Original article:

Study of relapse in leprosy: observational study

Dr Navdeep kaur*

Senior Resident in Blood Bank
Kalpana Chawla Medical College , Karnal , Hariyana
Corresponding author*

ABSTRACT

Leprosy is unique in terms of the nature of the causative organism (Mycobacterium leprae), the chronicity of the disease, its prolonged treatment and the definitions of "cure" and "relapse." The principal mode of assessing the efficacy of therapeutic regimens in leprosy is the "relapse rate." There are wide variations in estimates of relapse rates after the World Health Organization (WHO) multidrug therapy in different regions. The main differential diagnoses for relapse are reversal reactions, erythema nodosum leprosum and reactivation/resistance/reinfection. The most reliable criteria for making an accurate diagnosis of relapse include clinical, bacteriological and therapeutic criteria. Additional ones that may be used , depending on the setting, are histopathological and serologic criteria. Relapsed cases of leprosy should be identified and put back on chemotherapy as soon as possible to prevent further disability and transmission of infection. Factors that should be considered in choosing an appropriate regimen are the type of leprosy (PB or MB), previous treatment and drug resistance. Occasionally, clinicians may need to use their judgement to modify the standard WHO treatment regimens according to the scenario in each patient.

Key words: Leprosy, reactivation, reinfection, relapse, resistance.[1]

INTRODUCTION

Relapse of diseases, acute or chronic, caused by bacterial infections is quite common. Usually, relapse indicates a failure to treat the infection thoroughly, which is compounded by irregular treatment, particularly in chronic disease. The treatment of leprosy, compared with other infectious diseases, is unique in terms of the fixed dose and duration of regimens and also in terms of the definition of cure. Often, termination of treatment is based on completion of the recommended duration of treatment rather than disappearance of clinical signs and symptoms, which led to initiation of treatment in the first place. Thus, the principal mode of assessing the efficacy of the therapeutic regimens in leprosy is the relapse rate. A very low relapse rate over an adequate period of observation indicates that the regimen used has been effective and this is why prolonged periods of surveillance are recommended by the World Health Organization (WHO) for all patients who have been declared cured after receiving multidrug regimens.

The definition of .relapse. can be understood only in the context of the definition of .cure.. In the era of Dapsone monotherapy, a patient with multibacillary (MB) disease was declared .disease arrested. when skin lesions resolved and when 3 monthly consecutive skin smears were negative for acid-fast bacilli

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

(AFB), after which antileprosy treatment was continued for another 5.10 years or even a life time. A paucibacillary (PB) patient was declared disease free. When all skin lesions resolved, with no infiltration and no erythema and the nerves were no longer painful or tender, after which antileprosy treatment was continued for 3.5 years. With the advent of multidrug therapy (MDT), such rigid clinical criteria for cure have lost their importance. A leprosy patient is defined by the WHO as one who is found to have signs and symptoms of the disease and who requires chemotherapy. As of 1995,

WHO recommends 1 year of MDT for MB patients (12 pulses in 18 months) and 6 months (six pulses in 9 months) for PB patients. At any point in time during therapy, the patient should have ingested two-thirdof the pulses till that time. For operational purposes,once a patient receives adequate chemotherapy, he is considered cured. Histopathological resolution of the lesions and clinical subsidence of the disease take place months to years after antileprosy treatment is stopped.

MATERIALS AND METHODS:

Materials for the study of consisted of skin biopsies obtained from patients clinically diagnosed as leprosy who attended either OPD or leprosy clinics of Chigateri District Hospital, and Bapuji Hospitals that are attached to JJM Medical College, Davangere.

Skin biopsies for the study were obtained by incisional biopsy which was performed by the Dermatologist. These biopsies were sent to the Department of Pathology in 10 % formalin. After adequate fixation for about 8-12 hours, the biopsies were submitted into for routine processing , following which the paraffin embedded sections were stained with H and E for morphological analysis and Wade Fite staining for identifying the bacilii.

RESULTS:

In this present study there were total 100 cases , out of which 22 (22%) biopsies from the leprosy patients who were on or completed the treatment when the biopsy was undertaken . 78(78%) biopsies were from the patients who visited the clinic for the first time .

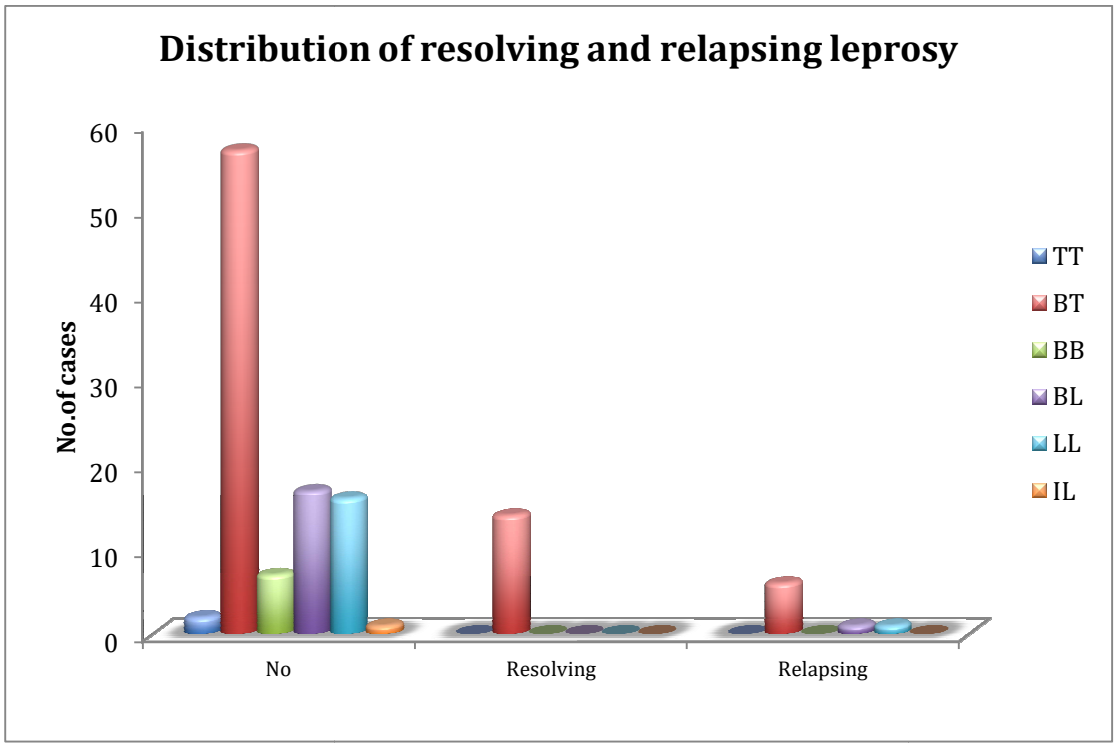
Types	**No**	**Resolving**	**Relapsing**	**Total**
TT	2			
BT	57	14	6	20
BB	7			
BL	17		1	1
LL	16		1	1
IL	1			
Total	**100**	**14(63.63%)**	**8(36.36%)**	**22(22%)**

Table 1) Cases distribution

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

Category	TT	BT	BB	BL	LL	IL	Total
Treated	-	20	-	1	1	-	22(22%)
Untreated	2	37	7	16	15	1	78(78%)

Table 2) Treated and untreated cases



Graph 1) Distribution and resolving and relapsing leprosy

Among the 22 treated cases, 14(63.63%) were resolving type and 8(36.36%) were relapsing type . Of them, 20 (90.90 %) biopsies were showing the features of BT type. Of these 20 biopsies, 14(70%) were of resolving type and 6 (30%) were of relapsing type . There was 1(4.54%) treated case of BL which showed features of relapse and 1(4.54%) treated case of LL which also showed features of relapse.

Histopathological examination can be of great assistance in identifying and confirming relapse in both MB and PB cases. To get the best results , serial biopsies , once every six months should be done , preferably of the same lesion or a similar lesion. Relapsed cases of leprosy should be identified and put back on chemotherapy as soon as possible to prevent further disability and transmission of infection .

Discussion:

The conventional method of confirming activity or relapse in an infectious disease is demonstration and/or culture of the etiologic agent. These methods unfortunately have limited utility in leprosy because of the difficulty in demonstrating bacilli in PB cases and absence of a method of in vitro

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

cultivation of M. leprae. Unlike PB leprosy, where the criteria for relapse depend heavily on clinical features, bacteriological parameters are useful in MB leprosy.

In the early phase of relapse, small and large foci of newly arrived spindle-shaped macrophages with a pink granular cytoplasm are identified along with a few small clumps of persisting foamy macrophages. Solid staining AFBs reappear in skin smears and biopsy specimens in patients who may or may not have become completely smear negative. Once the lesion is well established, the foamy change becomes obscuredby collections of spindle-shaped and immature macrophages. Skin adnexa are markedly atrophic and scanty, and dermal nerve bundles are few and show perineurial thickening and fibrosis. Macrophages,Schwann cells and endothelial cells are packed with solid-staining AFBs.

Occasionally, there is infiltration by polymorphs and it is also not uncommon to see LL patients relapsing with upgrading reactions in the form of BL or, rarely, BT lesions. Lesions of BL resolve much faster than polar LL cases and become bacteriologically negative much earlier. Histopathologically, BL lesions leave behind a few focal collections of mononuclear cells around the skin adnexa and foam cells are not usually seen. Relapses in BL manifest as LL, BL or, rarely, as BT.

Lesions in BT and TT leprosy are the result of a hypersensitive granulomatous response to the antigens of M. leprae and are not directly due to the presence of M. leprae. With treatment, there is reduction in the size of the granuloma without any fibrous replacement of the skin adnexa. Dermal collagen is destroyed during the inflammatory process, leading to an atrophied and wrinkled appearance of the healed skin lesions. Nerves undergo perineurial and intraneural fibrosis. M. leprae get buried alive in these nerves and also in the arrector pili muscle cells, thereby serving as a focus for relapse. The difficulty that arises in PB cases is the differentiation of relapse from reaction. Features that suggest a reaction include edema around the granuloma, dilated lymphatics and proliferating fibroblasts throughout the dermis. A true relapse can be detected histopathologically only after recording complete histological resolution of the lesion, which may take years. Relapse indicates that the bacilli have survived despite antileprosy therapy and have multiplied and released antigens to produce fresh granulomas. This manifests as the appearance of solid-staining organisms inside the fibrosed nerve bundles (where there were none earlier) and the reappearance of a granuloma at the site of the originallesion. This granuloma usually begins as a small focus of lymphocytes and epithelioid cells, which often starts in fibrosed nerve bundles or arrector pili muscle cells. Once the granuloma becomes well established, it grows and involves large portions of the dermis, becoming indistinguishable from the original lesion.Therefore, in PB patients, regular 6-monthly biopsies showing disappearance of the granuloma will confirm.cure and reappearance of the granuloma will identify. relapse.Rarely, PB cases will relapse as MB, and this is usually due to misdiagnosis of the spectrum of disease and the resultant inadequate treatment in the first place. [6]

PREDISPOSING FACTORS FOR RELAPSE[7]

Persisting organisms or .persisters. consist of permanently or partially dormant organisms that have the capacity to survive in the host despite adequate chemotherapy. They have been identified in immunologically favorable sites such as dermal nerves, smooth muscle, lymph nodes, iris, bone marrow and liver. These organisms, which are responsible for relapse, are present in about 10% of the MB patients, and their proportion may be higher in cases with higher BI.

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

Inadequate therapy

This is usually the result of clinical miscategorization of MB leprosy with few skin lesions as PB cases, who receive 6 months of MDT instead of 12 months, initially respond to treatment and eventually relapse.

Irregular therapy

Irregularity in ingesting self-administered clofazimine and dapsone either due to an irregular supply of drugs or non-compliance on the part of the patient, effectively resulting in a scenario of rifampicin monotherapy. This will lead to rifampicin resistance and subsequent relapse.

Monotherapy

The relapse rate is high among patients who have received dapsone monotherapy and did not later receive MDT. This is also due to the development of resistant organisms.

High initial BI

Patients who have a high BI initially are at greater risk of relapse after fixed duration MDT compared with patients who are smear negative or have a low BI.

Number of skin lesions and nerves

The number and extent of lesions including nerve lesions, when multiple, i.e. more than five and covering three or more areas of the body, correlate with a higher relapse rate. Mycobacterial antibodies have been found in TT leprosy with a large number of lesions and in BT leprosy with more than 10 lesions. Because this is evidence of a fairly large number of organisms, these patients may not be truly PB and treatment with two drugs for 6 months might be considered inadequate for these patients.

Relapse in PB leprosy

a) Skin lesions: Previously subsided skin lesions show signs of renewed activity, such as infiltration, erythema, increase in extent and appearance of satellite lesions. Often, there is an increase in the number of lesions as well.

b) Nerves: New nerves may become thickened and tender, accompanied by an extension of the area of sensory loss and an insidious onset of motor deficit. Patients may complain of aches and pains along the peripheral nerves with or without evidence of nerve damage. Relapse may occur only in nerves without skin involvement (neural relapse) and there may be a change in the spectrum of disease on relapsing.

Relapse in MB leprosy

a) Skin lesions: Relapse may present as localized areas of infiltration over the forehead, lower back, dorsa of hands and feet and the upper part of the buttocks. Soft, pink and shiny papules and nodules may be found at these sites, with or without a background of infiltration. Papules may enlarge to form plaques. Subcutaneous nodules may appear on the posterior arms and anterolateral thighs. They feel like peas in a pod and increase in size with time. Skin smears from the overlying skin may be negative; hence, the scalpel should be plunged deep into the core of the nodule while taking smears.

b) Nerves: Nodular swellings may occur along the course of cutaneous nerves and peripheral nerve trunks in addition to fresh nerve thickening and/or tenderness, with insidious loss of function.

c) Ocular lesions: Cases with pre-existing eyeinvolvement may relapse with iris pearls or, rarely, lepromata.

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

Patients with known or suspected drug resistance pose a treatment problem only in the case of rifampicin resistance, which is rare. MB patients who have received rifampicin as part of MDT are not at any significant risk of rifampicin resistance, unless they were infected with fully dapsone-resistant bacilli and either did not take their clofazimine or were not given another effective drug. Dapsone resistance occurs in the setting of prior dapsone monotherapy and such cases respond well to standard WHO MDT. Clofazimine resistance is extremely rare, if at all it occurs, and these cases also respond to the other two drugs in the standard WHO MDT.

Although drug resistance ideally is determined using the mouse foot-pad or other techniques, relatively few leprosy centers have such a facility available. Thus, the decision on drug resistance most often is based on clinical information alone.

This group includes patients who do not respond as expected in terms of clearance of skin lesions and bacilli after therapy is discontinued or patients who actually show disease progression during therapy. The former group contains potential relapse cases, but great care must be taken to rule out reaction and/or slow clearance of lesions and bacilli as a cause of poor response. The WHO defines a .satisfactory result from MDT.in a patient who complies with treatment as . one in which, after the start of therapy, bacilli begin to clear in MB cases and lesions generally, although not necessarily, rapidly improve in both PB and MB cases. Clearance of lesions is related more to the patient.s immune response than to antileprosy treatment; all lesions and bacilli should eventually clear even though clearance may be incomplete at the time treatment is discontinued.[11]

Conclusion:

A high proportion of patients who complete MDT have persistent lesions. Since histological resolution is delayed, many of them if biopsied would show persistent microscopic activity. A repeat course of therapy, knowing that MDT is highly effective with infrequent relapses, is not justifiable. Appreciating histological findings of regression and reparative changes noted in this study in correlation with clinical inactivity should prompt a clinician to take proper history of previous MDT in past and to follow up the patient for persistent activity or relapse rather than treating solely on the basis of presence of granulomas in biopsy. Also, a long sustained clinicopathological activity among patients of T-1R warrants close monitoring and long duration MDT may be administered.

REFERENCES:

1. Kaimal S, Thappa DM. Relapse in leprosy. Indian J Dermatol Venereol Leprol 2009;75:126-35
2. The Leprosy Unit, WHO. Risk of relapse in leprosy. Indian J Lepr 1995;67:13-26.
3. Boerrigter G, Ponnighaus JM, Fine PE, Wilson RJ. Four-year follow up results of a WHO-recommended multiple-drug regimen in paucibacillary leprosy patients in Malawi. Int J Lepr 1991;59:255-61
4. Pandian TD, Sithambaram M, Bharathi R, Ramu G. A study of relapse in non-lepromatous and intermediate groups of leprosy. Indian J Lepr 1985;57:149-58.
5. Katoch VM. Microbiological aspects of relapse in leprosy. Indian J Lepr 1995;67:85-98.

6. Job CK. Histopathological features of relapsed leprosy. Indian J Lepr 1995;67:69-80.
7. Ramu G. Clinical features and diagnosis of relapses in leprosy Indian J Lepr 1995;67:45-59.
8. Indian J Lepr 1995;67:45-59 Pfaltzgraff RE, Ramu G. Clinical leprosy. In: Hastings RC, Opromolla DV, editors. Leprosy. 2nd ed. Edinburgh: Churchi Livingstone; 1994. p. 237-87.
9. Sengupta U. Immunological aspects of relapse in leprosy. Indian J Lepr 1995;67:81-3. Ramu G. Clinical features and diagnosis of relapses in leprosy. Indian J Lepr 1995;67:45-59
10. Jacobson RR. Treatment of relapsed leprosy. Indian J Lepr 1995;67:99-102.

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858