

Changes in the size and number of skin lesions in PB leprosy on treatment and follow-up

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Summary

Background: The increase in size of existing skin lesions and appearance of new skin lesions are considered important signs of clinical activity both in untreated and treated leprosy. To confirm such activity, the number and size of lesions need to be recorded methodically prior to therapy and on follow-up, especially in PB leprosy where clinical signs alone define the reactivation of the disease. However, no systematic follow-up studies are available on changes in size and number of skin lesions in PB leprosy before and after therapy.

Objectives: To measure changes in the number and size of skin lesions in PB leprosy patients before starting MDT PB and after 18 months follow-up in order to evaluate their relevance in assessing clinical improvement and identifying possible relapses.

Design: In 32 untreated leprosy patients with 1–5 skin lesions, the number of skin lesions were recorded on body charts and their size measured using a grid chart method to arrive at total area of involvement in each patient prior to starting MDT PB and after 18 months. Skin smears and skin biopsies were performed at entry and follow-up to assist the clinical evaluation.

Results: Twenty three patients had single skin lesion (SSL), followed by three each with two and three skin lesions respectively, two with four and one with five skin lesions. The area of involvement ranged from six to 1686 sq cm. Few patients with SSL had higher areas of involvement than those who had multiple skin lesions. On follow-up at 18 months, in 14 (44%) patients skin lesions were not measurable, while in 18 (56%) they were measurable, with eight (25%) patients showing no change, three (9%) showing decrease and seven (22%) showing increase in area of involvement. Of the seven patients showing increase, in three it was due to the spread of existing skin lesions alone, in one it was due to a new skin lesion alone and in three due to the spread of existing skin lesions and the appearance of new skin lesions. New skin lesions were multiple (>3) in two patients. TIR was observed in three out of four patients with new skin lesions, and this was persistent at 18 months in

one patient. When histopathology at the entry and 18 month follow-up was compared, in one patient with persistent T1R with appearance of multiple new skin lesions, there was increase in GF from 10 to 40% with histological features of T1R and a BI of granuloma of 1+.

Conclusions: In 32 treated patients of PB leprosy on 18 month follow-up for changes in size and number of skin lesions, of six patients showing increase in area of involvement of existing skin lesions, 3 (50%) developed new skin lesions, indicating persistent disease activity. The new lesions which were associated with T1R increased the total number of skin lesions to >5 in two of these patients requiring a change of drug regimen from PB to MB MDT, with one of them fulfilling clinical and histopathological criteria for relapse of leprosy. Hence, although new lesions are known to occur as part of T1R in PB patients, they are events of great significance which need to be assessed in a methodical manner for their influence on classification and therapy of leprosy.

Introduction

The disease activity in leprosy is defined both by the natural progression of the disease as well as the reactions which occur during its course. The reactions of leprosy are known to occur not only in untreated patients but also in some of those who are under treatment or have completed their prescribed therapy, the commonest being late Type 1 reaction (T1R), also known as reversal reaction. However, the re-appearance of disease activity could also be due to relapse of leprosy and in PB leprosy it needs to be differentiated from late T1R. To confound the issue, further, a number of clinical signs which define disease activity are common to both relapse and late T1R.

Of these 'increase in size of existing skin lesions' and the 'appearance of new skin lesions' are the signs of clinical activity,^{1,2} common to both T1R and relapse in leprosy. Many workers consider them as important clinical signs defining relapse in treated leprosy patients.³⁻⁶ As the changes in size and number of skin lesions in PB leprosy are of significance, systematic recording of such changes could be a method to confirm and if possible differentiate between T1R and relapse of leprosy. For this reason, we undertook a study to measure changes in the number and size of skin lesions in PB leprosy patients before starting MDT PB and after 18 months follow-up in order to evaluate their relevance in assessing clinical improvement and identifying possible relapses.

In the present study, we have followed a cohort of 32 patients of PB leprosy with 1-5 skin lesions and recorded the number and size of all skin lesions in each to arrive at the total area of involvement before MDT PB and at 18 months follow-up, to observe changes in the number and size of skin lesions. We have also attempted to correlate these observations with response to therapy, reactions and histopathology wherever possible.

Patients and Methods

Thirty two consecutive untreated PB leprosy patients of both sexes between 12 and 50 years of age attending the leprosy out-patient clinic of Gandhi Hospital, Secunderabad, India, between March 2003 and July 2005 were included in the study. PB leprosy for this study was defined as patients who were slit skin smear negative and who had five or less than five skin

lesions with at least one cardinal sign of leprosy.⁷ The study was approved by the human ethics committee of Gandhi Hospital. The number of skin lesions in each patient was recorded on a body chart and the area of the skin lesions measured by the grid chart as described below. Skin smear examination and skin biopsy was performed on all patients at time of entry into the study. All patients were administered WHO MDT PB (consisting of Dapsone 100 mg daily and Rifampicin 600 mg once a month) for 6 months and were followed for a period of 18 months. Leprosy reactions observed were treated with appropriate oral corticosteroid therapy⁸ and other supportive measures. Clinically, T1R was diagnosed when skin lesions suddenly become inflamed, red and swollen with or without associated signs of neuritis.⁹ Areas of existing skin lesions and of new skin lesions if any, were measured in all patients at the end of 18 months of study. Follow-up biopsies were performed on the same skin lesion in those patients showing an increase in the area of involvement at 18 months of observation. Biopsies were stained by Haemotoxylin and Eosin stain and modified Fite stain. Histological assessment was done based on the Ridley-Jopling classification,¹⁰ and Granuloma Fraction (GF) and Bacillary Index of Granuloma (BIG) was arrived at based on standard methodology.¹¹

Histologically, the key features of T1R was dermal edema, separation of collagen, dilated vascular channels and intra and extra cellular edema of the granuloma.¹² Clinically, relapse was defined in terms of development of new lesions; new activity in existing lesions; extension of lesions and/or a positive BI in a previously negative patient.¹³ Histologically, when there was increased inflammatory cell response; higher Granuloma fraction and/or presence of bacilli in a biopsy when compared to the earlier biopsy in the same individual, a diagnosis of relapse was considered.¹⁴

MEASUREMENT OF THE AREA OF THE SKIN LESION WITH THE HELP OF THE GRID CHART¹⁵

A simple square grid chart method was used to measure the area of the skin lesion in the present study. A transparent polythene sheet of A4 size commonly used for overhead projectors was taken. With the help of a scale, equal squares measuring one square cm were drawn on it with permanent ink and the grid chart was thus prepared. The margins of the skin lesion(s) on the body of the patient were outlined with a skin marker pen. The grid chart was placed or wrapped firmly on the marked skin lesion and the number of squares occupied by the skin lesion counted (Figure 1).

Scoring was done in the following manner: Each full square = 1. Any incomplete square = $\frac{1}{2}$. Total size of a skin lesion (in Sq. cm): Number of full squares + Number of incomplete squares/2. Total area of involvement in each patient was arrived at by adding the sizes of all the skin lesions.

The data analysis was done with the help of SPSS – version 16.0 software. Statistical methods applied was paired ‘student t’ test. The data conclusion was carried out at 10% level of significance ($P =$ or < 0.10) as the sample size was small.

Results

In the present study of 32 (Male: 21, Female: 11) PB patients with one to five skin lesions, 24 were between 12 and 30 years of age and eight were between 30 and 50 years of age.

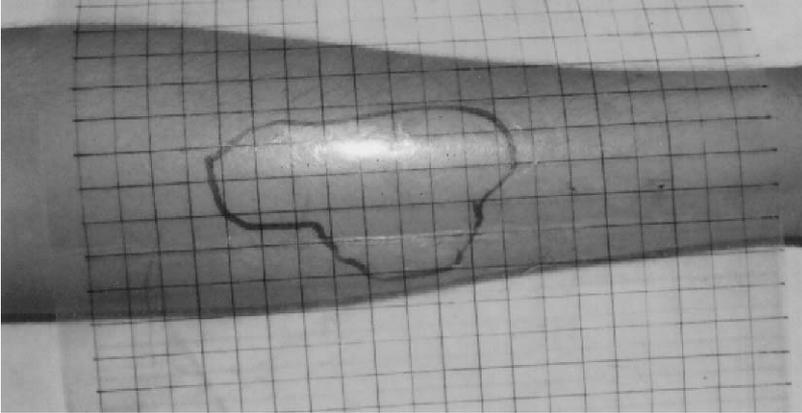


Figure 1. Method of measuring size of skin lesion by grid chart.

The clinical type of leprosy observed was tuberculoid leprosy (TT) in 11 and borderline tuberculoid (BT) leprosy in 21 patients. Skin smears for Acid Fast Bacilli (AFB) were negative in all patients. On the skin biopsies, histopathology was indeterminate leprosy (IL) in six, BT leprosy in 20, borderline lepromatous (BL) leprosy in two and non specific in four patients. AFB was observed in the skin biopsies of both the patients classified by histopathology as BL and in one patient of IL. BIG ranged from 1+ to 2+.

NUMBER OF SKIN LESIONS AND AREA OF INVOLVEMENT

When the PB patients were grouped based on the number of skin lesions, 23 patients had single skin lesion (SSL), two patients each had two and three skin lesions, one patient had four and two had five skin lesions. The area of skin involvement recorded by grid chart method in 32 PB patients grouped on basis of number of skin lesions is shown in Table 1.

The smallest area of skin involvement observed was 6 sq. cm in two patients with SSL. The largest total area measured in this study was 1686 sq. cm in a patient with two skin lesions. The largest skin lesion observed in the study (1120 sq. cm) was also in the same patient on his right lower limb. When the average area of skin involvement was considered, it was highest in patients with two skin lesions (775 sq cm) followed by patients with three, five and four skin lesions, and was least in SSL patients (65 sq cm). Overall, the average area of skin involvement in 32 PB patients under study was 166.25 sq. cm.

Table 1. Details of number of skin lesions and area of involvement at entry

Number of skin lesions	Number of patients (No. = 32)	Largest total area measured in a patient (sq cm)	Smallest total area Measured in a patient (sq cm)	Average total area of skin lesion(s) in a patient
1	23	315	6	65
2	3	1686	78	775
3	3	658	37	319
4	1	94	-	94
5	2	315	121	218

All the 32 patients completed their MDT PB within the prescribed period. T1R was seen in 10 patients; in four at the time of entry and in six it appeared between 6–12 months of observation. In one patient Type 1 reaction was unabated and persistent at 18 months despite adequate anti-reaction therapy. All the reactions were treated with a semi standardised regimen of oral corticosteroids and supportive therapy.⁵ One patient developed weakness of extensors of medial two fingers of the right hand (motor power: grade 3), which recovered fully with physiotherapy.

Patients could be classified into four groups based on changes in the area of involvement at the end of 18 months study (Table 2).

In 14 patients (44%) skin lesions regressed completely; eight (25%) showed no change, seven (22%) showed an increase in area, while three patients (9%) showed a decrease in the area of involvement. In the three patients with a decrease in the area of involvement, the average number of skin lesions at entry was four and by 18 months it was two.

Of the seven patients showing increase in total area of involvement (group 4 of Table 2), in three patients it was due to increase in the area of existing skin lesions along with the appearance of new skin lesions (4A), in three it was due to increase in area of existing skin lesions alone (4B), whereas in one patient it was only due to appearance of a new skin lesion (4C). When the values at entry and 18 month follow-up were analysed at 10% level of significance, for group three patients showing a decrease in the area of involvement, the difference was statistically significant ($P = 0.069$). The difference between entry and 18 month values in group 4A and group 4B was of borderline significance ($P = 0.109$ and $P = 0.101$ respectively). However, when all the seven patients of group four who had an increase in the area of involvement were tested together, the difference between entry and 18 month values were statistically significant ($P = 0.077$).

The clinical and histopathological details of seven patients with increase in area of skin involvement at 18 months are given in Table 3. New skin lesions were multiple (> 3) in

Table 2. Average area of involvement at entry and at the end of 18 months in PB patients grouped based on the type of response in skin lesions

Groups of patients at 18 months of observation	No of patients (Total: 32)	Average area at entry (sq. cm)	Average area at 18 months	LOS between entry and 18 months values
Group 1. Lesions regressed and borders indistinct	14 (44%)	172.2	Area not measurable	–
Group 2. No change in area of involvement	8 (25%)	174.0	174.0 sq. cm	–
Group 3. Decreased area of involvement	3 (9%)	159.0	96.3 sq. cm	Significant ($P = 0.069$)
Group 4 A: Increase in area of existing skin lesions only	3 (9%)	16	23 sq. cm	Borderline significance ($P = 0.109$)
Group 4 B: Increase in area of existing skin lesions with appearance of new skin lesions	3 (9%)	145.3	205.3 sq. cm	Borderline significance ($P = 0.101$)
Group 4 C: Increase in area due to appearance of new skin lesion only	1 (3%)	566	567 sq. cm	–

Difference between entry and 18 months values of group 4 (7) patients together was significant ($P = 0.077$). Note: 'Student t test' done at the 10% level of significance (LOS) as sample size is small.

Table 3. Clinical and histopathological details at entry and at 18 months follow-up in patients showing increase in area of involvement

S. No.	Clinical Diagno	No of lesions	Type 1 reaction	Area at entry (in sq cm)	Area at 18 months (in sq cm)	Number of new skin lesions	Histological observations					
							At entry			At 18 months		
							HP	GF (%)	BIG	HP	GF (%)	BIG
1	TT	1	No	19	31	–	BT	20	Neg	BT	20	Neg
2	TT	2	No	566	567	1	BL	30	2 +	–	–	–
3	TT	1	Yes	57	76	1	IL	20	1 +	IL	10	Neg
4	BT	5	Yes	315	400	3	BT	30	Neg	IL	10	Neg
5	BT	1	Yes	64	140	>10	IL	10	Neg	BT (T1R)	40	1 +
6	BT	1	No	16	20	–	BT	10	Neg	BT	10	Neg
7	BT	1	No	13	18	–	–	–	–	–	–	–

HP = Histopathological diagnosis, GF: Granuloma fraction, BIG = Bacterial index of granuloma, IL = Indeterminate leprosy, TT = Tuberculoid leprosy, BT = Borderline tuberculoid leprosy, BL = Borderline lepromatous leprosy, T1R = Type 1 reaction, Neg = Negative.

two patients. Type 1 reaction was observed in three out of four patients with new skin lesions. One patient continued to have persistent Type 1 reaction at 18 months of observation.

Histopathology results of biopsies taken at the entry and 18 month follow-up were available only for five out of these seven patients. All the histopathology slides were read by single pathologist (SS). All the three patients with clinical evidence of T1R had an initial and a final biopsy for comparison. In one of them the initial and final diagnosis was IL. In one patient the initial diagnosis was BT leprosy and the final diagnosis IL. In the third patient (5th in the table), the initial histological diagnosis was IL with a GF of only 10% but the final diagnosis was BT in T1R with a GF of 40% and a positive BIG. In addition, this patient clinically developed multiple new lesions after completing the full course of MDT and can probably be considered a confirmed relapse (clinical and histological).

Discussion

In the present study of 32 PB leprosy patients, we have charted the skin lesions with the help of body and grid charts at entry and at 18 months of follow-up to record the changes, both in the size and number of skin lesions. Grid charting was found to be an easy, reliable, repeatable and inexpensive method of recording changes in the skin lesions. The measurement of area of involvement in the present study has thrown up a few interesting findings. The SSL patient with the largest skin lesion had an area of 315 sq cm which was greater than the total surface area of lesions of some patients with three, four and five skin lesions (37, 94 and 121 sq cm respectively). In some patients with three-five skin lesions, the lesions were scattered over more than two body areas, which make them MB leprosy if classification based on count of body areas of involvement is followed^{16,17} which considers wider dispersal to be more indicative of severity of disease apart from the number of skin lesions.

In the present study, six out of 32 PB patients who had completed their MDT PB had an increase in the area of existing skin lesion with three (50%) of them developing new skin

lesions, indicating a possible association of these two clinical events (Table 2). T1R developed in all three of them, after completion of MDT, between 6–12 months of observation (late reversal reaction). In one of these patients, it was persistent at 18 months despite corticosteroid therapy along with the appearance of numerous new skin lesions (> 10) and positive BIG on skin biopsy, indicating non response to MDT PB and progression of the disease. Appearance of new lesions in patients especially in the tuberculoid spectrum during and after treatment is considered to be either due to Type 1 reaction or reactivation of the disease.¹ However, it is often nearly impossible to differentiate on clinical grounds between relapse and reversal reaction,^{18–20} especially since relapse is often accompanied by reversal reaction,²¹ which could be the case in this patient with multiple new skin lesions with persistent Type 1 reaction.

Some workers differentiate relapse from reversal reaction based on the onset; while a relapse usually has a slow insidious onset, a reversal reaction develops more rapidly. Nonetheless, patients often cannot tell whether or not the signs have developed gradually or rapidly.⁹ Moreover, even routine histopathology is not very helpful to differentiate relapse from reversal reaction.³ In the present study, on histological assessment in five out of seven patients (Table 3) who showed increase in the area of involvement; GF indicative of histological activity was similar in two, increased in one and decreased in two on follow-up biopsies. In the one patient with numerous new skin lesions, GF increased from 10% to 40% with BIG becoming positive, along with histological features of Type 1 reaction. As the diagnosis of a PB relapse can never be absolutely certain, the evidence for either a relapse or a reaction must be weighed and a decision made.¹⁹ The appearance of multiple new skin lesions post-MDT with an increase in GF and BIG turning positive surely points to relapse,²² which was observed in this patient.

The WHO also supports the use of a therapeutic trial of corticosteroids to help differentiate relapse from reaction. There will not be significant change in relapse when a course of steroids is given.¹⁹ Other studies suggest that when reversal reaction is clinically diagnosed in a treated patient and it is not possible to taper the steroids off even after 2–3 months, it is most likely to be relapse and MDT should be restarted.^{1,23} In the present study, in one patient with multiple new skin lesions, reversal reaction did not regress with the standard treatment with corticosteroids at 18 months of observation equating it to relapse of leprosy.

Let us examine the definitions to assess the significance of appearance of new skin lesions in treated leprosy patients. The recent definition of relapse by WHO is ‘the re-occurrence of the disease at any time after the completion of a full course of treatment with WHO recommended MDT and is diagnosed by the appearance of definite new skin lesions and/or an increase in the bacteriological index (BI) of two or more units at any single site compared to BI taken from the same site at a previous examination’.²⁴ It further states that PB relapses are difficult to differentiate from reversal reactions and the most useful distinguishing feature is the time that has passed since the person was treated: if it is less than 3 years a reaction is most likely while if it is more than 3 years, a relapse becomes more likely. Previous guidelines of leprosy programme of India suggested a time interval of 6 months after drug therapy has been discontinued for the diagnosis of relapse.²³ However, in both these guidelines the scientific basis or evidence in support of the time limit was not stated, and appears arbitrary. In the present study definite new skin lesions were recorded in four PB patients, with two of them developing multiple skin lesions at 18 months follow-up.

The appearance of new lesions in PB patients while on treatment are usually either unmasked old lesions missed during the initial examination or *real* new lesions developing

during observation, of which former is probably more common. Unmasking of existing lesions is either due to increase in their thickness and erythema due to T1R or due to increase in the pallor/hypopigmentation and xerosis of skin patch as erythema regresses with therapy. The latter occurrence is especially true in the coloured skin of Indian patients. The appearance of a few new skin lesions during the course of therapy is also possible due to the immunological recognition and expansion of dormant foci of granuloma in the skin following initiation of MDT therapy. In either case, the appearance of new lesions can raise a therapeutic question in few instances as observed in the present study. In two PB patients (4 and 5) of Table 3, new lesions increased the total number of skin lesions to >8 . PB leprosy patients by definition should have 1–5 skin lesions only. In this situation, as in the present study, they should be re-assigned to MDT MB as the total number of skin lesions have increased to >5 . However, there are no clear guidelines to this effect. These instances highlight the importance of recording of number of skin lesions by body charting in leprosy.

A summary of key observations in this study are as follows: Appearance of new skin lesions in a PB patient on treatment is a key event and should be recorded. When new lesions increase the skin lesion count to >5 in PB patients while on therapy or follow-up, treatment should be changed to MDT MB. Continued appearance of multiple new lesions in patients on follow-up (post MDT) could be due inadequate treatment or relapse. Increase in the size of existing lesions observed in six patients of present study may not be significant in itself, nonetheless in 50% of these patients it was associated with appearance of new skin lesion, hence deserves to be recorded.

In conclusion, if relapse is to be confirmed in PB patients, definite new skin lesions should be documented¹⁹ as bacteriological parameters are not relevant in this group. Hence it is necessary to monitor the size of existing skin lesions and also look for new skin lesions in these patients. One drawback of this hospital based study is its small sample size. Despite this limitation, it attempts to address the problems faced with PB classification and suggests the need to reclassify if lesions increase during the course of treatment or after, whether it is due to T1R or relapse. New lesions which appear or sub-clinical lesions which become apparent during T1R in PB patients call for change of classification to MB if the total number of skin lesions increase to >5 and should ideally be clubbed under 'wrong clinical classification'. However, there are no clear documented guidelines to this effect.

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