

Clinico-pathological overview of lepra reactions in the era of leprosy elimination

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Abstract

Background Lepra reactions are a chronic debilitating public health problem. It causes nerve damage, loss of limbs and deformities. They may occur during the natural course of the disease, throughout treatment or after it. Wide variations in clinical presentation make histopathology an important tool. There needs to be more inclusive histologic criteria for diagnosing lepra reactions.

Objective This study aims to analyse clinical diagnosis with histopathological findings, different histological types of lepra reactions and their changes, and the frequency of mycobacterial positive cases in lepra reaction cases using Modified Fite's stain.

Methods The clinically suspected cases of lepra reactions, irrespective of age and sex attending OPD in Department of Dermatology, at North Bengal Medical College and Hospital were biopsied.

Results Histopathological features based on the type of infiltrate predominance of neutrophilic infiltration, vasculitis, and supporting features like vasculitis, neutrophilic abscess formation within the dermis will help in clinching a diagnosis of ENL, while a predominant lymphocytic infiltrate, intra granuloma oedema along with presence of giant cells and oedema of papillary dermis will be commoner in TILR.

Conclusion Histopathology along with clinical findings will help in proper identification of atypical cases.

Key words

Lepra reaction, ENL, Type 1 lepra reaction, Type 2 lepra reaction.

Introduction

Leprosy is a chronic debilitating public health problem in most of the developing countries. It is a chronic infectious disease caused by *Mycobacterium leprae*. India has been successful to bring down the national prevalence down to “elimination as a public health problem” of less than 1/10,000 in December 2005 to even further down to 0.66/10,000 in 2016 by implementation of Multi-drug therapy (MDT).¹ Despite the massive success story of

India, several other challenges remain –delay in detection of new patients, persisting social stigma and discrimination against people, managing complications and rehabilitation of debilitating cases due to reactions.

Lepra reactions constitute the main complication of the disease, like nerve damage, loss of limbs and deformities. Females, widespread disease, multibacillary disease, HIV, pregnancy, lactation and immunosuppression have been identified as risk factors.² They may occur during the natural

course of the disease, throughout treatment or after it.^{3,4} The lepra reactions are the consequences of the dynamic nature of the immune response to *M. leprae*.⁵

Three types of reactions are recognized - Type 1 lepra reaction (cell-mediated hypersensitivity), Type 2 lepra reaction (immune complex-mediated) and Lucio phenomenon. Type 1 Lepra reaction (T1LR), also described as "reversal" reaction, occurs in borderline leprosy patients with cellular immune responses to *M. leprae* antigenic determinants.⁶ It presents with acute inflammation of pre-existing skin lesions or by the appearance of new lesions and/or neuritis. Approximately 95% of Type 1LR cases are diagnosed simultaneously with leprosy or during the first 2 years of MDT.⁷

Type 2 lepra reaction (T2LR) presents with skin lesions (red, painful, and tender subcutaneous nodules and plaques), fever, and systemic inflammation that may affect the nerves, eyes, joints, testes, and lymph nodes. Most of the Type 2 LR occur during the first year of MDT.⁶ Erythema nodosum leprosum (ENL) is the most common manifestation of type 2 LR (T2LR).

Lucio's phenomenon represents a severe cutaneous necrosis reaction that is characterized by bouts of slightly infiltrated erythematous macules, which evolve with central necrosis and subsequent ulceration.

Diagnosis of leprosy and lepra reactions is based on different clinical parameters which involve detailed examination of skin lesions, peripheral nerves and demonstration of acid-fast bacilli in slit skin smears. Wide variations in clinical presentation make histopathology an important tool for supporting clinical diagnosis. While leprosy is histopathologically relatively simpler to diagnose, lepra reactions are not always diagnosable under the microscope. Histological

features of type 1 lepra reactions have been described by Ridley and also in studies by Lockwood *et al.*⁸ and whereas histological features of type 2 reactions were studied by Lever *et al.* and Vijay Adhe *et al.*⁹

However there needs to be more inclusive histologic criteria for diagnosing lepra reactions. This study aims to analyse clinical diagnosis with histopathological findings, different histological types of lepra reactions and their changes, and the frequency of mycobacterial positive cases in lepra reaction cases using Modified Fite's stain.

Subjects and Methods

An observational cross-sectional study was performed in the Department of Pathology in collaboration with the Department of Dermatology, North Bengal Medical College and Hospital (NBMCH), Sushrutanagar, Darjeeling for a period of one year (July 2016 - June 2017). After obtaining necessary clearances, the clinically suspected cases of lepra reactions, irrespective of age and sex attending OPD in Department of Dermatology, at NBMCH were biopsied. Data collected was presented in number and percentages and analysed in Microsoft excel.

Results

A total of 179 cases of leprosy were received by the Department of Dermatology, NBMCH during the study period of which 44 patients were diagnosed clinically to have lepra reactions. Lepra reactions comprised of around 24.5% of all leprosy cases (**Chart 1**).

The age range of patients was between 12-65 yrs. of age, with a maximum incidence seen in 31-40 yrs. age group with an incidence of 31.8% cases (**Table 1**).

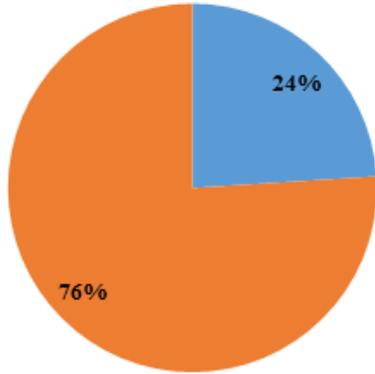


Chart 1 Incidence of lepra reactions in skin biopsies (n=44).

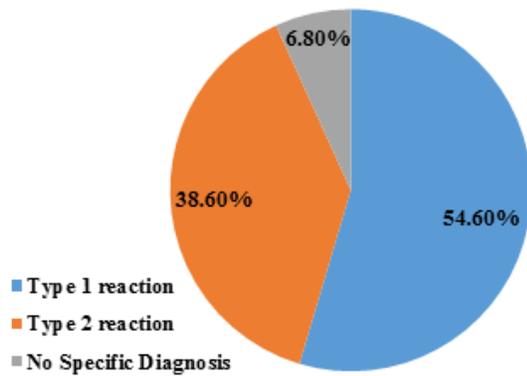


Chart 2 Histological types of diagnosis (n=44).

Clinically approximately 59% of the lepra reactions were of T1LR, while the rest of the patients had T2LR. On histopathological examination, out of 44 cases majority of cases were of T1LR 54.6%, while T2LR comprised of 38.6% (**Chart 2**).

A male preponderance of cases was noted with 61.3% and female cases accounted for 39.7% cases.

In the present study, anti-leprosy drugs constitute the major risk factor (52%) while other factors like -physiological stress (menstruation), extremes of climate (summer), concomitant infection and idiopathic causes together constitute 48% (**Chart 4**).

Table 1 Distribution of study subjects according to age (n=44).

Age in years	Number of cases	Percentage (%)
0-10	00	0
11-20	06	13.6
21-30	12	27.3
31-40	14	31.8
41-50	04	9.09
51-60	05	11.3
61-70	03	6.8
Total	44	100

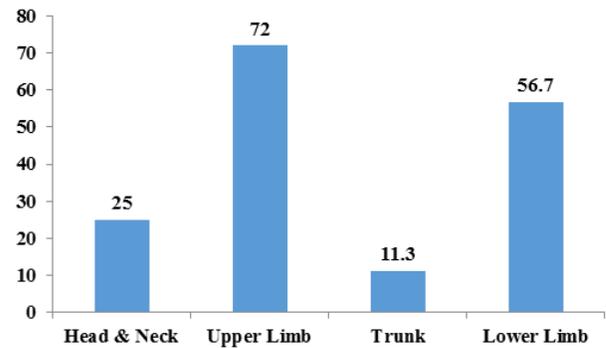


Chart 3 Site wise distribution of cases (n=44).

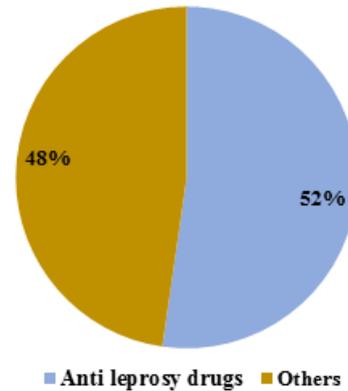


Chart 4 Precipitating Factors (n=44).

The most common presentation for T1LR was an erythema of existing lesions (75%) cases, followed by oedema, ulceration of existing lesions (66.6%) and appearance of new lesions (37.5%) cases. Neuritis (29.1%), fever (20.8%) and lymphadenopathy (4.1%) were other symptoms.

T2LR, mostly presented with erythematous nodular lesions with appearance of newer lesions apart from pre-existing lesions in 100%

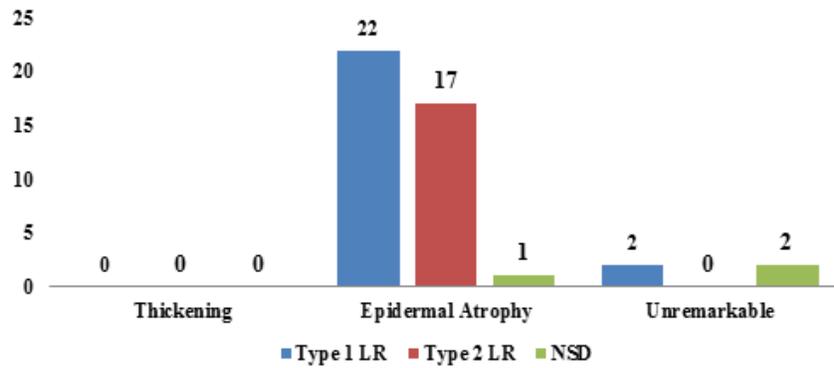


Chart 5 Epidermal changes (n=44).

cases, followed by fever, myalgia, joint pain (70.5%) of the cases. Oedema and ulceration of lesions (41.1%), neuritis (23.5%), lymphadenopathy and orchitis (35.2%) were also seen.

The histopathological changes were divided into epidermal changes and dermal changes for better understanding. 91.7% cases of type 1 LR showed epidermal atrophy, while 100% of the cases of Type 2 LR showed epidermal atrophy (Chart 5).

In the dermal changes we looked for presence of a well-defined grenz zone, intragranuloma oedema, presence of giant cell, dermal oedema, presence of type of infiltrate (lymphocytic/neutrophilic) around adnexal structures, panniculitis and also features like vasculitis, necrosis and extravasation of RBCs helped us in reaching a diagnosis in most of the cases.

A well-defined Grenz zone could be appreciated mostly in T2LR 62.5% of cases, than in T1LR 37.5% cases while granuloma formation was a much more common feature of T1LR 75% of cases. Inter-observer variation exists in appreciating intragranuloma oedema. Intragranuloma oedema could only be appreciated in 66.6% of cases of T1LR.

Dermal oedema was a commoner feature for

T2LR 88.2% cases and vasculitis with increased vascularity was present in 82.3% of cases. None of the cases of T1LR showed presence of vasculitis.

Based on the type of infiltrate, T1LR prominently showed presence of lymphocytic infiltrate, around peri-adnexal structures (66.6%) and around neurovascular bundles (45.8%). A notable feature i.e. folliculotropism of lymphocytes was also noted in 41.6% cases. On the other hand, for T2LR a predominance of neutrophilic infiltrate was noted, around peri-adnexal structures (70.5%), hair follicles (11.7%) and also around neurovascular bundles (29.4%). Presence of neutrophilic abscess formation was seen in 11.7% cases of T2LR.

Giant cells were much more common in T1LR 50% cases than T2LR. Lymphocytic panniculitis was seen in 45.8% of T1LR while neutrophilic panniculitis (58.8%) was noted for T2LR. However, other changes like - extravasation of RBCs and necrosis were seen in around 12.5% cases of T1LR.

AP- Arrector Pili ADX- Adnexa NVB- Neurovascular bundle HFO- Hair Follicle OTH- Others.

Modified Fite's stain on tissue sections was performed and T1LR reactions showed

Table 2 Frequency of *Mycobacterium leprae* positivity cases in tissue sections by Modified Fite's stain.

Types	Total number of cases	<i>Mycobacterium leprae</i> positivity Fite's stain	Percentage (%)
T1LR	24	04	16.6
T2LR	17	05	29.4
NSD	03	0	0
Total	44	09	20.5%

Mycobacterium leprae positivity in 16.6% cases while for T2LR *Mycobacterium leprae* positivity was seen in around 29.4% cases with an overall positivity of 20.5% in tissue sections (**Table 2**).

Discussion

The results of incidence were compared with similar other studies which have shown wide variation in incidence of lepra reactions. In the study of B. Debi *et al.*¹⁰ the incidence of lepra reactions (LR) is about 2.07% and is as high as 42.8% in the study of Sharma *et al.*¹¹ The high incidence of 24.5% in the present study is in concordance with the fact that main referral centres may report higher frequency from the very nature of the patients who attended there.

A majority of patients were noted in 31-40 yrs age, 31.8% cases which well corroborates with the study of Debi and Mohanty *et al.*¹⁰ that 41-60 years was the most common age group affected. Male preponderance was noted 61.3% of the cases and female cases accounted for 39.7% cases. Both Type 1 and Type 2 reactions were commoner in men than in women.

In the present study, clinically approximately 59% of had T1LR, while 41% of patients had T2LR. On histopathological examination, majority of cases were of T1LR 54.6%, while T2LR comprised of 38.6%, and a specific diagnosis of lepra reaction diagnosis could not be reached in 6.8%.

In the study of Kumar *et al.*¹² the incidence of T1LR was 71.5% whereas the incidence of T2LR was 28.5%. Scollard *et al.*⁵ found T1LR in 64.1% and T2LR in 35.9% of the patients while contrasting observations were made by Vijay Adhe *et al.*⁹ that T2LR were commoner than T1LR.

Upper Limb was the most common site of occurrence of lepra reaction. Anti-leprosy drugs constitute the major risk factor of lepra reactions. In the study of Kumar *et al.*¹² female gender, disseminated disease, (extent of clinical disease measured by involvement of a number of body areas, nerves, and skin lesions) at the time of diagnosis were the risk factors involved for T1LR. Nigam *et al.*¹³ also mentioned that 64.5% of patients developed reactions during dapsone therapy. In their series, reactions were mainly observed during summer months (61.9%).

The most common clinical presentation for T1LR was an erythematous lesion in 75% cases (**Figure 1**) with swelling and scaling (**Figure 2, 3**), followed by oedema and ulceration of existing lesions (66.6%).



Figure 1 Type 1 Lepra reaction: Multiple erythematous lesions over face.



Figure 2 Type 1 Lepra reaction: Swollen erythematous lesions with raised edges over face.



Figure 3 Type 1 Lepra reaction: Erythematous scaly lesions over back.

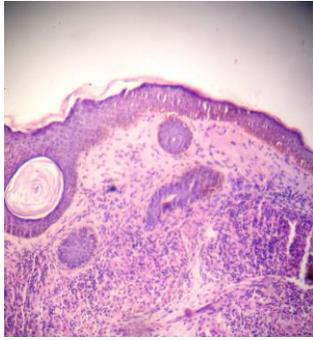


Figure 4 Type 1 Lepra reaction: Poorly delimited granulomas in upper dermis. (100X, H & E)

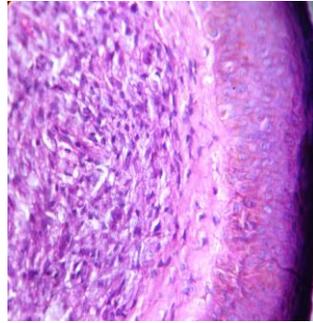


Figure 5 Type 1 Lepra reaction: Confluent poorly delimited granulomas in upper dermis. (400X, H&E)

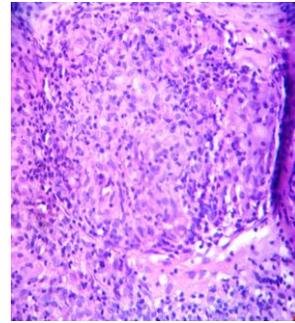


Figure 6A Type 1 Lepra reaction: Intragranuloma oedema along with dermal oedema (400X, H&E)

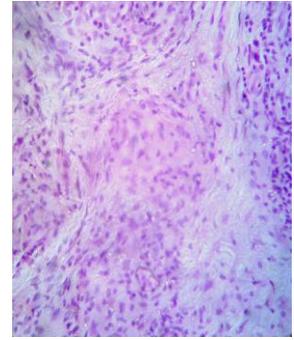


Figure 6B Type 1 Lepra reaction: Intragranuloma oedema along with dermal oedema (400X, H&E)

Neuritis (29.1%) and appearance of new lesions was seen in 37.5% cases. Constitutional symptoms like fever were found in 20.8% of patients. Sharma *et al.*¹¹ also found that predominant clinical presentation for T1LR was exacerbation of pre-existing skin lesions and or appearance of new lesions. In the study of Lockwood *et al.*⁸ 43.1% had skin lesions alone, while 22.7% had both skin lesions and neuritis and 31.8% had only neuritis without any ulceration.

T2LR, mostly presented with erythematous nodular lesions (**Figure 11, 12**) with appearance of newer lesions apart from pre-existing lesions in all 100% cases. Constitutional symptoms like fever, myalgia, and joint pain were much more common in T2LR (70.5%). Oedema, ulceration of lesions (41.1%) (**Figure 13**); neuritis (23.5%), lymphadenopathy and orchitis were seen in 35.2% cases. In the study by A. Mondal *et al.*² and T. Dhanamjaya Rao *et al.*¹⁴ T2LR presented mainly with erythematous, tender, evanescent nodules while Adhe *et al.*⁹ found papules, nodules, plaques as well as neuritis to be the predominant presentation. Constitutional symptoms of like fever, myalgia, and joint pain were commoner among patients of Type 2 lepra reactions than in T1LR.

Epidermal atrophy is a commoner feature in Type 2 LR (**Figure 16**). Dermal oedema,

loosening of granuloma, and predominance or increase in number of lymphocytes have been described as features of type 1 reaction in prior studies by Lockwood *et al.*⁸ A similar study by Sharma *et al.*¹¹ has stressed that histopathological features of T1LR patients showed presence of intra granuloma oedema (46.2%) along with presence giant cells and oedema of papillary dermis in 46.2% and 40% cases respectively.

In our study Intra granuloma oedema could be appreciated in 66.6% of cases of T1LR (**Figure 4-6**), giant cells (50%) cases (**Figure 8**) while dermal oedema (83.3%) is a prominent feature in T1LR reactions.

Lever *et al.*, has also stressed the predominance of lymphocytes in type I upgrading reactions. Our study also shows that T1LR prominently showed presence of lymphocytic infiltrate, around periadnexal structures and also around neurovascular bundles. However a mixed infiltrate should not deter diagnosis provided other features of T1LR are present. Other notable feature folliculotropism of lymphocytes (41.6%) cases and lymphocytic panniculitis (45.8%) (**Figure 9, 10**) cases were also seen.

Similar findings were shared in a study by T. Dhanamjaya Rao *et al.*¹⁴ histopathological examination of T1LR showed presence of

dermal oedema, lymphocytic panniculitis and

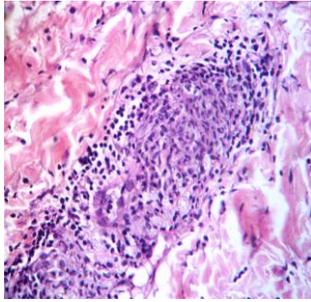


Figure 7 Type 1 Lepra reaction: Periadnexal granulomatous infiltrate. (400X, H&E).

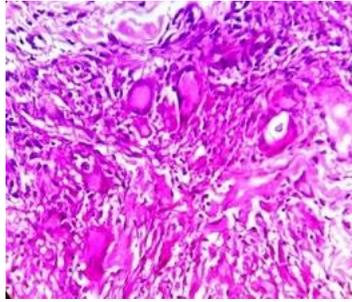


Figure 8 Type 1 Lepra reaction: Langhans giant cells (400X, H&E).

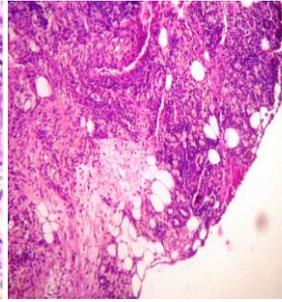


Figure 9 Type 1 Lepra reaction: Lymphocytic panniculitis and dermal oedema (100X, H&E).

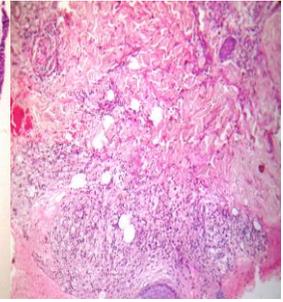


Figure 10 Foamy histiocytes (400X, H&E).



Figure 11 Type 2 Lepra reaction: Erythematous nodular lesions over hand.



Figure 12 Type 2 Lepra reaction: Erythematous nodular lesions involving ear lobule.



Figure 13 Type 2 Lepra reaction: Nodular and pustular lesions over hand.



Figure 14 Type 2 Lepra reaction: Loss of digits in a neglected case.

folliculotropism as key findings. In the another study conducted by V.Adhe *et al.*,⁹ among 22 patients of T1LR, histopathological features showed presence of lymphocytes in the granuloma for all 100% cases. 19(86%) cases showed oedema in the papillary dermis, while 17(77%) cases showed pyknosis of lymphocytes, and 16(73%) cases showed presence of intragranuloma oedema.

In our study intra granuloma oedema was a fairly uncommon finding for T2LR. Vasculitis (**Figure 17**) with increased vascularity was a prominent feature in 82.3% of cases. The histopathological spectrum of vasculitis ranged from endothelial swelling, neutrophilic infiltration of the vessel wall to destruction of the vessel walls. In ENL, the lesions are foci of acute inflammation superimposed on chronic multibacillary leprosy. Neutrophilic infiltrate around adnexal structures and neutrophilic panniculitis (**Figure 18**) was seen in 70.5% cases and 58.8% cases respectively. Polymorph

neutrophils may be scanty or so abundant as to form a dermal abscess with ulceration. 11.7% cases which showed presence of neutrophilic abscess (**Figure 19**) formation within the dermis. The dense collection of neutrophils in the epidermis and dermis is probably responsible for the clinical finding of pustules in ENL lesions.

In the study conducted by V.Adhe *et al.*⁹ among 42 patients of T2LR, histopathological features show presence of neutrophils within the granuloma in 100% cases. 34(81%) cases showed leukocytoclasia, and oedema of the papillary dermis. A predominant neutrophilic panniculitis was seen in 66% cases. Fibrin in vessel wall, neutrophilic spongiosis, fibrin thrombi, folliculotropism, and neutrophils in vessel wall were other prominent features. A small percentage of cases showed intradermal pustule formation, neutrophils in the sweat gland and 5% cases showed lymphocytes in the sebaceous glands.

Lever *et al.*, has also described predominance of



Figure 15 Nerve impairment in lepra reaction.

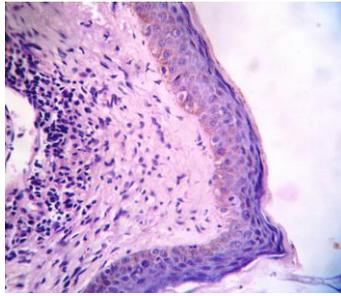


Figure 16 Type 2 Lepra reaction: Epidermal atrophy, grenz zone formation and polymorphs in the dermis. (100X, H&E).

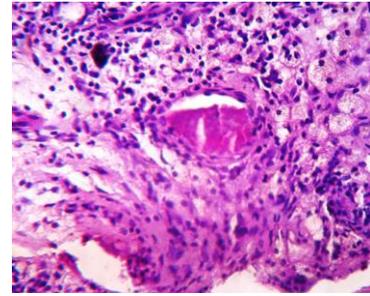


Figure 17 Type 2 Lepra reaction: Vasculitis. (100X, H&E).

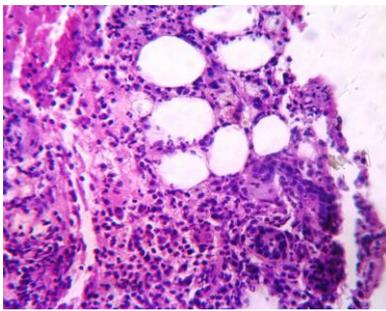


Figure 18 Type 2 Lepra reaction: Neutrophilic panniculitis (400X, H&E).

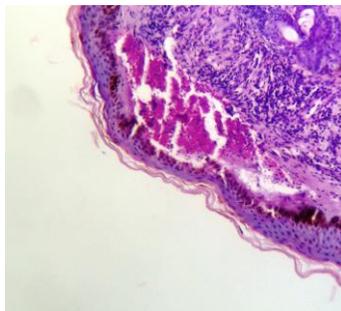


Figure 19 Type 2 Lepra reaction: Neutrophilic abscess formation within the dermis. (400X, H & E)

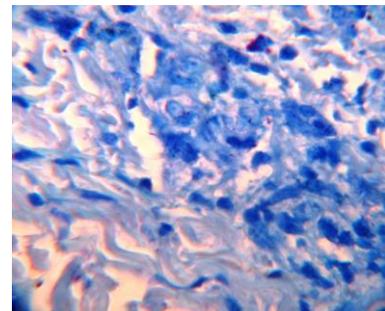


Figure 20 Type 2 Lepra reaction: Acid fast bacilli (1000X, Oil immersion Fite Faraco).

neutrophilic infiltration, vasculitis and occasional eosinophils in type 2 reaction which well corroborates our findings of neutrophil predominance in panniculitis and around adnexal structures.

Prompt detection of mycobacteria is a necessity for diagnosis as well as treatment. The diagnosis is confirmed by demonstration of Mycobacterium in tissue sections taken from the lesion. On Modified Fite's stain on tissue sections, T1LR showed mycobacterial positivity in 16.6% cases while for T2LR Mycobacterial positivity (**Figure 20**) was seen in 29.4% cases with an overall positivity of 20.5% in tissue sections.

In a study by Thomas EA *et al.*, out of 73 patients were of lepra reactions in type 1 Lepra reactions 9(16.9%) patients were positive for

lepra bacilli, while 17(85%) Type 2 patients showed presence of acid fast bacilli.¹⁵

Conclusion

Reaction is an important problem both for the patients and for the treating physician. The appearance of reactions not only indicates worsening of the disease but also raises doubts about curability of the disease.⁷ Histopathological features based on the type of infiltrate predominance of neutrophilic infiltration, vasculitis, and supporting features like vasculitis, neutrophilic abscess formation within the dermis will help in clinching a diagnosis of ENL, while a predominant lymphocytic infiltrate, intra granuloma oedema along with presence of giant cells and oedema of papillary dermis will be commoner in T1LR.

Histopathology along with clinical findings will help in proper identification of atypical cases.

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