

Case Series

Histopathological features of relapse cases in leprosy

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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 important predisposing factors for relapse include the presence of “persister” bacilli, monotherapy, inadequate/irregular therapy, presence of multiple skin lesions/thickened nerves and lepromin negativity. The conventional methods of confirming activity or relapse in an infectious disease (demonstration and/or culture of the etiologic agent) have limited utility in leprosy because of the difficulty in demonstrating bacilli in paucibacillary (PB) cases and absence of a method of in vitro cultivation of *M. leprae*. Bacteriological parameters are useful in multibacillary (MB) leprosy, whereas in PB leprosy, the criteria for relapse depend primarily on clinical features. Although there are no widely available serologic tests for leprosy other than in a research setting, various immunological tests may be useful for monitoring patients on chemotherapy as well as for confirming suspected cases of relapse. 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.

Keywords: Leprosy, Reactivation, Reinfection, Relapse, Resistance

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.¹

Objectives

The objective of this is to study the histopathology of relapse cases in leprosy.

CASE SERIES

Materials for the study of consisted of skin biopsies obtained from patients clinically diagnosed as leprosy who attended either Outpatient department (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 bacilli.

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.

Table 1: Types of leprosy.

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

Table 2: Distribution of resolving and relapsing leprosy.

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%)

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 borderline tuberculoid leprosy (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 borderline lepromatous leprosy (BL) which showed features of relapse and 1 (4.54%) treated case of lepromatous leprosy (LL) which also showed features of relapse.

Histopathological examination can be of great assistance in identifying and confirming relapse in both multibacillary (MB) and paucibacillary (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.

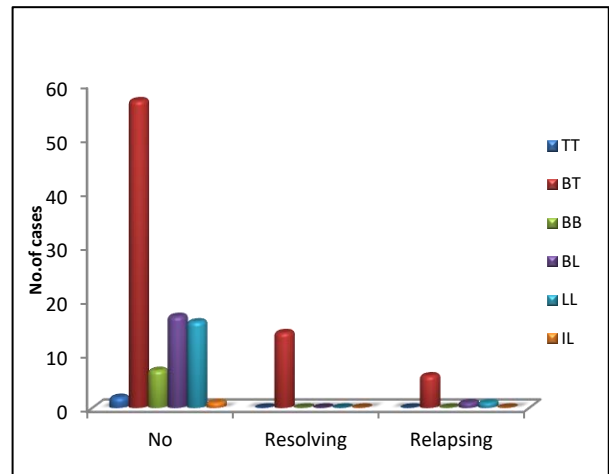


Figure 1: Distribution of resolving and relapsing leprosy.

DISCUSSION

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.

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.

Histopathology

Regular skin biopsies and skin smears, at least once in 6 months, from representative lesions should be studied during the period of treatment and the following 5 years after achieving negativity.

Histopathology of relapsed lesions in MB leprosy. As LL resolve under treatment, increasing number of macrophages become foamy, Schwann cells show foamy change, there is reactive proliferation of the perineurium and increasing fragmentation and granularity of the acid fast bacilli (AFB) in the granuloma are seen.

The granuloma gradually resolves, without any residual fibrosis or scar formation, and there is fibrous replacement of the perineurium and hyalinization of the nerve parenchyma. Foam cell collections are known to persist for long periods in the tissues, many years after the skin smears have become negative. A mild non-specific chronic inflammation characterized by small focal collections of lymphocytes around skin adnexa can also persist in resolved LL lesions for several years.

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 obscured by 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.

Histopathology of relapsed lesions in PB leprosy

Lesions in BT and tuberculoid leprosy (TT) 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 anti-leprosy 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 original lesion. 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.²

Predisposing factors for relapse

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.³

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 multi drug resistant tuberculosis (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.

Clinical features

Age

In MB cases, relapse is more common in the older age groups. PB leprosy with single skin lesions is more common in younger age groups and relapse is less common in this group.⁴

Sex

Relapses are more common in males, possibly because of the higher prevalence of leprosy in males. Relapses are seen in females in the setting of pregnancy and lactation.⁴

Relapse in PB leprosy

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.

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

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.

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.

Ocular lesions

Cases with pre-existing eye involvement may relapse with iris pearls or, rarely, lepromata.

Mucosal lesions

Papular or nodular lesions may be seen on the hard palate, inner lips and glans penis.⁴

Diagnosis

The diagnostic criteria for relapse are: increase in size and extent of existing lesion(s), appearance of new lesion(s), infiltration and erythema in lesions that had completely subsided and nerve involvement (thickening or tenderness).⁵

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-IR warrants close monitoring and long duration MDT may be administered.

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