Persistence of skin lesions after completion of treatment in paucibacillary leprosy: prevalence and its clinicopathological associations

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Abstract

Background: Leprosy is a chronic infectious disease caused by *Mycobacterium Leprae*. It usually affects skin and nerves. Diagnosis of leprosy is mainly clinical, however diagnosis can be confirmed by identification of bacilli and by finding of characteristic histopathological features. Persistence of skin lesions after completion of treatment is a great anxiety to the patient and the family. There were hardly any studies on persistent skin lesions.

Objectives: The main objective was to determine the histopathological changes of skin lesions after completion of 6 months multi drug treatment (MDT) in patients with paucibacillary (PB) leprosy. Other specific objectives were to determine the prevalence of persistent lesions after completion of treatment, to determine the association between persistent lesions and active granulomata in PB leprosy, and to determine the factors associated with persistent lesions.

Method: This study was carried out on a cohort of 77 patients with biopsy confirmed tuberculoid leprosy who have completed 6 months PB treatment, attending Colombo South Teaching Hospital from July 2012 to July 2013. Data was collected from interviewer administered questionnaire. Four mm size punch biopsies were performed, pre treatment and post treatment. Histology findings were compared.

Results: The study sample consisted of 77 patients. 57.1% were females. Age ranged from 6.5 years to 76 years and the mean age was 33.92 years (SD =18.62 years) with the median of 33 years. Most (42.9%) patients sought treatment after 1 to 2 years of the onset of the disease. Twenty one patients (24%) did not have persistent skin lesions after completion of treatment, whereas fifty six patients (73%) had persistent skin lesions. Small minority of 5.2% had type 1 reaction. Furthermore, most (54.5%) patients' drug regime had to change over to MDT (MB) without dapsone due to dapsone induced side effects. Interestingly, 17 (22.1%) patients who had persistent hypopigmented patches had persistent granulomata in the post treatment biopsy which is statistically significant. However, majority had resolving histological features such as basal hyperpigmentation, plasmacytoid cell infiltrate and sclerosis of the dermis even though they had persistent skin lesions.

There was no significant association between persistent skin lesions and drug regime, type I reaction, co-morbidities, and type of initial lesion.

Conclusion: In our study population, prevalence of persistent skin lesions was high. We should pay attention to this fact as some had active granulomata, even after completion of treatment. That may imply slowly resolving disease or drug resistance. In fact, two patients who had active granulomata in the post treatment biopsy developed new lesions on follow up. Hence, persistent skin lesions after treatment need to be followed up regularly to detect resistant cases. Further studies should be done involving larger samples to identify risk factors which could contribute to persistent skin lesions. In contrast, we can convince patients that skin lesions will disappear with time, even though it does not happen just after completion of treatment.

Introduction

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*.

In 1895 Armauer Hansen discovered the leprosy bacilli[1]. Before that leprosy was thought to be a hereditary disease. Danielsen and Boek classify leprosy as two types; Elephantiasis Graecorum tuberose and Elephantiasis Anesthetosa[1]. The mixed variety was also described and referred to as Lepra Leprosa by Carter of Mumba.

Out of several classification systems; Ridley and Jopling classification system, which was proposed in 1966 is widely accepted. The Ridley and Jopling classification is based on bacteriological, immunological, histopathological, and clinical features of leprosy. It is essentially a five group classification with two polar forms (TT, LL), which are immunologically stable. Between these poles lies immunologically unstable borderline group, which has been subdivided into three categories namely BT, BB, BL[4,5].

Event though the diagnosis of leprosy is clinical; laboratory investigations help to diagnose doubtful cases and early identification of the disease. Of all the laboratory tests available slit skin smear, which was first developed by Wade Boderigues in 1927, is the most simple and valuable one[2,3]. It has specificity of 100%. However the sensitivity of this examination alone is low, because smear positive patients represent

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10-50% of all patients as reported in various studies. Other commonly used method is the skin biopsy from the active edge of the skin lesion. Nerve biopsies are rarely performed. *Mycobacterium leprae* culture and serodiagnoses techniques are available in research centres[1,2].

According to WHO guidelines paucibacillary patients (TT, BT) are treated with monthly rifampicin and daily dapsone, whereas lepromatous pole (BB, BL, LL) are treated with monthly rifampicin, daily dapsone and clofazamine[6].

In some patients skin lesions persist several months after treatment. There have been hardly any studies conducted on persistent skin lesions after treatment. Biopsy of persistent skin lesions after treatment can show features of disease activity or inactivity. Presence of granuloma and lymphoytic infiltrate around adenexial structures imply disease activity, where as basal hyperpigmentation, myxoid changes, odema of the dermis, plasmacytoid cells, sclerotic dermis indicate healing process[7].

Hence, this study was conducted to determine histopathological changes after completion of 6 months MDT treatment in patients with paucibacillary leprosy, to determine the prevalence of persistent lesions after completion of treatment and to find out associations of persistent skin lesions.

Objectives

General objectives

To determine the histopathological changes after completion of 6 months MDT treatment in patients with paucibacillary leprosy.

Specific objectives

1. To determine the prevalence of persistent lesions after completion of treatment.
2. To determine the association between persistent lesions and active granulomata in PB leprosy.
3. To determine whether following are associated with persistent lesions:
    A. Duration of the illness before commencement of treatment.
    B. Type 1 reaction.
    C. Cormobidities.
    D. Type of initial lesion.

Method

The study was carried out on cohort of 77 patients with biopsy confirmed Tuberculoid leprosy who have completed 6 months PB treatment, attending Colombo South Teaching Hospital from July 2012 to July 2013. Patients with facial lesion and risk of keloidal tendency were excluded from the sample. Informed consent was taken from participants.

Data was collected from interviewer administered questionnaire and four mm size punch biopsies were performed. Subsequently, pre treatment biopsy was compared with post treatment biopsy.

Outcome of the post treatment biopsy was assessed as follows.

Basal pigmentation granuloma	+ +	- -
Odema of the perivascular, periadenexial adventia	+	-
Myxoid appearance of upper and mid dermis	+	-
Plasmacytoid cells with abundant amophilic cytoplasm	+	-
Thick sclerotic dermis	+	-
Normal histology	+	-

The statistical significance of the response was assessed by chi-square test for independence.

Results

The study was conducted at the Dermatology Clinic in Colombo South Teaching Hospital on 77 patients. All recruited subjects gave consent to participate in the study. Therefore, the respondent rate was 100 percent.

Age ranged from 6.5 years to 76 years and the mean age was 33.92 years (SD=18.62 years) with the median of 33 years. 58.4 percent of patients were below 34 years and 18.2% below 14 years of age. There was a female prominence in the sample, which was 57.1 percent and it was not statistically significant (p=0.076).

There were granulomatous lesions seen in 83.1 percent of patients and only 16.9 percent patients had indeterminate lesion in the initial biopsy.

Majority of the study sample did not have any co-morbidities (89.6 percent) and 5.2 percent were diabetic patients, whereas 1.3 percent had hypertension, hyperlipidaemias, fatty liver disease, and chronic liver disease.

There were 73 percent patients who had persistent skin lesions after completion of treatment. Hence, period prevalence of persistent skin lesions after completing the treatment in our study sample is seventy three.

When analyzing the histo-patholgical changes in post treatment biopsies majority (93.5%) had basal pigmentation, however 6.5% patients had normal histology. Seventeen patients (22.1%) had persistent granulomas. Almost similar percentages (27.3% and 26.0%) were found to have odema of the perivascular, periadenexial/adventia and myxoid appearance of upper and mid dermis respectively. Whereas 7% had plasmacytoid infiltrate, 16.9% had thick sclerotic dermis. There was a statistically significant association between persistent skin lesions and persistence of granulomata in the post treatment biopsy. On the other hand, majority (39 patients) had histopathological features suggestive of disease healing process such as dermal changes, myxoid appearance, plasmacytoid infiltrate, thick sclerotic dermis even-though they had persistent skin lesions.

Table 1. Granuloma vs. Persistent skin lesions

Granuloma	*Presence of persistent lesionss*		*Total*
	Yes	*No*	
Positive	17	0	17
Negative	39	21	60
Total	56	21	77

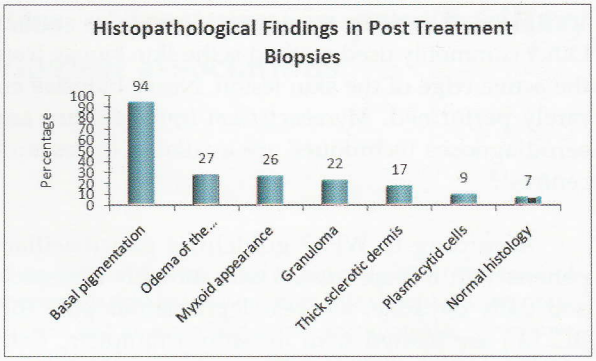

Figure 1.

Presence of persistent skin lesions was compared with variables like presence of active granulomata in post treatment skin biopsies, duration of the illness before commencement of treatment, type 1 reaction, drug regime, and co-morbidities.

Only four patients had reaction and majority did not have reaction (94.8 percent).

In more than half of the patients (54.5 percent) drug regimen was changed due to adverse effects of drugs and 45.5 percent of patient's drug regimen was not changed.

There was no significant association of persistent skin lesions with duration of the illness before commencing treatment, drug regime, type 1 reaction, co-morbidities, and type of initial lesion in the study sample.

Table 2. Presence of persistent skin lesions after completion of treatment according to patients and treatment characteristics

		Presence of persistent lesions			*Significance*
		Yes	*No*	*Total*	
Co-morbidity	No co-morbidities	49 (71.01)	20 (28.99)	69	$\chi^2 = 0.982$,
	Co-morbidity present #	7	1	8	df = 1,
	Total	56 (72.7)	21 (27.3)	77	p = 0.322
Type of initial lesion	Granulomatous	47 (73.4)	17 (26.6)	64	$\chi^2 = 0.096$,
	Indeterminate	9 (69.2)	4 (30.8)	13	df = 1,
	Total	56 (72.7)	21 (27.3)	77	p = 0.756
Drug changed due to adverse reaction	Drug changed	29 (69.1)	13 (30.9)	42	$\chi^2 = 0.631$,
	Not changed	27 (77.1)	8 (22.9)	35	df = 1,
	Total	56 (72.7)	21 (27.3)	77	p = 0.427
Relational status	Reaction present	3 (75.0)	1 (25.0)	4	$\chi^2 = 0.011$,
	Reaction absent	53 (72.6)	20 (27.4)	73	df = 1,
	Total	56 (72.7)	21 (27.3)	77	p = 0.917

Table 3.

Duration of illness before commencing treatment	*Presence of persistent lesions* Yes	No	*Total*	*Results of Chi-Square*
01 to 06 months	20 (66.7%)	10 (33.3%)	30	
06 to 12 months	4 (80.0%)	1 (20.0%)	5	
01 to 02 years	25 (75.8%)	8 (24.2%)	33	
3 Years	2 (66.7%)	1 (33.3%)	3	X^2=2.078,
4 Years	2 (100.0%)	0 (0.0%)	2	df=6,
5 Years	2 (66.7%)	1 (33.3%)	3	
6 Years	1 (100.0%)	0 (0.0%)	1	
Total	**56 (72.7%)**	**21 (27.3%)**	**77**	

Discussion

According to the results of our study majority of the cohort were females. (57.1%). However this is not statistically significant. In most prevalence studies, males outnumber females by 2:1 or 3:1 But this could be due to reporting bias instead of an increased male susceptibility[1].

We found histopathological features of post treatment skin biopsies of persistent skin lesions were similar to studies done in India[7,8]. Indeed, we saw both histopathological features of disease activity and inactivity in the post treatment biopsy samples.

We analyzed all patients just after completion of treatment irrespective of persistent skin lesions. In our study population 21/77 (27%) did not have persistent skin lesion and none showed active granulomata in post treatment skin biopsies. In our study prevalence of persistent skin lesion was 73%. Another study carried out by Lavonia, observed that 50% of patients had skin lesions at the end of 6 month treatment[8]. In our study sample prevalence of persistent skin lesion is quite high.

A significant proportion of subjects 17 (22.1%) had active granulomata at the end of 6 months. This was statistically significant. Interestingly, two patients developed new lesions on further follow up. This turned out to be active granulomata when biopsied. Similarly, there were several reports which showed active granulomata found in >50% of patients on completion of therapy[11, 12, 13, 14].

Eventhough, persistent skin lesion and suspected associations were not significantly strong, to determine the significance properly, a larger sample needs to be studied.

Conclusion

Persistent skin lesions after treatment need to be followed up regularly to detect resistant cases. On the other hand, we can convince patients that even though they have skin lesions just after completion of treatment, it will disappear with time.

Facilities should be extended to detect multi drug resistance of patients who develop new lesions after completion of treatment and patients with active granulomata after completion of treatment.

Further studies should be done involving larger samples to identify risk factors associated with persistent skin lesions.

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