histological and immunological features into five types (Ridley & Jopling 1966) tuberculoid (TT), borderline tuberculoid (BT), mid borderline (BB), borderline lepromatous (BL), and lepromatous leprosy (LL). The frequent lack of sensation on the skin, visible hypopigmented skin, hyperpigmented anesthetic, and hypoesthetic skin lesion are the main clinical presentations of leprosy (Alrehaili 2023). Clinical diagnosis and skin smear examination are required for early diagnosis and treatment to make the patient non-infectious. However, confirmation of diagnosis requires a histopathological examination (Pandya & Tailor 2008).

Multi drug therapy (MDT) is a crucial approach for leprosy control programs as recommended by WHO. However, with patients not showing clinical improvement after adult MDT, there is a need to evaluate the changing trends in clinical and histological parameters.

A fairly high percentage of patients with leprosy who complete recommended fixed duration of MDT are left with residual skin lesions, which are a great source of anxiety to the patient and the family (Joshi 2011). A small number of patients go on to develop new lesions after completion of the course of treatment which are regarded as either late reactions or relapse (Joshi 2011).

The present study highlights the importance of histopathological examination for exact subtyping of leprosy in order to determine the correlation between the clinical and histopathological features in cases of leprosy.

Materials and Methods

Sixty patients diagnosed with various types of leprosy and lepra reactions, were included in a prospective study, evaluating the clinical, histological and bacteriological changes, before and after taking 6 months of adult MB MDT. The study was done at Dhiraj Hospital, Gujarat after approval from Ethics committee. All 46 newly diagnosed leprosy cases >12 years of age (patients between 12 – 18 years weighing <40kgs were treated with multidrug therapy as per weight – rifampicin {10mg/kg once a month}, dapsone {2mg/kg daily}, clofazimine {100 mg once a month, 50 mg twice weekly}), 14 patients who had commenced treatment within the last 6 months (with or without reactional states) and had stopped the treatment on their own accord (no records available) were considered as defaulters and were included in the study as new cases. Thorough clinical examination was done and details were recorded in a predesigned proforma. Depending on the number of lesions, their morphology and nerve involvement, patients were classified in the Ridley-Jopling spectrum as tuberculoid (TT), borderline tuberculoid (BT), mid-borderline (BB), borderline lepromatous (BL) and lepromatous (LL), indeterminate (I), histoid leprosy (HL), Type 1 and 2 lepra reactions. Patients were started on MB -MDT comprising of rifampicin (600 mg once a month), clofazimine (300 mg once a month and 50 mg daily), dapsone (100 mg daily) for 12 months (Huang et al 2024). Patients were subjected to slit skin smear (SSS) and skin biopsy from active lesions at 1st visit (Day 0) and again after 6 months (Day 180) of starting MDT. SSS was taken from right earlobe, right eyebrow, left eyebrow and left earlobe and were subjected to modified Ziehl – Neelsen staining which included covering the slide with concentrated carbol fuchsin followed by applying heat beneath it for 15 mins. The stain was then tipped away and 5 % sulfuric acid was poured onto the slide until it decolorized to faintly pink and then washed in running water. The slide was later counter stained with 1% methylene blue for 10 seconds, washed in running water and allowed to dry and examined under the microscope (Mohan et al 2023).

After 6 months of MDT, clinical changes in skin lesions, nerve involvement, deformity, reactional states were noted. Histopathological exam and BI (SSS) was performed. Histopathological

features assessed included epidermal changes, involvement of the sub-epidermal zone, character and extent of granuloma, density of lymphocytic infiltrate, epithelioid cells and other cellular elements, nerve involvement and the presence of *M. leprae*.

MDT was given for 1 year and all patients were on a regular follow up during the surveillance period.

Statistical method used **:**

All the data was tabulated in Microsoft Excel (2019) and further analysed using frequency tables and graphs. The correlation between different variables was established using the SPSS software.

Results

Age of these 60 patients enrolled in the present study ranging from ranged from 12 to 70 years (mean age = 38.85 years). Number of male patients were 41(68.33%), which was higher than female patients : 19 (31.67%) with ratio of 2.15:1 (Table 1).

Out of the 60 patients, most common clinical diagnosis made was lepromatous leprosy (LL) (29 patients, 48.3%), followed by borderline lepromatous (BL) (20 patients, 33.3%), borderline tuberculoid (BT)- (5 patients, 8.33%) (Table 2).

Maximum number of patients (34, 56.6%) presented between 1-5 years of onset of symptoms with a maximum in LL (19 patients) followed by BL (11 patients). 24 (40%) patients presented within 1 year of onset of symptoms and least number of patients (2, 3.33%) presented after 5 years of onset of symptoms (Fig. 1).

Type 1 reaction was observed in 4 patients (6.67%), where 3 patients belonged to BL and 1 patient belonged to BT. Type 2 Reaction (ENL) was seen in a total of 25 patients (41.67%). Out of

Table 1: Age Distribution of patients studied.

Age	Number and percentage of patients
11-20 Years	6 (10.00%)
21-30 Years	15 (25.00%)
31-40 Years	14 (23.33%)
41-50 Years	10 (16.67%)
51-60 Years	12 (20.00%)
>60 Years	3 (5.00%)

Table 2: Clinical diagnosis (Ridley & Jopling) of patients included in the study.

Clinical Diagnosis	Number	Percentage
TT	2	3.33%
BT	5	8.33%
BB	1	1.67%
BL	20	33.33%
LL	29	48.33%
HL	3	5.00%
Total	60	100.00%

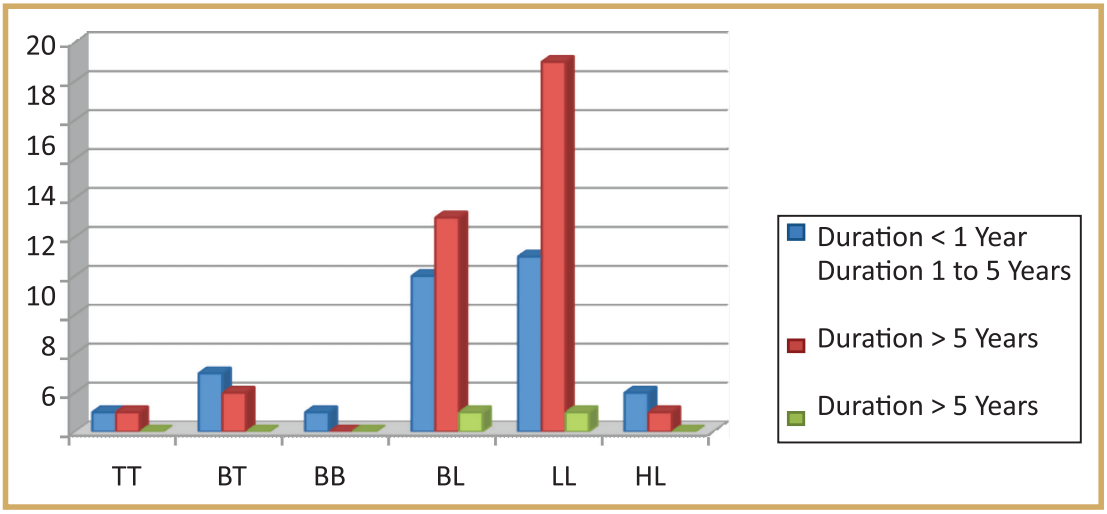

Fig. 1: Duration of onset of clinical features before starting treatment.

Table 3: Clinical presentation of cases especially pertaining to those having neuritis, reactions, deformities and trophic ulcers.

Clinical Diagnosis	Neuritis		Lepra reactions				Deformity				Trophic ulcer	
	Absent	Present	Type 1		Type 2 (ENL)		Hand		Foot		Absent	Present
			Absent	Present	Absent	Present	Absent	Present	Absent	Present		
TT	2	0	2	0	2	0	2	0	2	0	2	0
BT	3	2	4	1	4	1	3	2	5	0	5	0
BB	1	0	1	0	1	0	1	0	1	0	1	0
BL	17	3	17	3	17	3	17	3	18	2	17	3
LL	14	15	29	0	8	21	12	17	26	3	22	7
HL	2	1	3	0	3	0	3	0	3	0	2	1
Total	39	21	56	4	35	25	38	22	55	5	49	11
Grand Total	60		60		60		60		60		60	

this, 21 patients belonged to LL, 3 patients to BL and 1 patient to BT. Out of the total 60 patients, 22 patients (36.67%) had deformity of the hand and 5 patients (8.3%) had deformity of the foot. Maximum number of patients with deformity of the hand was seen in LL (17) followed by BL (3), BT (2) and of the foot was seen in LL (3) followed by BL (2) (Table 3).

The most common nerve affected in leprosy was ulnar nerve in 48 (80%) patients, out of which maximum patients belonged to LL (24) followed by BL (18). Other nerves commonly affected

in leprosy were lateral popliteal nerve in 38 (63.33%) patients (LL-17, BL-15) ; radiocutaneous nerve in 32 (53.33%) patients (LL- 17, BL-10); radial nerve in 26 (43.33%) patients (LL-15, BL-9) and posterior tibial nerve in 22 (36.67%) patients (LL-10, BL-7). The least common nerves affected are supratrochlear nerve and infraorbital nerve in 1 (1.67%) patient each of LL. 11 patients (18.3%) developed trophic ulcer. Maximum number of patients with trophic ulcers were seen in LL (7), followed by BL (3) and HL (1) (Table 3).

At first visit (Day 0), out of the total 60 patients, clinicohistopathological correlation was observed in 44 patients (73.3%), where 100% concordance was present in BB (1 patient) and HL (3 patients), 89.6% (26 out of 29 patients) in LL, 60% (3 out of 5 patients) in BT and least being 50% each in TT (1 out of 2 patients) and BL (10 out of 20 patients). Of these 60 patients, 46 were newly diagnosed cases, 14 were partially treated cases but the past records were unavailable to verify the months of treatment taken.

The correlation between clinical and histopathological diagnosis at first visit was statistically significant (p value < 0.05) (Table 4).

At 6 months follow up, out of the total 60 patients, clinicohistopathological correlation was observed in 43 patients (71.6%), where 100%

Table 4: Clinicohistopathological correlation at 1st visit.

Clinical diagnosis (1st visit)	Histopathological diagnosis (1st visit)						Total	% Concordance	p value
	TT	BT	BB	BL	LL	HL			
TT	1	1	0	0	0	0	**2**	**50.0**	
BT	1	3	0	1	0	0	**5**	**60.0**	
BB	0	0	1	0	0	0	**1**	**100.0**	
BL	0	6	1	10	3	0	**20**	**50.0**	**0.0001**
LL	0	0	1	2	26	0	**29**	**89.6**	
HL	0	0	0	0	0	3	**3**	**100.0**	
Total	**2**	**10**	**3**	**13**	**29**	**3**	**60**	**73.3**	

Table 5: Clinicohistopathological correlation at 6 months of treatment.

Clinical diagnosis (1st visit)	Histopathological diagnosis (at 6 months)						Total	% Concordance	p value
	TT	BT	BB	BL	LL	HL			
TT	1	1	0	0	0	0	2	**50**	
BT	0	2	2	0	1	0	5	**40**	**0.0001**
BB	0	0	1	0	0	0	1	**100**	
BL	1	3	1	11	4	0	20	**55**	
LL	0	0	0	1	28	0	29	**96.5**	
HL	0	0	0	0	3	0	3	**0**	
Total	**2**	**6**	**4**	**12**	**36**	**0**	**60**	**71.6**	

concordance was present in BB (1 patient), 96.5% (28 out of 29 patients) in LL, 55% (11 out of 20 patients) in BL, 50% (1 out of 2 patients) in TT, 40% in BT (2 out of 5 patients) and least being 0% in HL (0 out of 3 patients). The correlation between clinical and histopathological diagnosis at 6 months follow up was statistically significant (p value < 0.05) (Table 5).

Table 6 shows the histopathological changes across the spectrum of leprosy after 1st and 6th months of MDT. At the end of 6 months, few patients showed histopathological features suggestive of borderline lepromatous, mid borderline and lepromatous leprosy. Hence, accounting to increase in numbers.

After 6 months of treatment, epidermal changes, i.e., atrophy and hyperkeratosis have decreased from 86.67% to 85% and 25% to16.67% respectively and rete pegs shortening and flattened basal layer have increased from 63.33% to 75% and 3.33% to 8.33% respectively. Over 6 months of treatment, dermal changes, i.e., superficial dermal infiltrate have decreased from 66.67% to 58.33%, epithelioid granuloma from 33.33% to 20%, foamy histiocytes from 20% to 13.33%, giant cells from 16.67% to 6.67% and histiocytic granuloma from 11.67% to 8.33%. The most evident decrease was observed in Grenz zone among the dermal changes, where they reduced dramatically from 3.33% to 0%. Other changes such as periappendageal infiltrate increased from 55% to 58.33%, deep dermal infiltrate from 35% to 36.67% and foamy macrophages from 36.67% to 40%. However, none of the changes were statistically significant implying there was no potential marker to monitor.

Histopathological changes in different types of leprosy cases in untreated and post six months in a few representative cases are shown in Figs. 2 to 7.

In untreated TT case, epidermis showed mild acanthosis and basket weave hyperkeratosis (black arrow). There was presence of superficial

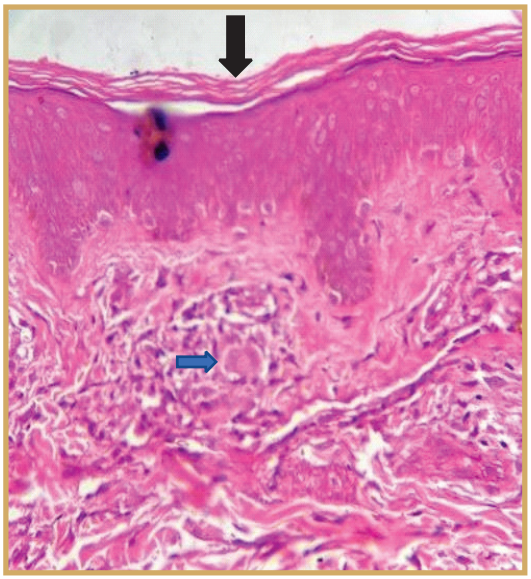

Fig. 2a: Tuberculoid (TT) leprosy – 1st visit (H and E, x40)

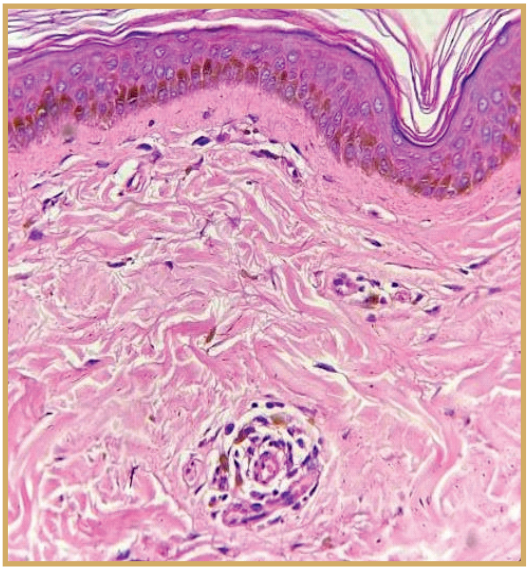

Fig. 2b: Tuberculoid leprosy – at 6th month (H and E, X40).

Table 6: Histopathological changes after 6 months of MDT.

Histopathological findings	No. of patients (%)											
	TT		BT		BB		BL		LL		HL	
	1st visit	6th Month	1st visit	6th Month	1st visit	6th Month	1st visit	6th Month	1st visit	6th Month	1st visit	6th Month
Epidermal changes												
Atrophy	2	2	9	6	2	4	12	11	24	28	3	1
Rete pegs shortening	2	2	7	6	1	3	10	6	16	28	2	3
Hyperkeratosis	1	0	3	1	1	1	4	1	6	7	0	0
Flattened basal layer	0	0	0	0	0	0	0	2	2	3	0	0
Dermal changes												
Grenz zone	0	0	0	0	0	0	1	0	1	0	0	0
Epithelioid granuloma	1	0	9	5	2	0	1	3	7	4	0	0
Histiocytic granuloma	0	0	1	1	0	0	1	0	5	4	0	2
Giant cells	1	0	3	2	0	0	1	0	5	2	0	0
Foamy macrophages	0	0	2	2	1	1	3	4	16	17	0	1
Periappendageal Infiltrate	2	0	3	2	2	3	7	7	17	23	2	1
Foamy histiocytes	0	0	0	2	0	0	2	0	8	6	2	2
Superficial dermal infiltrate	0	0	5	3	2	2	9	3	22	27	2	3
Deep dermal infiltrate	0	0	1	0	3	2	1	0	13	20	3	3

mild inflammatory infiltrate of lymphocytes which focally damage the basal layer of epithelium. There was also presence of langhans giant cells (blue arrow). Deep dermis showed infiltration of lymphocytes and histiocytes. (Fig. 2a).

At 6 six months of treatment in TT case, acanthosis was found to be reduced- no elongation of rete pegs. Inflammation markedly reduced in epidermis and dermis (Fig. 2b).

In untreated BB case, the epidermis showed thinning. Shortening of rete pegs seen. Full thickness dermis showed lymphocytic infiltrates (black arrow). Ill formed granulomas can be seen (Fig. 3a).

At six months in this BB case, the epidermis was slightly less thickened, rete pegs were seen. Dermis showed decreased inflammatory infiltrate (Fig. 3b).

Thinning of epidermis noted and flattening of rete pegs was seen in a untreated LL case. Grenz zone was present (black arrow). Chronic inflammatory infiltrate comprising of histiocytes, lymphocytes and foamy macrophages was seen. Periadnexal and perineural lymphocytic infiltration was also observed (Fig. 4a).

After six months of treatment in this LL case, epidermis showed slight thickening, Rete pegs starting to appear and dermis shows marked reduction in periadnexal and perineural infiltration (Fig. 4b).

In an untreated BT case, thinning of epidermis along with loss of rete pegs was seen. Ill formed granulomas comprising of lymphocytes and histiocytes were seen in dermis (black arrow) (Fig. 5a)

After six months of treatment in this BT case, epidermis showed slight appearance of rete pegs. Granulomas showed resolution with scattered histiocytes in the dermis (Fig.5b)

In untreated BL case, the epidermis showed thinning with loss of rete pegs. Scattered inflammatory infiltrate with lymphocytes and

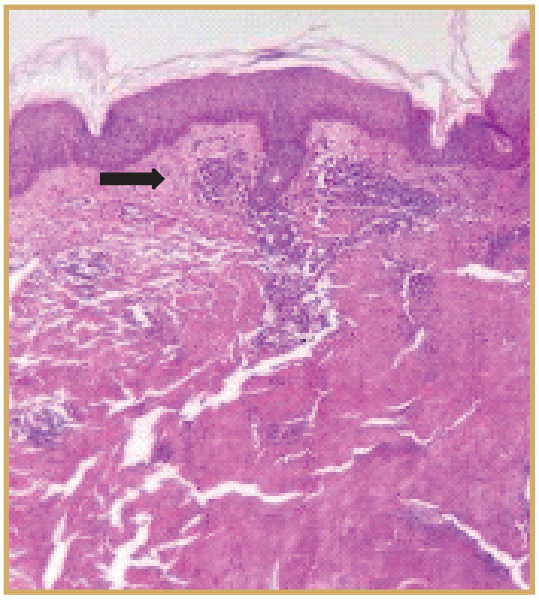

Fig. 3a: Mid Borderline (BB) leprosy – 1st visit (H and E, x40)

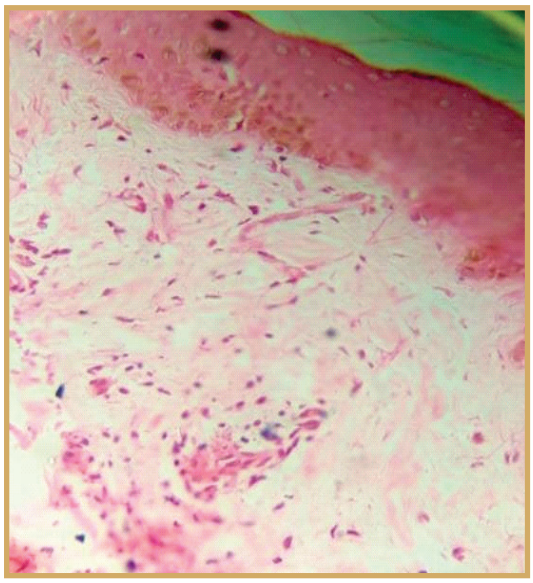

Fig. 3b: Mid Borderline (BB) leprosy – at 6 months (H and E, X 40).

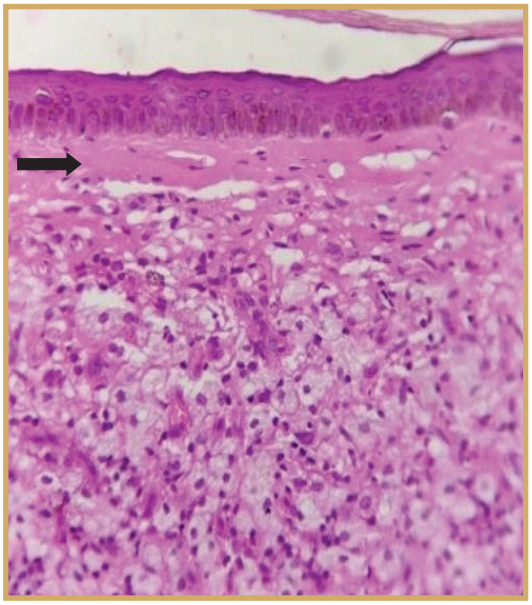

Fig. 4a: Lepromatous (LL) leprosy – at 1st visit (H and E, X40).

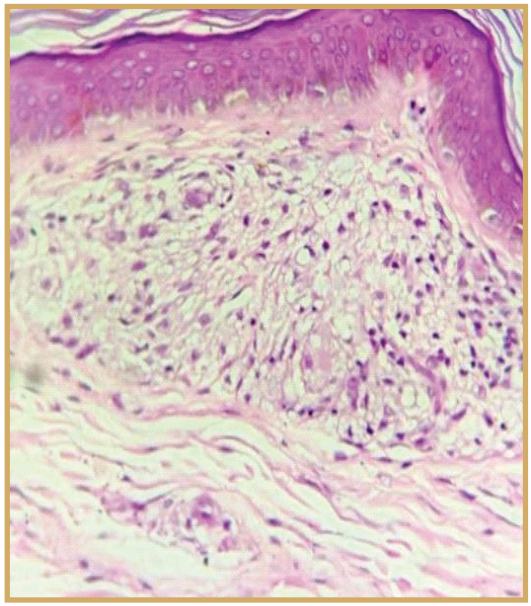

Fig. 4b: Lepromatous (LL) leprosy – at 6 months (H and E, X40).

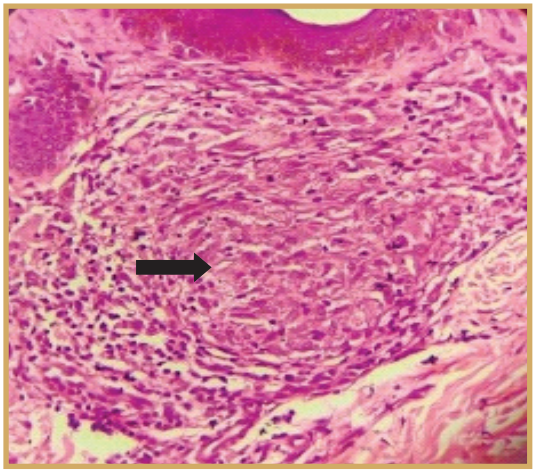

Fig. 5a: Borderline Tuberculoid (BT) leprosy – at 1st visit (H and E, X40).

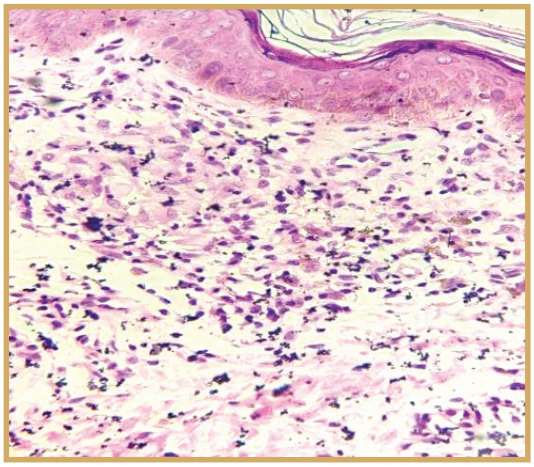

Fig. 5b: Borderline Tuberculoid (BT) leprosy – at 6 months (H and E, X40).

histiocytes but no granulomas were seen (Fig.6a).

After six months of treatment in this BL case, epidermis showed mild thickening with reappearance of rete pegs. Dermis shows reduced inflammatory infiltrate (Fig. 6b).

In untreated histoid leprosy, epidermis showed mild acanthosis and hyperkeratosis. There was presence of Grenz zone (black arrow). Superficial

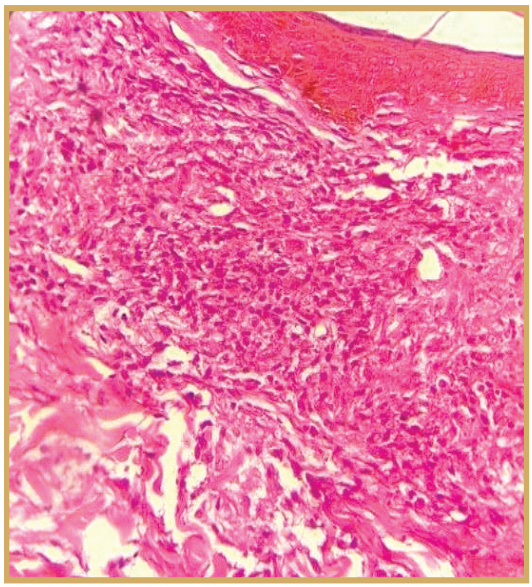

Fig. 6a: Borderline Lepromatous (BL) leprosy - at 1st visit (H and E, X40).

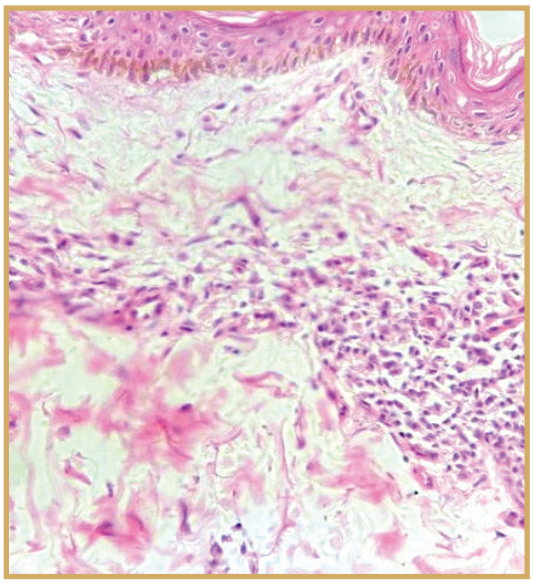

Fig. 6b: Borderline Lepromatous(BL) leprosy – at 6 months (H and E, x40).

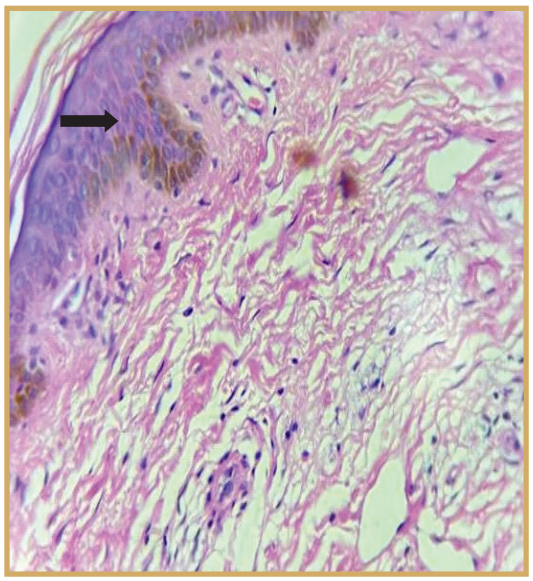

Fig. 7a: Histoid leprosy –1st visit (H and E, X40).

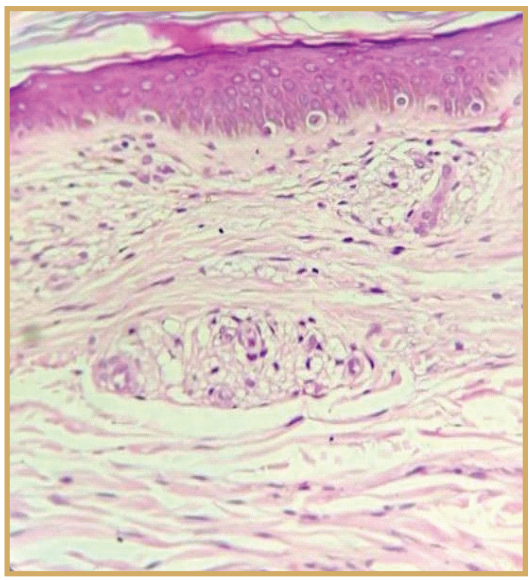

Fig. 7 b: Histoid leprosy – at 6 months (H and E, X40).

Table 7: Changes in bacteriological positivity and mean bacteriological index (BI) after 6months of treatment.

Clinical Diagnosis	Slit Skin Smear – Bacteriological positivity				Mean Bacteriological index at 1st visit, at 6th Months	
	BI Negative		BI Positive			
	1st Visit	6th Month	1st Visit	6th Month	Mean BI at 1st Visit	Mean BI at 6th Months
TT	2	2	0	0		
BT	5	5	0	0	0	0
BB	1	1	0	0	0	0
BL	12	16	8	4	0.8	0.25
LL	16	23	13	6	1.06	0.3
HL	0	1	3	2	5.3	2.3
Total	**36**	**48**	**24**	**12**	**7.16**	**2.85**

Table 8a: Clinical and histopathological characteristics of smear negative borderline lepromatous cases.

BL (SSS Negative) (N=12)	**Histo-pathological Changes**	**Epidermal**	Atrophy	75% (n=9)
			Hyperkeratosis	16.67% (n=2)
			Rete pegs shortening	58.3%(n=7)
			Flattened basal layer	0%(n=0)
		Dermal	Epithelioid granuloma	0%(n=0)
			Histiocytic Granuloma	8.33%(n=1)
			Giant cells	8.33%(n=1)
			Grenz zone	8.3%(n=1)
			Superficial dermal infiltrate	75%(n=9)
			Deep dermal infiltrate	33.33%(n=4)
			Periappendageal infiltrate	33.33%(n=4)
			Foamy macrophages	33.33%(n=4)
			Foamy histiocytes	8.33%(n=1)
		FF Stain		25%(n=3)
	Clinical Aspect	**Loss of sensation**	Lesional	16.67%(n=2)
			Periphery (glove&stocking)	50%(n=6)
		Nerve Examination	Radial Nerve	41.67%(n=5)
			Ulnar Nerve	83.33%(n=10)
			Lateral Popliteal Nerve	58.33%(n=7)
			Posterior Tibial Nerve	25%(n=3)
		Neuritis		8.33%(n=1)

Table 8b: Clinical and histopathological characteristics of smear negative lepromatous leprosy cases.

LL (SSS Negative) (N=16)	**Histo-pathological Changes**	**Epidermal**	Atrophy	93.75%(n=15)
			Hyperkeratosis	25%(n=4)
			Rete pegs shortening	68.75%(n=11)
			Flattened basal layer	6.25%(n=1)
		Dermal	Epithelioid granuloma	0%(n=0)
			Histiocytic granuloma	6.25%%(n=1)
			Giant cells	6.25%(n=1)
			Grenz zone	6.25%(n=1)
			Superficial dermal infiltrate	75%(n=12)
			Deep dermal infiltrate	43.75%(n=7)
			Periappendageal infiltrate	62.5%(n=10)
			Foamy macrophages	87.5%(n=14)
			Foamy histiocytes	37.5%(n=6)
		FF Stain		25%(n=4)
	Clinical Aspect	**Loss of sensation**	Lesional	6.25%(n=1)
			Periphery (glove & stocking)	62.5%(n=10)
		Nerve Examination	Radial Nerve	62.5%(n=10)
			Ulnar nerve	87.5%(n=14)
			Lateral Popliteal nerve	75%(n=12)
			Posterior Tibial Nerve	43.75%(n=7)
		Neuritis		62.5%(n=10)

Table 9: Comparison of clinicohistopathological correlation in various studies.

Clinicohistopathological correlation (%)					
Type of leprosy	**Present study (first visit)**	**Suri et al (2014)**	**Kumar et al (2014)**	**Atram et al (2020)**	**Soni et al (2019)**
TT	50	33.3	81.8	88.4	75
BT	60	94.1	34.5	86.4	75
BB	100	100	54.1	96.1	0
BL	50	62.5	21.3	95.1	0
LL	89.6	50	64.3	97.1	63.6
HL	100	50	87.5	98	100
Total	**73.3**	**75.5**	**62.9**	**92.4**	**65.8**

dermis showed perivascular, interstitial and periadnexal infiltrate of vacuolated histiocytes (Fig. 7a). After six months of treatment epidermis showed reduction in acanthosis and hyperkeratosis. There was marked reduction in perivascular, interstitial and periadnexal infiltrate (Fig. 7b).

Slit-skin smear (SSS) positivity : At first visit, out of the total 60 patients, SSS were positive for acid fast bacilli in 24 patients (40%).

At 6 months follow up, 12 patients (20%) showed positive SSS (bacteriological index). Mean BI showed a decrease after 6 months of MDT in BL, LL, and HL types of leprosy. It remained negative in TT, BT and BB type of leprosy. The correlation between clinical diagnosis and microbiological changes (Bacteriological Index) at 1st visit and at 6 months follow up were statistically significant (p value < 0.05) (Table 7).

Interestingly, among smear negative BL cases, grenz zone was seen in 8.3% of cases, Fite Faraco (FF) stain was positive only in 25% of patients and superficial dermal infiltrate was seen in 75% of patients Clinically, neuritis was observed only in 1 patient. (Table 8a).

Among SSS negative lepromatous cases, Fite Faraco stain was positive in 25% of patients. Histiocytic granuloma was noted in 6.25% of patients. Deep dermal infiltrates were seen in 43.75% cases. Lesional anesthesia probably represents patients who have downgraded from tuberculoid to lepromatous pole (Table 8b).

Discussion

During the study period of 18 months in the present study, a total 60 patients of leprosy were evaluated. In the present study, spectrum of patients with leprosy ranged from 12 to 70 years with a mean age of 38.85 years which was concordant with studies done by Kumar et al (2014). (40.1 years), Soni et al (2019) (32.64 years) and Tiwari et al (2015) (32.66 years). Maximum frequency (25%) was found in the age group of 21–30 years which was comparable to the results of Kumar et al (2014)(23.9%), Soni et al (2019) (41.46%) and Manandhar et al (2013) while our findings differed with Nadia et al (2015) who reported maximum cases in the age group of 31–40 years. The male preponderance observed in the present study (2.15:1) is similar to studies done by Tiwari et al (2015) (1.4:1), Soni et al (2019) (1.56:1) and Nadia et al (2015) (1.8:1). Kumar et al (2014) and Manandhar et al (2013) also reported male preponderance; however, in these studies, the ratio was higher ranging from 2.3 to 3:1.

Among the clinical types lepromatous leprosy (LL), 29 patients (48.3%) was the most common type of leprosy in the present study, in contrast to studies conducted by Soni et al (2019), where TT was the most common type and Suri et al (2014), where BT was the most common type. In our study, BL leprosy was the second most common type. The frequency of LL (48.3%) was much higher compared to Suri et al (2014) (18%) and Nadia et al (2015) (20.3%).

Correlation of clinical classification and histopathological findings is known to vary in different studies (Table 9). In the present study, the maximum correlation at first visit was seen in BB and HL (100%) followed by LL (89.6%), BT (60%) and least, TT and BL (50% each). At 6 months follow up, 43 patients (71.6%) showed correlation between clinical and histopathological diagnoses. The maximum correlation was seen in BB (100% each) followed by LL (96.5%), BL (55%), TT (50%), BT (40%) and least, HL (0%). The cases which are towards the borderline spectrum histopathologically are likely to experience more reactional episodes thus warranting a clinicohistopathological correlation for efficient management of such cases.

The frequency of type 1 and type 2 lepra reaction (ENL) in our study was 6.67% and 41.67%

respectively, which was much higher than those reported by Kumar et al (2014) (0%, 17.9%) and Soni et al (2019) (7.32%, 17.07%). Apart from the fact that maximum patients were from lepromatous pole with high bacillary load in our study, there is a rising trend towards reactional states in recent times probably because of increased cases of bacterial resistance.

In the present study, at first visit, SSS (bacteriological index) was positive in 24 (40%) patients, while in a study conducted by Soni et al (2019), it was positive for 48.7% patients and for 40% patients by Suri et al (2014). At 6 months follow up, in the present study, only 12 patients (20%) showed positive SSS (bacteriological index). The decrease in BI after 6 months of MDT was statistically significant (p value < 0.05) in the present study. Most of the studies have been long term studies which did not focus on bacteriological index over 6 months. The sensitivity and specificity of SSS is reported to be as low as 75% and 69.23%, respectively (Swapna et al 2021).

Further, there is a higher probability of detecting AFB in biopsy specimens stained by ZN stain and Wade Fite stain than that of detection by SSS (Roy et al 2020).

In the present study, amongst epidermal changes, atrophy (86.67%) was the most common change which was consistent with the findings by Suri et al (2014), where atrophy was 66.67%, however Atram et al (2020) reported atrophy in only 32.27% cases. The least common epidermal change observed in our study was flattened basal layer (8.33%) whereas that in the study by Atram et al (2020) was ulceration (12.69%). The most common dermal change observed in the present study was superficial dermal infiltrate (66.67%) and in the study by Atram et al (2020), it was periappendageal lymphocytes (66.67%) and by Suri et al (2014), it was grenz zone (51.1%). The least common dermal change in our study was Grenz zone (3.33%). On the contrary, Atram et al (2020), observed dermal edema (3.7%) as the least common dermal change and Suri et al (2014), observed giant cells as the least common dermal change. A dramatic change with treatment over 6 months was observed in the grenz zone where they reduced from 3.33% to 0%. As grenz zone has reduced from 3.33% to 0% as observed in our study after 6 months of treatment, perhaps this may serve as a marker for follow up in patients on MDT.

In the present study, at first visit, Wade Fite stain was positive in 24 (40%) patients, which was comparative by studies conducted by Soni et al (2019) (42.46%), Atram et al (2020) (51.85%), Tiwari et al (2015) (55%), while it was considerably higher than Manandhar et al (2013) (25%) and Nadia et al (2015) (23.7%) At 6 months follow up, in the present study, only 9 patients (15%) showed positive Wade Fite stain. In the present study, with 6 months of treatment, there was a reduction in atrophy (86.67% to 85%), hyperkeratosis (25% to 16.67%) in epidermal changes and superficial dermal infiltrate (66.67% to 58.33%), epithelioid granuloma (33.33% to 20%), foamy histiocytes (20% to 13.33%), giant cells (16.67% to 6.67%) and histiocytic granuloma (11.67% to 8.33%) in dermal changes. However, an increase in rete pegs shortening (63.33% to 75%) and flattened basal layer (3.33% to 8.33%) in epidermal changes and periappendageal infiltrate (55% to 58.33%), deep dermal infiltrate (35% to 36.67%) and foamy macrophages (36.67% to 40%) in dermal changes was observed. The foamy macrophages found in the dermis earlier in the lepromatous pole of disease get converted to lipid laden macrophages with treatment, which appear similar to the former on histopathology. In a study by Podder et al (2018), granuloma was present in about 34.9% and 4.65% cases before and after treatment, respectively. Most cases (85%) showed normal epidermis (Podder et al 2018). Lymphocytic infiltration in the dermis

reduced significantly after 6 months of MDT (Podder et al 2018). Jain et al (2016) concluded that histological regression is delayed compared to clinical resolution.

Combining immunotherapy (Mw/BCG) with chemotherapy accelerated the bacteriological and histopathological granuloma fraction clearance as observed in the study conducted by Katoch et al (2004)**.** Thus, the prolonged clearance duration could possibly be attributed to the emergence of resistance and timely done histopathological examinations could aid in suspecting and investigating the same.

Conclusion

Histopathology forms the basis of accurate diagnosis of any dermatological disease, leprosy is no different. This study has evaluated the clinical as well as histopathological role of 6 months of MDT. Large scale studies of histopathological changes following MDT are needed to assess the efficacy in the changing times of emergence of resistance and treatment failure in some cases. Many factors influence the histopathological diagnosis like number of cases of each type, number of sections stained with Ziehl–Neelsen stain, duration of lesion, depth of biopsy, quality of the histopathological section, immune status of the patient, different criteria used to select the cases, and any previous treatment taken by the patient. Biopsy taken early in the disease course has more chances for clinicohistopathological discordance. Interobserver variation, clinically and histopathologically, is also an important influencing factor.

***Limitation of the study*:**

The study was done for 6 months, however longer follow up is recommended for accurate clinical and histopathological analysis of efficacy of MDT. Since the sample size is small, large number of patients are required to corroborate the results.

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