

Analytical Study of Histopathological and Haematological Analysis with Epidemiological Evidences Among Type-I and Type-II Lepra Reactions

S PREMALATHA¹, V PALANIAPPAN², S RAVI³, SUDHANDHIRAN⁴

ABSTRACT

Introduction: Leprosy is still a burden to India, even though it is under control but still it persists due to decreased level of immune defense mechanism against the infection. Immune mechanism plays a vital role in treatment and in producing some adverse lepra reactions. So it is indeed to analyse the lepra reaction using varying parameter such as histopathological and haematological examination which pave a way for early detection and control of disease in future.

Aim: To study the histopathological pattern among patients of leprosy patients with lepra reactions and to compare the histopathological, hematological and epidemiological variation among the patients of type-I and type-II lepra reactions.

Materials and Methods: This study was proposed and conducted in the Chengalpattu Medical College Hospital and Central Leprosy Teaching and Research Institute (CLTRI). A retrospective study of clinico-pathological analysis of 30 skin biopsies of patients with lepra reaction visiting a tertiary care centre and CLTRI for three months duration during the year of 2017 was done. The skin biopsies were immediately fixed in 10% formalin and processed routinely. Four microns sections were taken from the tissues and stained with haematoxylin and eosin and findings were recorded. Sections were also

stained with special stain using AFB staining for detection of Lepra bacilli which would be very helpful to rule out lepra reactions. Each section was analysed for the presence of histopathological findings of type 1 and type 2 reactions. The results and observations were tabulated and analysed for their significance.

Results: Histopathological observations were tested by applying test of significance for statistical significance. It was noted that significant association between presence of neutrophilic infiltration in granuloma was noted in type-II reaction. While lymphocytes in perigranuloma was significantly observed in type-I lepra reactions. Intra-granuloma lymphocytes were significantly higher in type-I lepra reaction. It was also noted that fibrin in granuloma is present in significantly higher number among type-II lepra reactions.

Conclusion: The study concludes that significant histopathological features of type-I lepra reactions are Giant cells in granuloma, Perigranuloma lymphocytes in granuloma, Oedema within granuloma, Exocytosis, and parakeratosis in epidermis. The significant histopathological features of type-II lepra reactions are Neutrophil infiltrated granuloma, fibrin in granuloma, fibrin within the vessel wall and intra-epidermal pustules.

Keywords: Granuloma, Lymphocyte, Skin biopsy

INTRODUCTION

Leprosy is a chronic infectious disease affecting the skin and the nervous system caused by intracellular bacteria, *Mycobacterium leprae*. Lepra reactions are the histopathological response to the bacterial antigen and a least understood phenomenon since several centuries of research. These reactions are acute episodes that interrupt the usual chronic course and clinical stability of leprosy. The reactions, which are major causes of tissue injury and morbidity, have been subdivided into two types as type-I and type-II lepra reaction (erythema nodosum leprosum).

Lepra (type-I) reactions usually occur in borderline leprosy with a shift toward the tuberculoid pole (upgrading) as a result of an increase in delayed hypersensitivity but sometime the shift is towards the lepromatous pole (a downgrading reaction) were also noted. Lepra reactions are often seen in the first six months of therapy, but sometimes occur in untreated patient with pregnancy, stress and intercurrent infections. Type-I reactions clinically presents with oedema and erythema of skin lesions but the most important aspect of type 1 reactions is not the skin lesion but the condition of the peripheral nerve. The upgrading and downgrading reactions differentiation is difficult to make and may require serial examinations. In upgrading reactions, the granuloma becomes more epithelioid

and activated, and Langhans giant cells are larger and there may be erosion of granulomas into the lower epidermis, and there may be fibrinoid necrosis within granulomas and even within dermal nerves. In downgrading reactions, necrosis is much less common, and over time the density of bacilli increases [1].

Erythema nodosum leprosum (type-II reaction) usually occurs in all cases of lepromatous leprosy. This lesion clinically presents with crops of painful, erythematous, and violaceous nodules, mainly involving the extremities. In type-II reaction, neutrophils will be seen in abundant to form a dermal abscess or may be scant sometimes [2].

As the lepra reactions are immune modulated, the anti-inflammatory agents are mainstay of the treatment. Most of the patients require steroids to control these reactions. It was noted from previous studies that among many patients, the lepra reactions were refractory to steroids. The cause for the failure of steroids among these patients was also inconclusive.

In the era of leprosy elimination, there is an increasing incidence of leprosy and lepra reaction when compared to previous decline, hence analysis of haematological parameters in correlation with histopathological findings of lepra reaction may be helpful for early diagnosis and prevention of complications of lepra reaction. Aim

of present study was to find the socio-demographic characteristic features of leprosy patient based on age, gender and family history and to study about the clinical features most commonly seen along with changes occurring in haematological parameters among the patient with leprosy reaction. To compare the histopathological variations among the patients of type-I and type-II leprosy reactions.

MATERIALS AND METHODS

This study was proposed and conducted in the Chengalpattu Medical College Hospital and Central Leprosy Teaching and Research Institute (CLTRI), Chengalpattu, Tamil Nadu, India. A retrospective study was done and approval of the ethical committee was obtained in Chengalpattu Medical College and Hospital on 09.06.2017 and this study was conducted between the periods, from June 9th to September 9th 2017 for three months duration. This study was preceded after obtaining proper consent from the patient.

A total number of 60 cases presenting with features of leprosy reaction examined, in that 30 patients were selected for this study based on a set of inclusion and exclusion criteria.

Those patients who reported to CLTRI and diagnosed as suffering from leprosy reactions with following clinical presentation such as erythema of skin and painful erythematous nodules were included in present study and those patients without proper differentiation of types of leprosy reactions and already on treatment for reaction were excluded.

Sample size was selected using cross-section study and the following simple formula was used for calculating the adequate sample size $n = Z^2 P(1-P)/d^2$ Where, n is the sample size, Z is statistic corresponding to level of confidence, P is expected prevalence (that can be obtained from same studies or a pilot study conducted by the researchers) and d is precision (corresponding to effect size).

Data Collection

CLTRI, Chengalpattu is the apex leprosy institute of Govt. of India. Leprosy patients from all over India are being referred to this institute for expert consultation and management. The patients reported to CLTRI diagnosed as leprosy reactions were the potential study participants.

Written informed consent was obtained from each participant before enrolment. Only the consented participants were selected for the study. The socio-epidemiological information including history of symptoms and treatment was obtained. They were subjected to standard management protocol according to the guidelines of National Leprosy Eradication Programme.

Using automated analyser, SYSMEX (TX 121), the complete analysis of blood cells was done, in that WBC profile in particular was studied in all the patients.

Biopsy was carried out at the CLTRI, Thirumani, Chengalpattu and the received specimens were immediately fixed in 10% formalin and processed routinely. Four micron sections were taken from both the tissues and stained with haematoxylin and eosin and findings were recorded. The histopathological pattern was studied and compared.

STATISTICAL ANALYSIS

The data were entered into spread sheet programme and further analysed by using SPSS statistical software version 16. T-test and chi-square test were used for quantitative and qualitative analysis respectively.

RESULTS

The results are tabulated as

- I. Socio-demographic characteristics of study subjects.
- II. Clinical characteristics of study subjects according to type of leprosy reaction.

III. Histopathological variations among patients of type-I and type-II leprosy reaction.

I. Socio-demographic characteristics of study subjects

Socio-demographic variables used in the study were age, sex and family history of leprosy, etc. [Table/Fig-1] shows that 47% of patient has type I leprosy reaction and 53% of patient has type-II leprosy reaction.

| Type of leprosy reaction | Male (%) | Female (%) | Total (%) |
|--------------------------|------------|------------|-----------|
| Type-I | 10 (71%) | 4 (29%) | 14 (47%) |
| Type-II | 10 (62.5%) | 6 (37.5%) | 16 (53%) |

[Table/Fig-1]: Distribution of study subjects according to type of leprosy reactions.

[Table/Fig-2] shows both gender of patient below 30 years have equal incidence of getting leprosy reactions, but above 30 years, male gender have high incidence of getting leprosy.

| Age | Male | Female | Total |
|-------|-------------|-------------|-------------|
| <30 | 5 (50%) | 5 (50%) | 10 (33.33%) |
| >30 | 15 (75%) | 5 (25%) | 20 (66.67%) |
| Total | 20 (66.67%) | 10 (33.33%) | 30 (100%) |

[Table/Fig-2]: Distribution of study participants according to age and gender.

[Table/Fig-3] indicates, majority of patient (99.67%) had no family history of leprosy but only one female presented with positive family history, as her mother was affected with leprosy.

| Family h/o leprosy | Male | Female | Total |
|--------------------|-------------|------------|-------------|
| Yes | 0 (0%) | 1 (100%) | 1 (3.33%) |
| No | 20 (63.33%) | 9 (36.67%) | 29 (96.67%) |

[Table/Fig-3]: Distribution of study participants with family history of leprosy.

II. Clinical presentation of study subjects according to type of leprosy reaction:

[Table/Fig-4] shows hypopigmentation was seen in majority of patient with type-I reaction while larger part of patient with Type-II reaction are presented with skin nodule [Table/Fig-5,6].

| Characteristic of skin patch | Type-I (%) | Type-II (%) | Total (%) |
|------------------------------|------------|-------------|------------|
| Hypopigmentation | 6 (60) | 4 (40) | 10 (33.33) |
| Anaesthesia | 5 (55.56) | 4 (44.44) | 9 (30) |
| Erythema | 3 (37.5) | 5 (62.5) | 8 (26.67) |
| Nodule | 3 (18.75) | 13 (81.25) | 16 (53.33) |

[Table/Fig-4]: Presenting complaints of patients according to type of leprosy reaction.



[Table/Fig-5]: Shows type 1 reaction with markedly erythematous papules.

[Table/Fig-7] shows ulnar nerve was highly involved in both type of leprosy reactions while greater auricular nerve was least involved.



[Table/Fig-6]: Shows type 2 reaction with erythema nodosum.

| Nerve Involvement | Type-I (%) | Type-II (%) | Total (%) |
|----------------------|------------|-------------|------------|
| Greater auricular | 0 (0) | 1 (100) | 1 (3.33) |
| Ulnar | 7 (53.85) | 6 (46.15) | 13 (43.33) |
| Radial cutaneous | 4 (33.33) | 2 (33.33) | 6 (20) |
| Lateral Popliteal | 3 (33.33) | 6 (66.67) | 9 (30) |
| Sural | 1 (33.33) | 2 (66.67) | 3 (10) |
| Posterior tibial | 6 (50) | 6 (50) | 12 (40) |
| Superficial peroneal | 2 (50) | 2 (50) | 4 (13.33) |
| Median nerve | 3 (60) | 2 (40) | 5 (6.66) |

[Table/Fig-7]: Involvement of nerves according to type of lepra reaction.

[Table/Fig-8] concludes that even person with normal BMI index was also prone of leprosy and its reaction.

| BMI | Male (%) | Female (%) | Total (%) | Remarks |
|-------------|-----------|------------|-------------|--------------|
| <18.5 | 1 (25%) | 3 (75%) | 4 (13.33%) | Under weight |
| 18.5 to <25 | 12 (75%) | 4 (25%) | 16 (53.33%) | Normal |
| 25 to <30 | 8 (88.8%) | 1 (11.1%) | 9 (30%) | Overweight |
| ≥30 | 0 (0%) | 1 (100%) | 1 (3.33%) | Obese |

[Table/Fig-8]: Anthropometric characteristics of study subjects.
BMI=Weight (Kg)÷Height (M²)

[Table/Fig-9] shows that oedema was a significant clinical feature in leprosy that too in male patient, followed by generalised oedema and anemia in equal proposition in both gender.

| General clinical examination features | Male (%) | Female (%) | Total (%) |
|---------------------------------------|------------|------------|------------|
| Anaemia | 1 (50.00) | 1 (50.00) | 2 (8.00) |
| Oedema | 11 (73.33) | 4 (26.66) | 15 (60.00) |
| Lymphadenopathy | 4 (50.00) | 4 (50.00) | 8 (32.00) |

[Table/Fig-9]: Clinical characteristics of study subjects based on general physical examination.

It was observed that, 85.71% of patient was normal within which 71% were males and 29% were females. A 14.28% of patient had leukocytosis and 7.14% of patient had leukopenia [Table/Fig-10].

| WBC profile | Male (%) | Female (%) | Total (%) |
|--------------|----------|------------|-------------|
| Leucopenia | 1 (50%) | 1 (50%) | 2 (7.14%) |
| Normal | 17 (71%) | 7 (29%) | 24 (85.71%) |
| Leucocytosis | 2 (50%) | 2 (50%) | 4 (14.28%) |

[Table/Fig-10]: Distribution of study subjects based of leukocytosis with the help of haematological profile.

III. Histopathological features of lepra reactions among study participants:

[Table/Fig-11] shows epidermal atrophy and spongiosis was more commonly associated in both type of reactions.

| Histopathology features | Presence/Absence | Type-I (%) | Type-II (%) | Total (%) |
|---------------------------|------------------|------------|-------------|------------|
| Epidermal features | | | | |
| Atrophy | Yes | 14 (100) | 15 (93.75) | 29 (96.67) |
| | No | 0 | 1 (6.25) | 1 (3.33) |
| Spongiosis | Yes | 11 (78.50) | 12 (75) | 23 (76.67) |
| | No | 3 (21.50) | 4 (25) | 7 (23.33) |
| Exocytosis | Yes | 3 (21.50) | 0 (0) | 3 (10) |
| | No | 11 (78.50) | 16 (100) | 27 (90) |
| Parakeratosis | Yes | 2 (14.30) | 0 (0) | 2 (6.67) |
| | No | 12 (85.70) | 16 (100) | 28 (93.33) |

| | | | | |
|-----------------------------------|-----|----------|---------|------------|
| Sub Epidermal features | | | | |
| Erosion of epidermis by granuloma | Yes | 0 (0) | 4 (25) | 4 (13.33) |
| | No | 14 (100) | 12 (75) | 26 (86.67) |

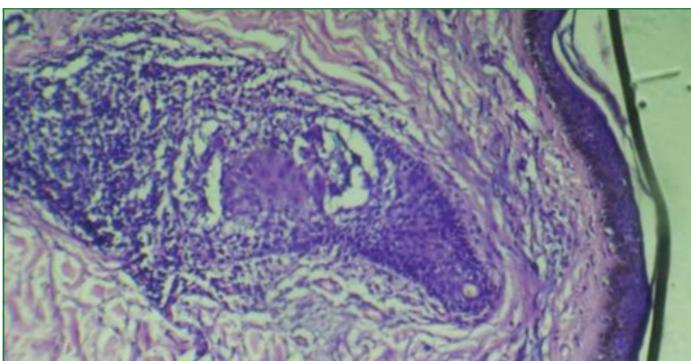
[Table/Fig-11]: Epidermal histopathology of the skin lesions among lepra reaction patients.

[Table/Fig-12] shows association between perigranuloma lymphocytes, intragranuloma lymphocytes and giant cells which was statistically significant with type-I reaction while association between neutrophilic infiltration granuloma and fibrin in granuloma with type II reaction was statistically significant [Table/Fig-13-18].

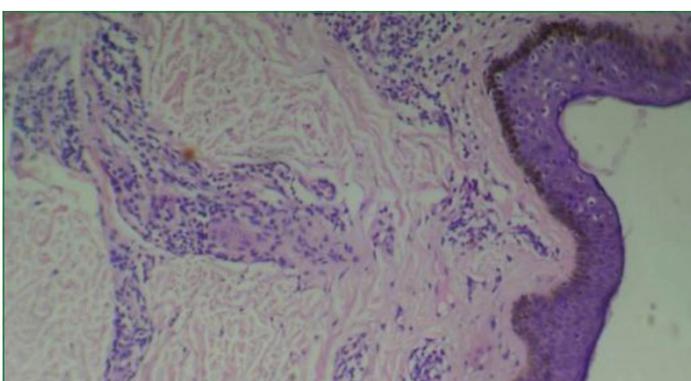
| Histopathological features | Type-I (%) | Type-II (%) | Total (%) | Statistical significance |
|---|------------|-------------|------------|---------------------------|
| Oedema in papillary dermis | | | | |
| Yes | 13 (93) | 16 (100) | 29 (96.67) | TOS not required |
| No | 1 (7) | 0 (0) | 1 (3.33) | |
| Neutrophilic infiltration of granuloma | | | | |
| Yes | 2 (14.3) | 11 (68.75) | 13 (43.33) | Chi-Sq=9.02 p=0.002 |
| No | 12 (85.7) | 5 (31.25) | 17 (56.67) | |
| Morphology | | | | |
| Oedema | 7 (50) | 6 (37.5) | 13 (43.33) | Chi-Sq=0.47 p=0.49 |
| No Oedema | 7 (50) | 10 (62.5) | 17 (56.67) | |
| Epitheloid cell maturity | | | | |
| Yes | 3 (21.4) | 0 (0) | 3 (10) | TOS not required |
| No | 11 (78.6) | 16 (100) | 27 (90) | |
| Perigranuloma lymphocytes | | | | |
| Yes | 12 (85.7) | 1 (6.25) | 13 (43.33) | Chi-Sq=19.20 p=0.00001 |
| No | 2 (14.3) | 15 (93.75) | 17 (56.67) | |
| Perigranuloma Plasma cells | | | | |
| Yes | 0 (0) | 1 (6.25) | 1 (3.33) | TOS not required |
| No | 14 (100) | 15 (93.75) | 29 (96.67) | |
| Intragranuloma plasma cells | | | | |
| Yes | 0 (0) | 0 (0) | 0 (0) | TOS not required |
| No | 14 (100) | 16 (100) | 30 (100) | |
| Intra-granuloma lymphocytes | | | | |
| Yes | 10 (71.4) | 1 (6.25) | 11 (36.67) | Chi-Sq=13.66 p=0.0002 |
| No | 4 (28.6) | 15 (93.75) | 19 (63.33) | |
| Giant cells | | | | |
| Present | 10 (71.4) | 1 (6.25) | 11 (36.67) | Chi-Sq=13.66 p=0.0002 |
| Absent | 4 (28.6) | 15 (93.75) | 19 (63.33) | |
| Histiocytes | | | | |
| Present | 1 (7.14) | 1 (6.25) | 2 (6.67) | Chi-Sq=0.0096 p=0.9 |
| Absent | 13 (92.86) | 15 (93.75) | 28 (93.33) | |
| Fibrin in blood vessel wall | | | | |
| Present | 0 (0) | 12 (75) | 12 (40) | TOS not required |
| Absent | 14 (100) | 4 (25) | 18 (60) | |

| Fibrin in granuloma | | | | |
|--------------------------|------------|-----------|------------|------------------------|
| Present | 1 (7.14) | 10 (62.5) | 11 (36.67) | Chi-Sq=9.85 p=0.001 |
| Absent | 13 (92.86) | 6 (37.5) | 19 (63.33) | |
| Intra-epidermal pustules | | | | |
| Present | 4 (26) | 10 (62.5) | 14 (46.67) | Chi-Sq=3.45 p=0.06 |
| Absent | 10 (74) | 6 (37.5) | 16 (53.33) | |

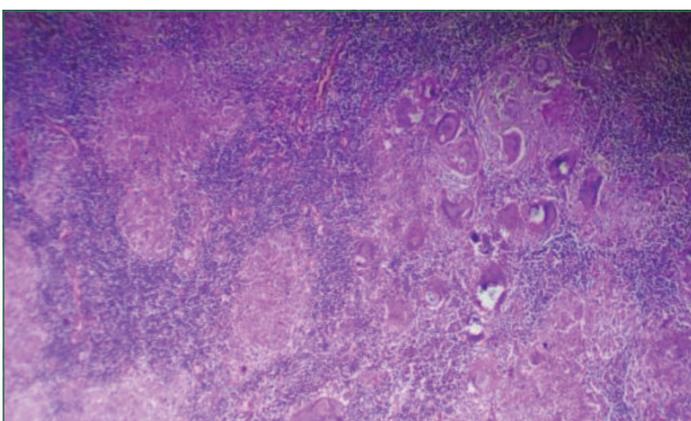
[Table/Fig-12]: Dermal histopathology of the skin lesions of study subjects.



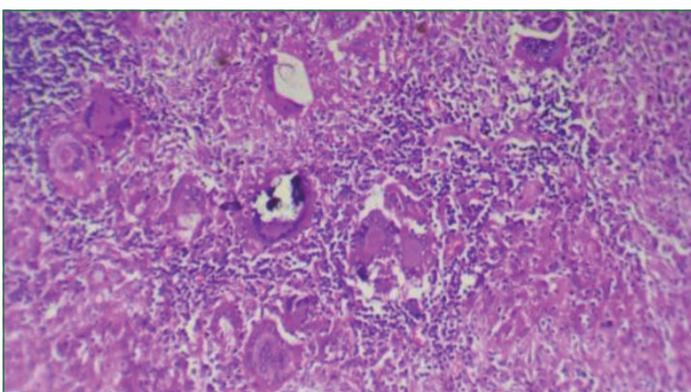
[Table/Fig-13]: Perigranuloma lymphocytic infiltrate in type 1 reaction (H&E 40X).



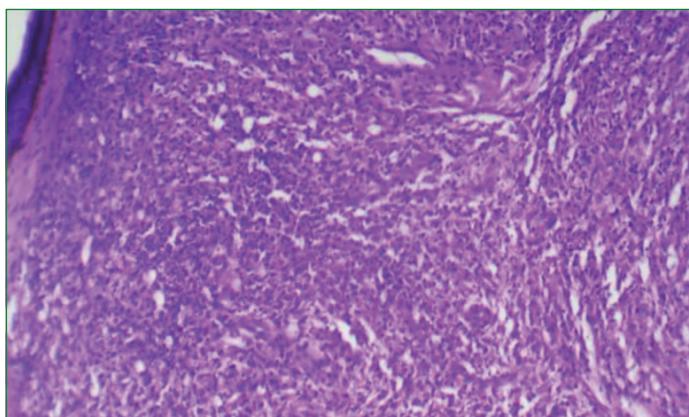
[Table/Fig-14]: Intragranuloma lymphocytic infiltrate in type 1 reaction (H&E 40X).



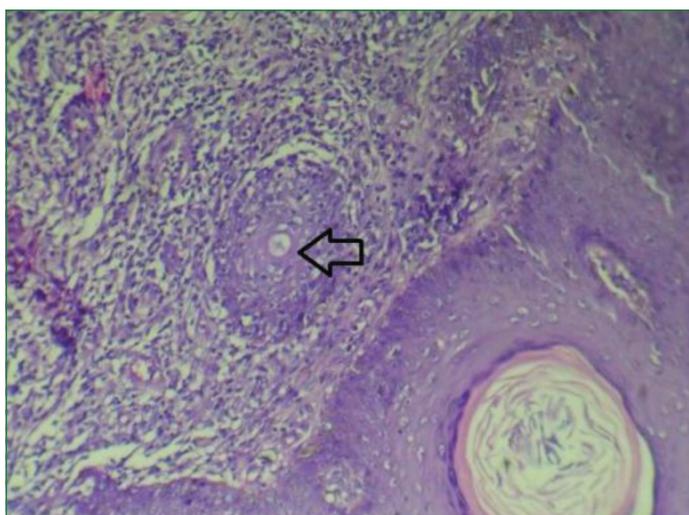
[Table/Fig-15]: Multinucleated giant cells in type 1 reaction (H&E 10X).



[Table/Fig-16]: Multinucleated giant cells in type 1 reaction (H&E 40X).



[Table/Fig-17]: Neutrophilic infiltration with in granuloma in type 2 reaction (H&E 40X).



[Table/Fig-18]: Fibrin in granuloma in type 2 reaction (H&E 40X).

DISCUSSION

The study was aimed at analysing the histopathological, epidemiological and clinical data among type I and type-II leprosy reactions. Persons with low socio-economic status where mostly affected with leprosy. It is also seen that they are isolated from family. Regarding the gender distribution of cases, men (66.67%) outnumbered women (33.33%) [Table/Fig-2], which is very well correlated with previous study conducted by Adhe V et al., [3] who found 65.62% were males and 34.37% are females. All the study subjects were multi-bacillary cases treated with Multidrug therapy with variable duration of time.

Often patients were presented with lesions involving skin patch such as hypo-pigmentation (that was more common in type-I reaction), loss of sensation over the particular area, erythema and nodules (that was more common in type-II reaction) [Table/Fig-4]. In current scenario, all the leprosy reaction patients were treated with prednisolone whereas thalidomide used in previous days were stopped due to its adverse effects.

On anthropometric analysis, more than half of the patients were normal while very few were obese, overweight and underweight category [Table/Fig-8]. It is observed that few type-II leprosy reaction patients are clinically presented with anaemia, oedema of feet and lymphadenopathy whereas in type-I leprosy reaction patients, mostly they were presented with oedema and anaemia [Table/Fig-9].

In reference with WBC count, 85.71% were normal, leukocytosis is next to that (14.28%) and leucopenia was least (7.14%) which proves that leprosy reactions are based on immune modulated mechanism [Table/Fig-10].

The present study shows epidermal atrophy and spongiosis are more commonly associated in both type of reactions [Table/Fig-11], Which was well correlated by the previous study done by Lazaro-Medina A et al., and Lucas S et al., [4,5].

Lockwood DN et al., in a prospective study compared skin lesions with type-I reaction with non-reactional controls, in that they noted increase in giant cell size and giant cell numbers in type-I reaction which was very well correlated in the current study [6].

In this study, we found perigranuloma lymphocytes (85.7%) and intragranuloma lymphocytes (71.4%) were significantly higher in the findings [Table/Fig-12] in type-I reaction but study done by Adhe V et al., shows papillary dermal oedema (86%) followed by pyknosis of lymphocytes (77%) were the common dermal findings, which contradicts with this study [3].

Our study shows that neutrophilic infiltration of granuloma (68.75%) in dermis is significantly higher in type-II reaction [Table/Fig-12] and this observation correlates well with that of Adhe V et al., who found 100% positivity of neutrophils within the granuloma [3].

Among the vascular changes in Type-II reaction, vasculitis was more predominantly seen in the study conducted by Palit A et al., and Job CK et al., but in the current study we noted following vascular changes such as fibrin in blood vessel wall alone which was about 75% [7,8].

LIMITATION

The major limitation of this study was lack of ability to identify histopathological variation of patient those already on treatment for reaction. Those patients without proper differentiation of types of lepra reactions clinically were also brought under limitation of study.

CONCLUSION

The study concludes that among leprosy patient; young age groups, males, even patient with normal BMI are more prone for both type of lepra reaction. Arriving at clinical findings, most of the patients in both type-I and type-II reactions are presented with pedal oedema and generalised lymphadenopathy.

Histopathological findings reveals atrophy and spongiosis were most common epidermal findings in both types of reactions. Histopathological findings of dermis shows that lymphocytes

surrounding the granuloma, intra-granuloma lymphocytes and giant cells are significantly higher in type-I lepra reaction, while neutrophilic infiltration in granuloma and fibrin in granuloma was noted significantly higher in type-II reaction.

In the current scenario of leprosy elimination, lepra reaction management is a major burden for physicians, presently there is no uniformly acceptable laboratory investigation for lepra reaction. Therefore, we conclude that present study of histopathological with epidemiological evidences among type-I and type-II lepra reactions may be helpful for early diagnosis and prevention of consequences of lepra reactions.

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PARTICULARS OF CONTRIBUTORS:

1. Associate Professor, Department of Pathology, Omendurar Medical College, Chennai, Tamil Nadu, India.
2. Assistant Professor, Department of Pathology, Chengalpattu Medical College, Chengalpattu, Tamil Nadu, India.
3. Professor, Department of Pathology, Chengalpattu Medical College, Chengalpattu, Tamil Nadu, India.
4. Student, Department of Pathology, Chengalpattu Medical College, Chengalpattu, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. V Palaniappan,
Department of Pathology, Chengalpattu Medical College, Chengalpattu-603001, Tamil Nadu, India.
E-mail: palani829@gmail.com

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