

## **A study on histological features of lepra reactions in patients attending the Dermatology Department of the Government Medical College, Calicut, Kerala, India**

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Accepted for publication 24 January 2013

### *Summary*

*Objectives* 1. To study and compare the clinical and histological features of Type 1 and Type 2 lepra reactions. 2. To document the histological patterns of Type 1 and Type 2 lepra reactions observed in the study population.

*Design* Two year cross sectional study. Patients attending the outpatient department of our tertiary care hospital, during the 2 year study period with clinical evidence of Type 1 (T1R) or Type 2 (T2R) lepra reactions were included in this study after obtaining written informed consent. During this period 34 T1R patients and 14 T2R patients attended our hospital. Biopsies were taken from reacting skin lesions of all patients and histological features were studied.

*Results* Dermal or intragranuloma oedema was evident in 50% of T1R patients and all of them had clinically severe reactions. The T1R patients showed three different histological patterns – upgrading reactions, downgrading reactions and reactions without upgrading or downgrading. Among T2R patients 8/14 showed neutrophil infiltration histologically, 5/14 showed no histological evidence of neutrophil infiltration and only one patient had features of neutrophilic vasculitis. Dermal oedema was seen in 11/14 cases.

*Conclusions* Histology revealing dermal or intragranuloma oedema on a background of leprosy granuloma favours the diagnosis of lepra reaction. A careful analysis of subtle variations in the cells constituting the granuloma may aid in differentiating between upgrading T1R, downgrading T1R or T1R without upgrading or downgrading. Histology can also be useful in distinguishing T2R from T1R, in the absence of typical erythema nodosum leprosum (ENL) lesions. Neutrophils are the major inflammatory cells in the former where as lymphocytes or macrophages

predominate in the latter. We recommend that histopathological analysis should form an integral part of the evaluation of all lepra reactions.

## Introduction

Dharmendra described reactions as acute bouts of exacerbations during the otherwise chronic course of leprosy.<sup>1</sup> Jopling classified reactions into Type 1 and Type 2 lepra reactions.<sup>2</sup> Ridley and Radia<sup>3</sup> suggested that T1R can be of different types based on the immunological events taking place during reactions: upgrading reaction (associated with a rapid increase in specific cell mediated immunity (CMI) against *M. leprae*), downgrading reaction (associated with a rapid decline in CMI) and static reaction (without any change in the immunity). When compared to the pre-reaction biopsy, histopathology specimens from reacting skin lesions of patients with upgrading T1R revealed an increase in lymphocytes, epithelioid cells and giant cells, whereas downgrading reactions were characterised by presence of fewer lymphocytes and epithelioid cells and paucity or absence of giant cells.<sup>3</sup> Static reactions had features of underlying leprosy alone and were considered to be ineffective attempts at upgrading.<sup>3</sup>

Ramu and Desikan described two histological patterns in T1R – borderline exacerbations and reversal reactions corresponding to the static and upgrading T1R respectively, in Ridley's classification.<sup>4</sup> Ramu and Desikan noted marked dermal oedema in borderline exacerbations, but Ridley and Radia considered dermal oedema to be a significant feature of upgrading and downgrading T1R alone.<sup>3,4</sup>

In T2R variability has been noted in both clinical and histological features. The clinical picture in T2R can vary from a mild disease limited to few erythema nodosum leprosum (ENL) lesions to severe systemic disease with constitutional symptoms and multiorgan involvement. Apart from the common ENL lesions, a wide variety of skin manifestations are reported in T2R.

Hussain *et al.*<sup>5</sup> have documented two distinct histology patterns in ENL – neutrophil infiltration on a background of macrophage granuloma and macrophage granuloma without neutrophil infiltration.

Though many studies are available on reactions, these intriguing exacerbations still remain poorly understood. Hence we considered it worthwhile to study and compare the clinical and histological features of lepra reactions and to document the histological patterns of T1R and T2R observed in the study population.

## Material and Methods

### STUDY DESIGN – TWO YEAR CROSS SECTIONAL STUDY

Aims: 1. To study and compare the clinical and histological features of Type 1 and Type 2 lepra reactions. 2. To document the histological patterns of T1R and T2R observed in the study population.

Patients attending the Dermatology outpatient department of our Tertiary Care Hospital with clinical features of Type 1 lepra reaction or Type 2 lepra reaction were included in this study. Written informed consent was collected from each study subject using a standard consent form. The study adhered to the International Guidelines for Biomedical Research

Involving Human Subjects and the institutional ethics committee of Calicut Medical College gave ethical approval on 8.06.2004.

A clinical diagnosis of T1R was made when a patient in the borderline spectrum of leprosy had acute onset of erythema and oedema of skin lesions with or without neuritis and oedema of the hands, feet and face.<sup>6</sup>

T2R was diagnosed when a borderline lepromatous (BL) or lepromatous leprosy (LL) patient had crops of tender subcutaneous skin lesions with or without accompanying neuritis, iritis, arthritis, orchitis, dactylitis, lymphadenopathy, oedema and fever.<sup>6</sup>

Patients were thoroughly examined and the clinical features of lepra reactions were carefully documented. Depending on clinical severity T1R cases were classified into mild, moderate and severe.

*Mild:* T1R patient showing reactional changes limited to erythema, oedema and tenderness of skin lesions.

*Moderate:* T1R patient showing the changes mentioned above with joint effusion and/or oedema of hands, feet and face.

*Severe:* T1R patient manifesting sudden onset of neuritis/constitutional symptoms/ulcerated skin lesions.

T2R cases were also classified into mild, moderate and severe.

*Mild:* When T2R patient had temperature below 100°F and few reacting skin lesions confined to one or two extremities.

*Moderate:* When T2R patient had temperature between 100°F and 102°F and numerous skin lesions affecting all the four limbs, with a few on the trunk and face with or without extra-cutaneous signs like lymphadenopathy, arthritis and bone tenderness.

*Severe:* When T2R patient had temperature above 102°F along with cutaneous vesiculation/ pustulation/visceral involvement in the form of proteinuria, elevated liver enzymes, hepatomegaly or splenomegaly.

Biopsies were taken from the reacting skin lesions in all patients. In T2R patients, who showed skin lesions other than ENL as part of T2R, biopsies were taken from both the ENL and the clinically different lesions. Sections were stained with Haematoxylin and Eosin stain to study morphology and Wade Fite stain to identify acid fast bacilli (AFB). Bacteriological (BI) and morphological (MI) indices were determined. Histology was analysed in all cases.

For patients who developed T1R while on multi-drug therapy (MDT), histology of reactional biopsy specimens was compared with the histological features documented at the time of initiating MDT and was classified into upgrading T1R, downgrading T1R or T1R without upgrading or downgrading.

#### UPGRADING T1R

Reactional biopsy had features of a higher spectrum of leprosy or biopsy during reaction revealed leprosy histology with infiltration by plenty of protective cells like lymphocytes or giant cells, when compared to the pre-reaction biopsy.

#### DOWNGRADING T1R

Reactional biopsy had features of a lower spectrum of leprosy with paucity of lymphocytes and/or giant cells, when compared to the pre-reaction biopsy or when the reactional specimen showed a rise in morphological index with respect to the pre-reaction MI.

## T1R WITHOUT UPGRADING OR DOWNGRADING

When pre-reaction and reactional biopsy specimens were of the same spectrum of leprosy histologically. Patients who did not have a pre-reaction biopsy for comparison, were also classified into the above three groups by the careful analysis of cells constituting the granuloma.

*Upgrading T1R:* When histology revealed leprosy with presence of richer infiltrate of protective cells like lymphocytes and/or giant cells with respect to leprosy of similar spectrum without reaction.

*Downgrading T1R:* When histology revealed leprosy with paucity of lymphocytes and/or giant cells with respect to leprosy of similar spectrum without reaction.

*T1R without upgrading or downgrading:* When histology revealed leprosy without abundance/paucity of giant cells and/or lymphocytes with respect to leprosy of similar spectrum without reaction.

T2R patients were also classified histologically into three groups.

*Type 1:* T2R with features of underlying leprosy alone.

*Type 2:* T2R with neutrophil infiltration on a background of macrophage granuloma.

*Type 3:* T2R with neutrophil vasculitis on a background of macrophage granuloma.

A thorough assessment and documentation of the clinical and histological features at the time of the lepra reaction were carried out in individual patients. This was a cross sectional study and the study group was not followed up further.

## Results

During the 2 year study period, 34 patients having T1R and 14 patients having T2R attended the Dermatology outpatient department of our hospital. Skin biopsies were taken from all the patients.

Of the 34 T1R patients, 22 had reaction at the time of diagnosis, seven patients developed T1R for the first time while on MDT and five were cases of late T1R (T1R after completion of MDT) (Table 1). All those who developed T1R, while on MDT, did so for the first time within the first six months of treatment itself.

Nineteen among the 34 T1R patients had severe reactions. Fourteen of 22 of those who had T1R at the time of diagnosis, and five out of seven of those who developed it during MDT had severe reactions, but none of the late T1R were severe (Table 2).

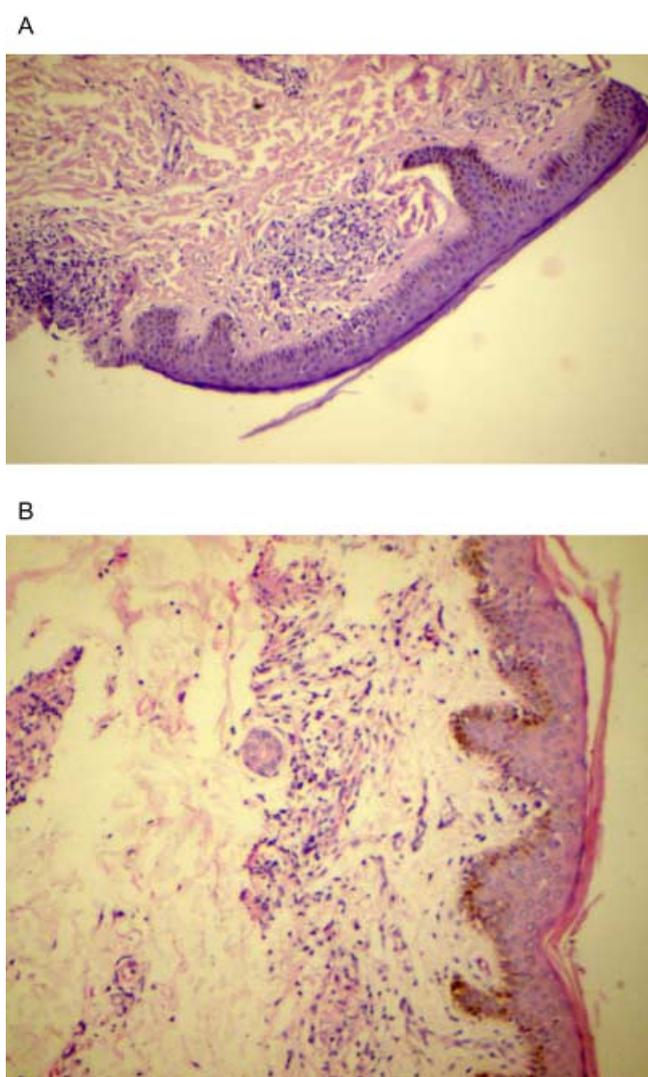
Biopsies from the reactional skin lesions of 34 patients were studied. Dermal [Figure 1B] or intragranuloma oedema which is considered as an important feature of lepra reaction by

**Table 1.** Type 1 Reaction - First Episode of T1R and MDT

	T1R No
Before starting MDT	22
While on MDT	7
Late reaction	5
Total	34

**Table 2.** Clinical Severity of T1R & MDT

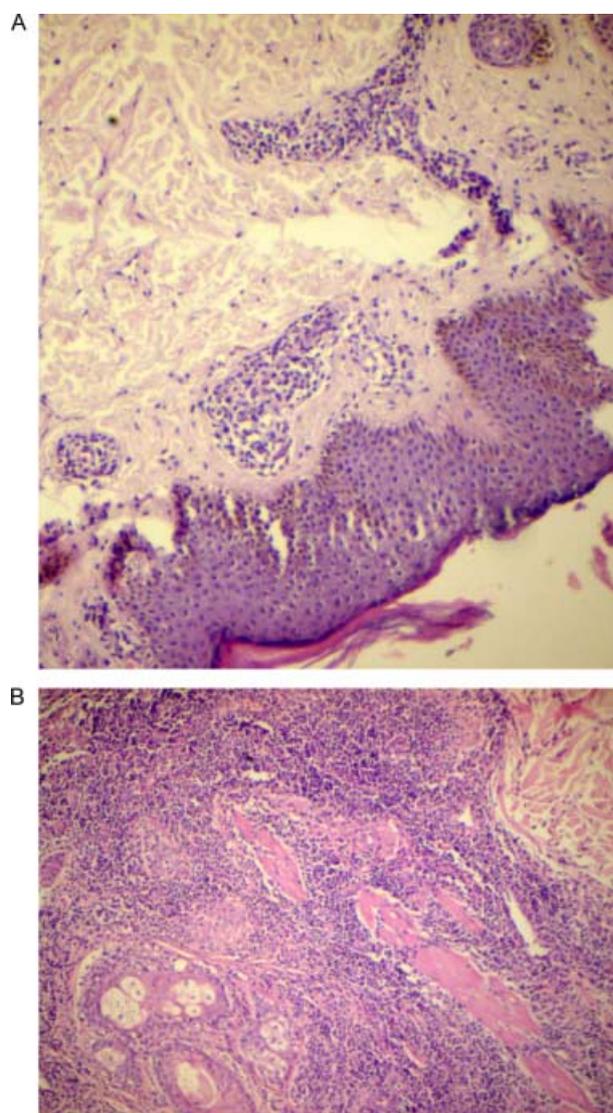
MDT	Severity of T1R			Total
	Mild	Moderate	Severe	
Pre MDT	3	5	14	22
On MDT	1	1	5	7
Late reaction	4	1	0	5
Total	8	7	19	34



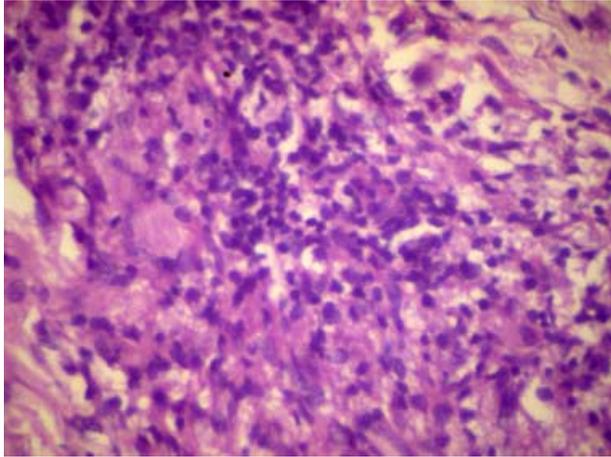
**Figure 1.** (A) Pre reaction biopsy. BT, H and E, X100. (B) Biopsy during reaction. Dermal oedema with separation of collagen. BT with Type 1 reaction without upgrading or downgrading, H and E, X100.

**Table 3.** Histological Patterns of TIR

Histology	No. of patients
Upgrading reactions	16
Reactions without upgrading or downgrading	17
Downgrading reactions	1
Total	34



**Figure 2.** (A) Pre reaction biopsy. BT, H and E, X100. (B) Biopsy during reaction. BT with heavy lymphocytic infiltrate. BT with upgrading Type 1 reaction, H and E, X100.



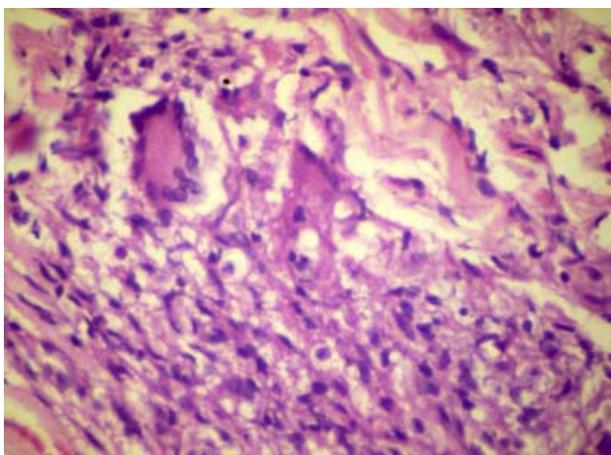
**Figure 3.** Biopsy during reaction. Compact epithelioid granuloma with Langhan's giant cells and heavy lymphocytic infiltrate. BT with upgrading T1R, H and E, X400.

many authors, was evident in only 50% of specimens (17 patients). All these patients clinically had severe T1R. In addition to this, three histological patterns were observed in our patients (Table 3).

Of the seven patients who developed T1R during MDT, four were upgrading [Figures 2A, 2B] and three were without upgrading or downgrading [Figures 1A, 1B]. None developed downgrading reaction while on treatment. Of the 22 patients who presented with reactions, 13 were without upgrading or downgrading and nine were upgrading T1R.

Of the 16 upgrading reactions, 9 were observed in patients who presented with reactions [Figures 3, 4, 5A, 5B], 4 in those on MDT and 3 in patients having late T1R [6A, 6A1, 6B, 6B1] (Table 4).

Seven of 12 patients who received MDT (either completed treatment or on treatment) as against nine out of 22 of those not on MDT had upgrading reactions.



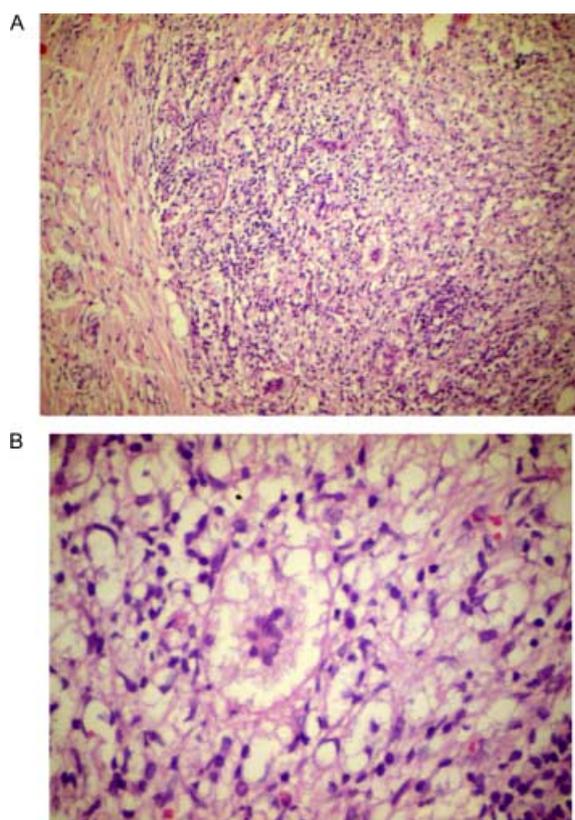
**Figure 4.** Biopsy during reaction. Diffuse epithelioid granuloma with Langhan's giant cells and heavy lymphocytic infiltrate. BT with upgrading T1R with dermal oedema, H and E, X400.

**Table 4.** Histology Pattern of T1R and Treatment Received

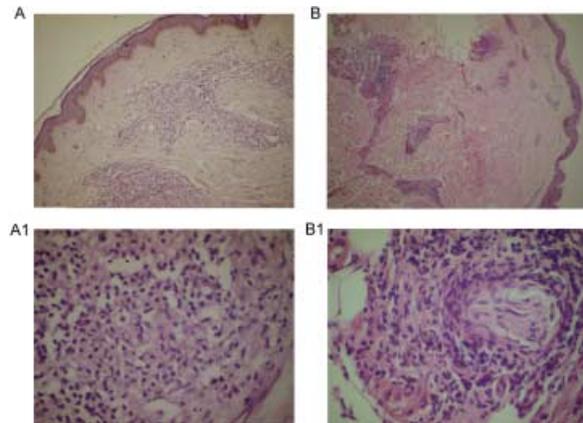
Treatment	HISTOLOGY			Total
	Upgrading reactions	Reactions Without upgrading or downgrading	Downgrading reactions	
Pre MDT	9	13	Nil	22
On MDT	4	3	Nil	7
Late T1R	3	1	1	5
Total	16	17	1	34

Except for the finding that dermal oedema was seen exclusively in severe reactions, no other differences were observed between the clinical features of T1R patients with different histological findings.

Ten out of 14 patients had their first episode of T2R while on MDT (Table 5). Two patients gave a history of aggravation of symptoms with each monthly pulse of Rifampicin and Clofazimine, which subsided by itself within 3-4 days.



**Figure 5.** (A) Biopsy during reaction. Macrophage granuloma with foreign body giant cells and heavy lymphocytic infiltrate. BL with upgrading T1R, H and E, X100. (B) Biopsy during reaction. Macrophage granuloma with foreign body giant cells and heavy lymphocytic infiltrate. BL with upgrading T1R, H and E, X400.



**Figure 6.** (A) Pre reaction biopsy. BL, H and E, X100. (A1) Pre reaction biopsy. BL, H and E, X400. (B) Biopsy during reaction. BT with upgrading late T1R, H and E, X100. (B1) Biopsy during reaction. BT with upgrading late T1R, H and E, X400.

Six out of 10 patients who developed T2R while on MDT, had moderate to severe reactions, whereas two of three who had T2R at the time of diagnosis developed reaction of moderate clinical severity (Table 6). The onset of T2R had a strong association with administration of MDT, but the severity of reactions in untreated patients was similar to that in patients who were on MDT. Only one patient developed severe T2R as manifested by erythema necroticans lesions and high grade fever above 102°F. The only case of late T2R was a moderately severe reaction.

All 14 patients had typical ENL lesions. In addition, erythema multiforme-like (EM) lesions, erythema necroticans and exacerbation of existing leprosy lesions (lepromatous exacerbation) were observed in one patient each.

The observed histology could be classified into three categories (Table 7).

Five of 14 patients showed no histological evidence of neutrophil infiltration. Clinically there were no differences between patients having neutrophil infiltration [Figure 7] and those without.

Only one patient without histologic evidence of neutrophil infiltration had dermal oedema. Clinically there was nothing to differentiate between those having dermal oedema and those not having it. Histological features of vasculitis were present in one patient who had severe T2R with erythema necroticans [Figure 8]. The biopsies taken from EM lesions and

**Table 5.** Type 2 Lepra Reaction - Relation between onset of T2R and MDT

Onset of Reaction	No.
At the time of diagnosis	3
Within 6/12 months of treatment	6
After 6/12 months of treatment	4
Late reaction	1
Total	14

**Table 6.** Clinical Severity of T2R and MDT

MDT	Clinical Severity			Total
	Mild	Moderate	Severe	
Pre MDT	1	2	Nil	3
Within 6/12 of MDT	2	4	Nil	6
After 6/12 of MDT	1	2	1	4
Late reaction	Nil	1	Nil	1
Total	4	9	1	14

exacerbation of existing skin lesions showed neutrophil infiltration on a background of macrophage granuloma.

## Discussion

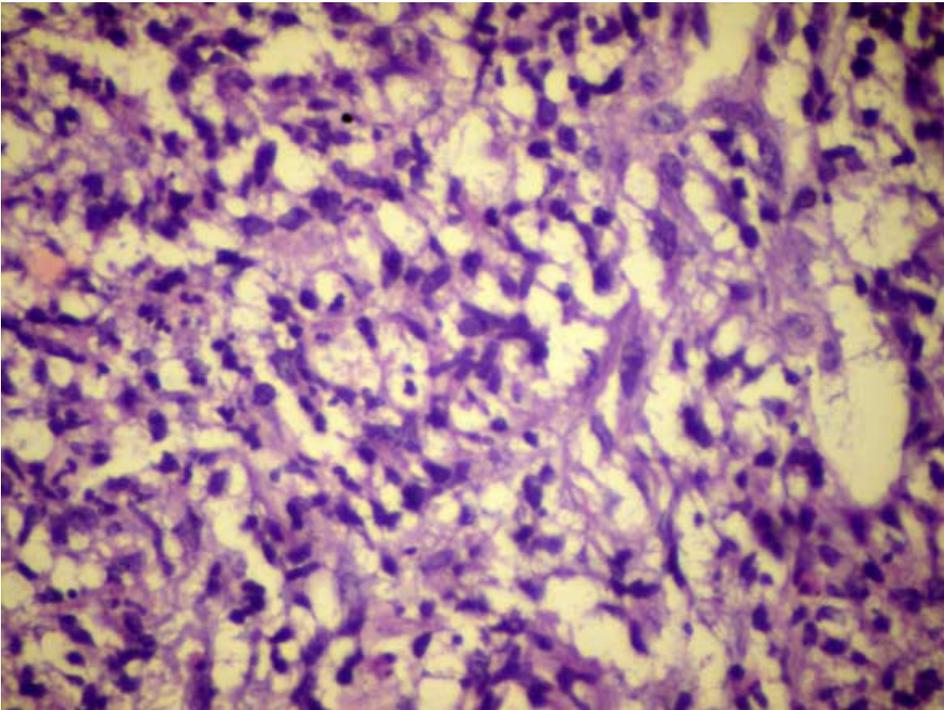
Nineteen of 34 of our T1R patients suffered from severe reaction. This may be due to the fact that this study was conducted in a tertiary referral centre and most of the subjects were referred cases with severe symptoms. One significant feature noted in our study was the relatively mild nature of late T1R. None of the late T1R was severe, whereas 14/22 and five of seven of those with T1R at the time of diagnosis and during MDT, respectively, had severe reactions. Milder T1R in patients who completed MDT could be due to the minimal immunological alterations in them as most of the bacillary antigens are already cleared by the host's immune system.

Dermal oedema, considered by many authors as an important feature of T1R,<sup>7,8</sup> was observed in only 17 (50%) of our T1R cases and all of them had clinically severe reactions. However, if the biopsy is taken later in the course of a reaction, oedema may not be a prominent feature.<sup>3</sup> This could be the reason for all our patients with clinically severe T1R manifesting dermal oedema. Such patients because of the severity of their symptoms might have sought medical advice earlier and in them the biopsy may have been done at an early stage of T1R.

Ten out of 17 cases with no histological evidence of upgrading or downgrading in our study had dermal oedema, contrary to the observations made by Ridley and Radia that static reactions are characterised by minimal dermal oedema.<sup>3</sup>

**Table 7.** Histopathology of T2R

Histology	No. of patients
Histological features of underlying HD only	5
Neutrophil infiltration on a background of macrophage granuloma with dermal oedema	8
Neutrophil vasculitis on a background of macrophage granuloma with dermal oedema	1
Total	14

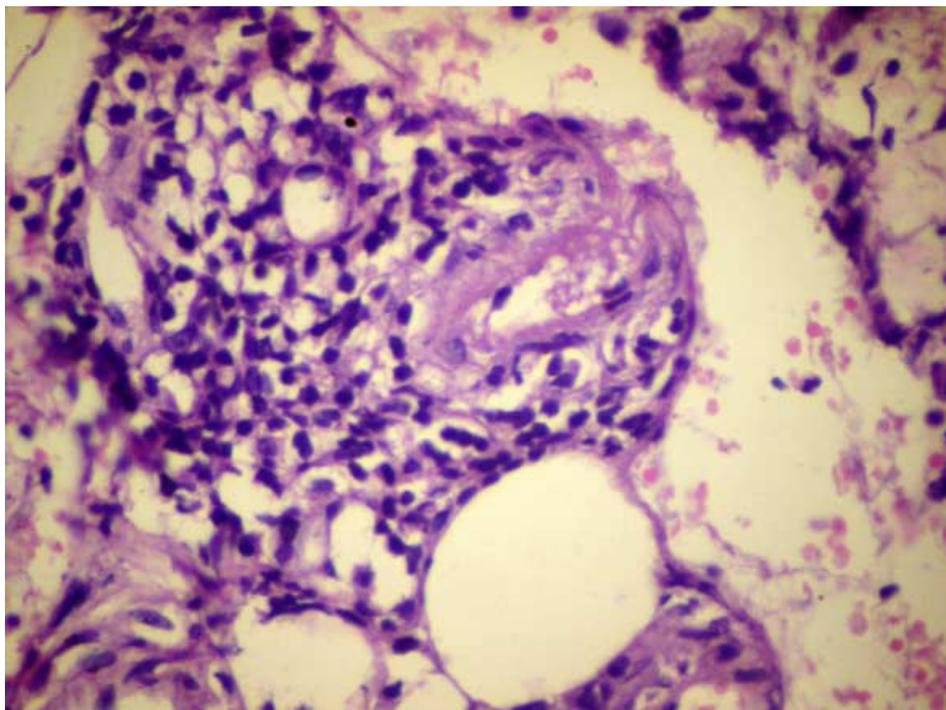


**Figure 7.** Biopsy during reaction. Macrophage granuloma with neutrophil infiltration. BL with T2R, H and E, X400.

Among the five late T1R cases in our study, three patients developed T1R 1-3 years after completion of treatment. Two were treated BL [Figures 6A, 6A1] cases who developed new lesions which were erythematous, oedematous and tender to the touch. Histology revealed borderline tuberculoid leprosy (BT) [Figures 6B, 6B1] in both.

The third late T1R patient had exacerbation of previously treated BT lesion and the present biopsy was indicative of tuberculoid leprosy (TT). We made a diagnosis of upgrading late T1R in all three, and the lesions resolved completely on treatment with prednisolone within a period of 2 months.

Two patients who had completed treatment, one with LL and another with BT, featured late T1R (manifested as sudden appearance of erythema, oedema and tenderness of previously treated leprosy lesions) within a year of completion of treatment, and in both, histology was suggestive of the original spectrum. The BT patient responded to a therapeutic trial of prednisolone and we considered it as T1R without upgrading or downgrading. The LL patient whose morphological index (MI) at the time of completion of treatment was zero, revealed an MI of five at the time of reaction. As a rise in MI in a treated patient was suggestive of relapse, we considered a diagnosis of LL relapse with late downgrading T1R in this patient, as relapse alone could not explain the acute manifestations in her. We believe that a rise in MI during T1R, points to a downgrading reaction. We restarted her on MB MDT and the patient showed clinical and bacteriological improvement. This patient had undergone a medical termination of pregnancy 3 weeks prior to the reactional episode and we suggest that the emotional and physical stress associated with the procedure might have precipitated the



**Figure 8.** Biopsy during reaction. Macrophage granuloma with neutrophil infiltration and fibrinoid necrosis of vessel wall. LL with T2R, H and E, X400.

downgrading reaction. This presentation of downgrading reaction as a late T1R highlights the fact that a total lack of immunity against *M. leprae* exists in lepromatous patients, rendering them vulnerable to the disease again under favourable circumstances.

In some patients who presented in reaction, histology revealed features of underlying leprosy with or without dermal oedema. Some patients on histological examination revealed epithelioid granulomas with plenty of lymphocytes and Langhan's giant cells [Figure 3]. Few of the above mentioned patients featured diffuse granuloma which we considered to be due to dermal oedema [Figure 4]. Epithelioid granulomas with Langhan's giant cells are seen in tuberculoid leprosy and we assumed that these patients might have upgraded to tuberculoid leprosy (TT) from a lower spectrum, as otherwise TIR in TT was unlikely and a diagnosis of upgrading T1R was made in them. Some other patients, in the lepromatous spectrum who presented in reaction, had plenty of lymphocytes infiltrating the macrophage granuloma, and we made a diagnosis of upgrading T1R in these patients also [Figures 5A and 5B], as usually there is a paucity of lymphocytes in lepromatous spectrum.

Though it is widely believed that upgrading reaction is a manifestation that follows treatment, a significant proportion of untreated patients in our study showed features of upgrading. This may be due to immunity developed in the study population by exposure to the infective agent, as leprosy is not an uncommon disease in this part of the world and also due to the universality of BCG administration in our country conferring some protection against *M. leprae*. Similarly, the rarity of downgrading reactions in the present study may be due to the heightened immunity in the study population as well as due to incorrect classification.

Downgrading reactions are usually seen in untreated patients. In patients presenting with reactions, categorisation into upgrading, downgrading or reactions without upgrading or downgrading is difficult (in the absence of pre-reactional biopsies for comparison). Hence we might have incorrectly classified some downgrading reactions as reactions without upgrading or downgrading.

The manifestation of self-limiting ENL with each monthly pulse of rifampicin and clofazimine noted in our study has been reported previously,<sup>9</sup> and may be due to the sudden release of large quantities of bacillary antigens induced by effective killing of *M. leprae* by the pulse dose of bactericidal drugs.

Contrary to previous reports,<sup>10,11</sup> 5/14 of our T2R patients showed no neutrophilic infiltrate histologically. Hussain *et al.*<sup>5</sup> described a similar finding in 36% of T2R cases and proposed the following mechanisms for this histology: (a) the biopsy was done at a later period on neutrophil negative patients; (b) IL-6 which stimulates production of CRP is produced in higher quantities by the neutrophil positive group. In our study only 1/5 patients without a neutrophilic infiltrate had dermal oedema histologically as against 7/9 with neutrophilic infiltrate or vasculitis. We suggest this points to a delay between the onset of reaction and the time of the biopsy in those without neutrophilic infiltrate, as dermal oedema may be missed in older reactional lesions.

As in the study by Hussain *et al.*,<sup>5</sup> there was nothing in our study to differentiate between neutrophil negative and neutrophil positive patients clinically. Though previous reports suggest that vasculitis as part of T2R is more commonly seen in Indian patients,<sup>12</sup> only one of our patients (who had severe T2R with erythema necroticans lesion) showed evidence of vasculitis. Patients who had EM lesions and exacerbation of existing skin lesions showed neutrophil infiltrate in macrophage granuloma indicating that histologically they were similar to ENL. Similar observations have been made by previous authors.<sup>13</sup> Unlike earlier reports,<sup>14</sup> the patient who showed exacerbation of existing leprosy lesions as part of T2R showed mainly granular forms of bacilli thereby suggesting that lepromatous exacerbation does not signify worsening of disease.

The main limitation of our study was the small sample size. The study group included only 34 T1R and 14 T2R cases. In spite of this, we were able to observe and analyse the mild, moderate and severe forms of both lepra reactions and the different histological patterns, as the population studied comprised of patients seeking treatment in a tertiary care institution.

## Summary

The presence of dermal or intragranuloma oedema on a background of leprosy granuloma favours the diagnosis of lepra reaction and this finding may be missed in biopsies taken later in the course of reaction. A careful analysis of subtle variations in the cells constituting the granuloma may aid in differentiating between upgrading T1R, downgrading T1R, or T1R without upgrading or downgrading, which can be of help in assessing the disease prognosis. EM lesions and lepromatous exacerbation occurring as part of T2R were histologically similar to ENL, whereas erythema necroticans on histology revealed neutrophil vasculitis on a background of macrophage granuloma. Histology can also be useful in distinguishing lepromatous exacerbation from T1R (neutrophils are the predominant cells infiltrating the granuloma in the former whereas lymphocytes or macrophages are the significant cells in the latter). We recommend histopathological study of all leprosy cases in reaction (irrespective of

whether they had a previous biopsy or not), as it can throw light on the immunological changes taking place during these acute episodes, as well as predict the response to treatment in patients developing T1R while on MDT.

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