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Original Research Article

Clinical and histopathological features in lepra reaction: a study of 50 cases

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ABSTRACT

Background: Lepra reactions remain a major persistent problem in leprosy. Type 1 and type 2 (erythema nodosum leprosum-ENL) reactions are the major causes of nerve damage and permanent disabilities. Diagnosing lepra reactions correctly is important for timely institution of therapy to prevent and treat disability and morbidity. Aim and objectives of the study were to make detailed observations on clinical and histopathological features of type1 and type 2 lepra reactions.
Methods: In this study we included 50 patients diagnosed during a 1-year period as lepra reactions based on clinic-histopathological corelation.
Results: Out of the 50 patients, 4 were of type 1 reaction and 46 of type 2 reaction from which recurrence was more commonly seen with type 2 reactions. The most consistent histopathological findings in type1 reaction were periadnexal inflammatory infiltrates (100%) and lymphocytes in granuloma (100%), followed by papillary dermal edema and intercellular edema within granuloma (75%). Surprisingly, folliculotropism of and lymphocytic panniculitis was seen in 50% cases. In ENL, the most common histological findings were periadnexal inflammatory infiltrates (95.6%), presence of neutrophils within the granuloma (86.9%), foamy macrophages followed by papillary dermal edema (69.5%), and neutrophilic panniculitis (43.4%). Vasculitis like changes was noted in only 46% cases.
Conclusions: Infiltration of macrophage granulomas by neutrophils is a reliable sign of ENL. Classical signs of vasculitis are not always present in ENL. Folliculotropism and lymphocytic panniculitis are frequent in type1 reactions while neutrophilic panniculitis is common with ENL.

Keywords: Erythema nodosum leprosum, Lepra reaction, Type 1 reaction

INTRODUCTION

Leprosy is a chronic granulomatous disease caused by *Mycobacterium leprae*. It is also known as Hansen's disease. Leprosy is a chronic progressive infection in man but suddenly when conditions are favourable, "reactional states" can occur in leprosy, which is a major problem in the management of leprosy patients. These reactions are the consequences of the dynamic nature of the immune response to *M. leprae)* that may occur before, during or following the completion of multi-drug therapy (MDT). Clinically, the word reaction is described as the appearance of symptoms and signs of acute inflammation in lesions of a patient with leprosy. And immunologically, reactions are episodes of acute hypersensitivity to bacterial antigens, due to disturbance in the pre-existing immunological balance.

There are two major types of lepra reactions (LR), type 1 and type 2 reactions. Type 1 LR (T1LR), also described as "reversal" reaction, is a delayed type hypersensitivity (type IV hypersensitivity) reaction, that occurs in

borderline leprosy patients with cellular immune responses to *M. leprae* antigenic determinants.[1] It is characterized by acute inflammation of pre-existing skin lesions which may become erythematous or oedematous and may desquamate or rarely ulcerate. Rarely new lesions also can appear.[2] Nerves often become tender with loss of sensory and motor functions called as neuritis. Occasionally, oedema of the face, hands or feet is the presenting symptom, but constitutional symptoms are unusual. Type 1 LR may occur at any time but common after starting multidrug therapy (MDT) or during puerperium.[3]

Type 2 LR (T2LR), also known as erythema nodosum leprosum (ENL), is an immune complex mediated (type III hypersensitivity) complication of multibacillary disease (LL and BL). They may occur before, during or after treatment. Higher the original bacteriological index, the more likely it is that ENL would develop. Development of ENL is a bad prognostic significance. Up to 50% of LL and 15% of BL patients may experience ENL reactions. Attacks are often acute at first, but may be prolonged or recurrent over several years and eventually remain quiescent but insidious, especially in the eye. ENL manifests most commonly as painful erythematous nodules on the face and extensor surfaces of limbs. The lesions may be superficial or deep, with suppuration, ulceration or brawny induration when chronic and eventually fade away. ENL is a systemic disorder producing fever and malaise and may be accompanied by uveitis, dactylitis, arthritis, neuritis, lymphadenitis, myositis and orchitis. Peripheral neuritis and uveitis with its complications of synechiae, cataract and glaucoma are the most serious complications of ENL.[4] Most of the T2 LRs occur during the first year of MDT.[5]

Reactions are responsible for most of the permanent nerve damage, deformity, and disability.[6] Clinically detectable nerve function impairment (NFI) occurs in approximately 10% of paucibacillary and 40% of multibacillary leprosy patients.[7] It has however been suggested that "silent neuropathy" due to sub-clinical neural involvement may take place in virtually all leprosy patients because 30% of the nerve fibres need to be destroyed before sensory impairment manifest.[8]

Histologically, in type 1 reactions lymphocytes are present within the lesions, severe oedema with disruption of the granuloma and giant cell formation. In type 2 (ENL) reactions, neutrophils infiltrate the granuloma and there is vasculitis and macrophage degeneration with the breakdown of foam cells.[9]

The basic characteristics noted by pathologists to diagnose type1 reaction were those described by Ridley.[10] The present study used the pre-agreed criteria used by Lockwood et al as follows.[11]

Edema: dermal edema was defined as separation of collagen with pallor and dilated vasculature. Intra-granuloma edema was said to be present when the granuloma was not compact and the inflammatory cells were separated by intercellular spaces.

Epidermal erosion: defined as the presence of granulomatous inflammatory destruction of basal epidermis.

Spongiosis: defined as separation of keratinocytes by intercellular edema.

Lockwood et al found that five histological findings, i.e., intra-granuloma edema, giant cell size, giant cell numbers, dermal oedema, and HLA-DR expression correlated with clinical type1 reactions.

The objective of this study is to make detailed observations on clinical and histopathological features of type1 and type 2 lepra reactions.

METHODS

This clinico-histopathological study was conducted at the Department of Dermatology, Venereology and Leprosy at a tertiary care centre (P.D.U Government Medical College and Hospital, Rajkot, Gujarat, India) during a one year period (October 2017-November 2018). Biopsy was taken of all the patients clinically diagnosed as lepra reaction. Acid fast bacilli (AFB) staining, all routine investigations including haemoglobin level, total WBC count, differential count, ESR, urine for albumin, sugar and microscopy, liver function tests and renal function tests to rule out any underlying systemic disorder were done. We included skin biopsy specimens of patients of all ages, diagnosed as lepra reaction (type 1 and type 2) after clinico-pathological correlation. Those with doubtful diagnosis were clinically reviewed and if needed, excluded from the study. Data collected was presented in number and percentages and analysed in Microsoft excel.

RESULTS

In Type 1 reaction, all patients were male and in type 2 reaction, the male:female ratio was 1.93:1. Overall, the most common age group affected was 31-40 years (42%) followed by 41-50 years (28%) and 21-30 years (18%) (Figure 1).

Out of the 50 patients, 4 were of type 1 reaction and 46 cases were of ENL. Recurrence was more commonly seen with ENL (69.6%) than type 1 reaction (25%) (Figure 2).

Most common type of leprosy showing type 1 reaction (reversal reaction) was borderline tuberculoid leprosy (75%) followed by borderline lepromatous leprosy (25%), while most common type of leprosy showing type

2 reaction (ENL) was lepromatous leprosy (97.8%) followed by borderline lepromatous leprosy (2.1%) (Figure 3).

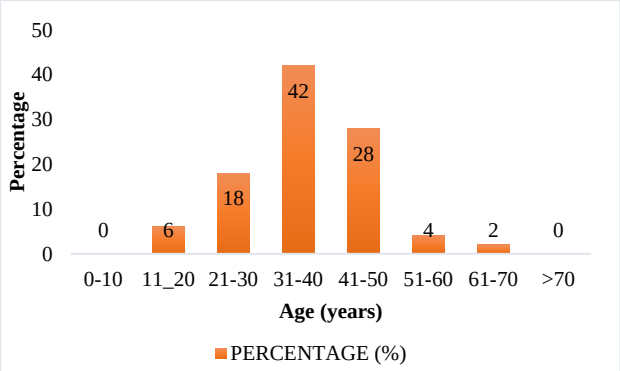

Figure 1: Age wise distribution.

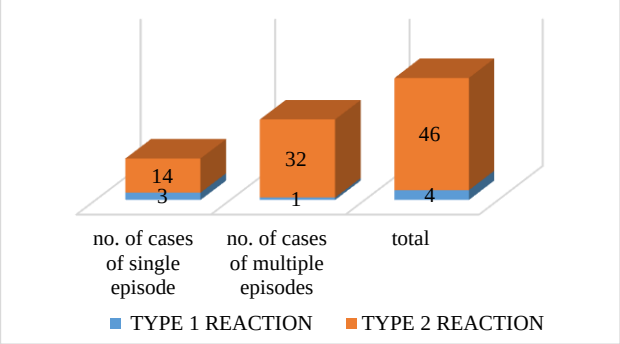

Figure 2: Recurrence rate in reactions.

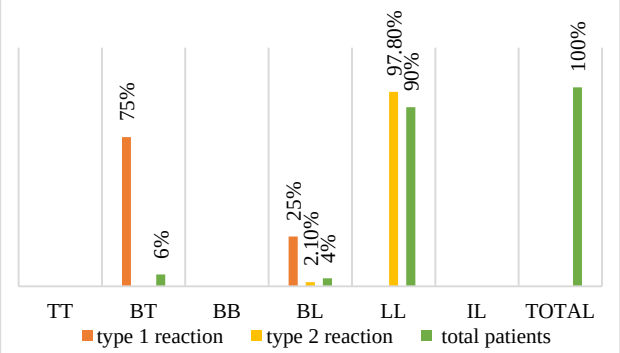

Figure 3: Type of reactions in different types of leprosy.

In type 1 reaction, all patients (100%) showed erythema and swelling of previous lesions (Figure 4) with neuritis, followed by fever (75%), pedal edema (50%) and deformity (25%). In type 2 reaction (ENL), most consistent finding was fresh crops of tender erythematous nodules (100%), followed by fever (82.6%), myalgia (76%), joint pain(69.5%), neuritis(69.5%), pedal edema (69.5%), lymphadenopathy (60.8%), iritis (43.4%), orchitis (4.34), deformity (17.39%) and ulcerated lesions (8.69%) (Figure 5 and 6).

Figure 4: Raised and inflamed lesions of type1 reaction in borderline lepromatous leprosy.

Figure 5: Multiple ulceration over previously existing lesions of ENL.

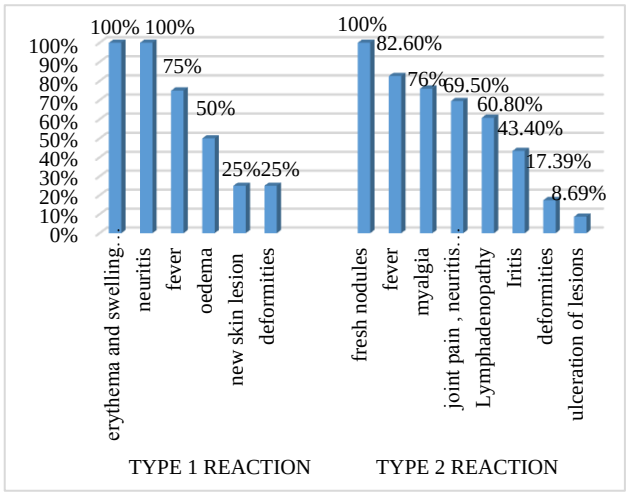

Figure 6: Clinical features of type 1 and type 2 reaction.

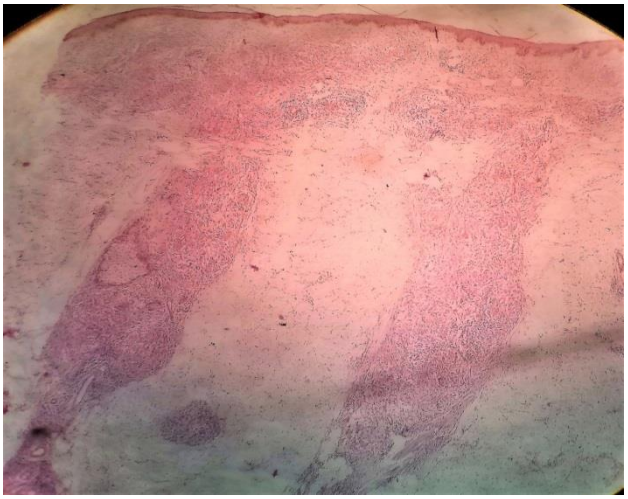

Figure 7: Folliculotropism of lymphocytes in type1 reaction.

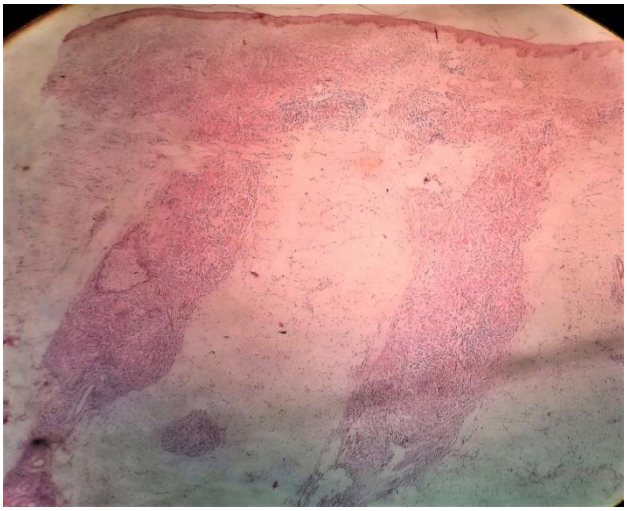

Figure 8: Lymphocytic panniculitis.

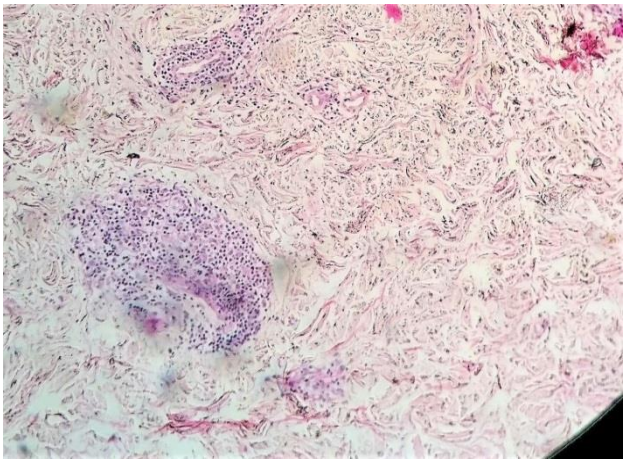

Figure 9: Dermal edema with perivascular neutrophilic inflammatory infiltrates.

The most consistent finding in type 1 reaction was periadnexal inflammatory infiltrates (100%) and lymphocytes in granuloma (100%), followed by papillary dermal edema and intercellular edema within the granuloma (75%). Surprisingly, folliculotropism of lymphocytes (Figure 7) was seen in 50% cases and and lymphocytic panniculitis (Figure 8) was observed in 50% cases. In some cases, subcutaneous infiltration and extravasation of RBCs were also seen.In ENL, the most common finding was periadnexal inflammatory infiltrates (95.6%), presence of neutrophils within the granuloma (86.9%) and foamy macrophages, followed by papillary dermal edema (69.5%) (Figure 9), and neutrophilic panniculitis (43.4%). Fibrin deposition in the vessel wall and vasculitis like changes were noted in only 46% casesand vascular edema was seen in 10% cases (Figure 10).

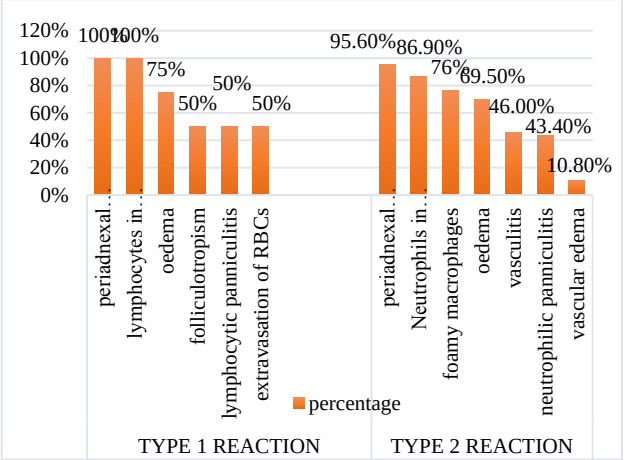

Figure 10: Histo-pathology of type 1 and type 2 reaction.

DISCUSSION

Several interesting observations were made in our study. 70% of the patients of both Type I and Type II lepra reactions were in the 31-50 years of age group, while the most common age group noted in a study done by Prasannan et al was 21-40 years (44.4%). The male:female ratio was 1.93:1 in our study which clearly correlates with the findings of the previous studies done by Prasannan et al, which showed 2:1 male:female ratio.[12]

Rate of recurrence in type 1 reactions was 25% in our study which correlated with the findings of Kumar et al which also shows recurrence in 29.4%.[13] Rate of recurrence in type 2 reaction was more in 69.6% of patients in our study, which was almost similar to the studies conducted by Kumar et al (87.9%).

In our study, 75% of the patients in Type I reaction belonged to the borderline tuberculoid spectrum, as compared to 92.85% cases each in Kumar et al study and in Type II reaction 100% of patients the belonged to the lepromatous spectrum, as compared to 65% cases in Kumar et al study.[13]

Apart from raised erythematous skin lesions, the predominant feature in Type I reaction, neuritis was also seen in our patients. Deformities like claw hand was seen in 25% of patients in our study while Sharma et al reported that 7.9% of patients developed claw hand during and after MDT.[14]

In patients with type II reaction, fever was noted in 82.6% cases, arthralgia in 69.5%, neuritis in 69.5%, edema of extremities in 69.5% of the cases, deformities like claw hand, auto-amputation of fingers-toes was seen in 17.39% and ulceration of lesions in 8.69% in our study, whereas in the study by Kumar et al, fever was noted in all (100%) cases, arthralgia in 70%, edema of extremities in 85% and neuritis in 40% of the cases.

In the present study, the predominant histopathological features observed in type -1 reaction were infiltration by lymphocytes (100%), oedema of the dermis (75%), giant cells (25%), lymphocytic panniculitis (50%), folliculotropism (50%), while these findings were seen in 100%, 86%, 59%, 36%, and 58% cases respectively in the study conducted by Adhe et al and dermal edema was seen in 50% cases in the study conducted by Sarita et al.[15,16]

Histopathological features of type -2 reaction noted in our study were infiltration by neutrophils in 86.9% of the patients, dermal oedema in 69.5% cases, vasculitis in 46% cases and neutrophilic panniculitis in 43.4% patients, Whereas in the study conducted by Adhe et al, histopathological features of type-2 reaction showed neutrophils in the granuloma in all cases (100%), 81% cases with edema in the papillary dermis and 66% cases had neutrophilic panniculitis. In the another study conducted by Sarita et al, histopathological features of type-2 reaction observed were 57.1% cases with neutrophilic infiltrate on a background of macrophage granuloma with dermal edema, and 7.1% case with neutrophilic vasculitis on a background of macrophage granuloma with dermal edema. In type 2 lepra reactions, because of the immune complex deposition, neutrophils are attracted in these lesions. Neutrophils are present either within the granulomatous infiltrate or/and in the interstitium with or without leukocytoclasia.

CONCLUSION

Lepra reactions are more common in the patients above 20 years of age because these people are more exposed to the disease. Male preponderance is seen because men go out for work more and get higher exposure and hence have more possibilities of getting infected. Type I reaction was more among borderline group and type II reaction was more among LL patients, which is an established fact. With regard to the recurrences, single episode was more common in type I reaction and multiple episodes (recurrence) was more in type II reaction. It is very essential to recognize the reactional leprosy irrespective of the type of reaction. This is because the patients with type I reaction are more prone for deformities whereas the patients with type II reactions are more prone for systemic complications. Infiltration of macrophage granulomas by neutrophils is a reliable sign of ENL. Classical signs of vasculitis are not always present in ENL. Folliculotropism and lymphocytic panniculitis are frequent in type 1 reactions while neutrophilic panniculitis is common with ENL. Histopathology has more prognostic than diagnostic significance.

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