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Pathology

A HISTOPATHOLOGICAL STUDY OF LEPROSY ALONG WITH CLINICAL CORRELATION.

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ABSTRACT **Background:** Leprosy or Hansen's disease is a chronic infectious disease that mainly affects skin and peripheral nerves. Histopathology and demonstration of lepra bacilli is an essential tool to supplement clinical examination and diagnosis for correct classification and therefore treatment of patients.

Aim: To study histopathology of leprosy cases and identify histological types in patients in a tertiary care centre, Asram hospital in Eluru.

Materials and Methods: 18 skin biopsies diagnosed as leprosy over a period of two years from January 2018 to December 2019 were studied. Haematoxylin-eosin and Fite-Faraco staining for demonstrating lepra bacilli were done.

Results: Male to female ratio of patients was 4.5:1. Maximum number of cases was seen in the 3rd and fourth decades of life. The commonest histological type was borderline tuberculoid (5 cases, 28%) and indeterminate type, lepromatous type (3 cases, 16%); followed by tuberculoid leprosy and erythema nodosum leprosum (2 cases, 11%), the least common cases were of lepromatous leprosy to borderline tuberculoid leprosy (1cases, 6%). The most common site was upper limb (26%). All 3/18(24%) patients with affected nerves showed ulnar and auricular nerve involvement. Hypopigmented, anaesthetic plaque was the commonest clinical feature followed by erythematous lesions. All cases of borderline tuberculoid, borderline lepromatous, lepromatous, midboderline and indeterminate showed acid-fast bacilli on Fite stain. Tuberculoid cases showed well-formed granulomas, borderline tuberculoid type showed additional feature of giant cells and lepromatous types showed grenz zone and no granulomas.

Conclusion: Histopathological examination is the gold standard for accurate diagnosis and typing of leprosy. It should be done in all leprosy cases presenting to the clinician.

KEYWORDS : leprosy, histomorphology, borderline tuberculoid, lepromatous, granuloma, Skin, biopsy

INTRODUCTION

Leprosy is one of the most ancient diseases known to mankind. It is a chronic, debilitating, granulomatous disease caused by Mycobacterium leprae. The bacteria was discovered by Hansen in 1837. Interestingly, the organism cannot be cultured. [1] It is an important public health menace, being prevalent throughout many areas in India and still carrying a social stigma for the patients affected. Leprosy mainly affects the skin, causing lesions and anaesthesia, along with enlarged and thickened peripheral nerves. [2] It has different histopathological forms depending on the immunity of the patient. [3] The Ridley-Jopling classification is the most widely used and divides the disease into tuberculoid (TT), borderline tuberculoid (BT), mid-borderline (BB), borderline lepromatous (BL) and lepromatous leprosy (LL), based on clinical, immunological and histomorphological factors. [4] Indeterminate forms include types that do not fit into any of the five categories. Histoid leprosy is an uncommon type of LL that shows nodules or plaques over apparently normal skin. [5] This article aims to study the various histological types of leprosy in a tertiary care hospital over a period of two years.

MATERIALS AND METHODS

This was a retrospective study carried out over a period of two years from January 2018 to December 2019 at a tertiary care hospital in Eluru. Those cases diagnosed as leprosy on histopathological examination from the skin biopsies sent from the Department of Dermatology were included. Routine haematoxylin-eosin stain and Fite-Faraco stains were used for diagnosis.

RESULTS

The study shows a marked male predominance in cases diagnosed as leprosy (11 cases, 82%) as compared to females (7 cases, 18%). The male to female ratio was 4.5:1. Maximum number of cases was seen in the age group of 30 -50years, majority in third and fourth decades of life. Maximum individual number of female and male patients were between the ages of 30-50 years (table 3). Age group varied from 1st decade to 7th decade. The youngest patient was of 10 years old while the oldest was 70 years old.

Table 1: Distribution of clinically 18 diagnosed cases of leprosy

S.NO	CLINICAL DIAGNOSIS	NUMBER OF CASES	PERCENTAGE
1.	Erythema nodosum leprosum	6 cases	34%
2.	Borderline tuberculoid hansens	3 cases	17%
3.	Mid boderline	1 case	6%
4.	Borderline lepromatous leprosy	2 cases	11%
5.	Borderline Hansen	1 case	6%
6.	Hansen's disease	4 cases	22%
7.	Indeterminate leprosy	1 case	6%
8.	Actinic keratosis	1 case	6%

Table 2: Distribution of 18 histopathologically diagnosed cases of leprosy

S.NO	Histopathological diagnosis	Number of cases	percentage
1.	Indeterminate leprosy	5 cases	28%
2.	Borderline tuberculoid	5 cases	28%
3.	Lepromatous leprosy	3 cases	16%
4.	Erythema nodosum leprosum	2cases	11%
5.	Tuberculoid leprosy	2cases	11%
6.	Lepromatous leprosy with tuberculoid leprosy	1 case	6%

Histopathologically out of the 18 cases of leprosy , 5 cases (28%) were

of Borderline Tuberculoid and 5 cases of indeterminate leprosy , followed by 3 cases (16%) of Lepromatous Leprosy, 2 cases(12%) of Tuberculoid leprosy and Erythema nodosum leprosum, only 1 case of Lepromatous leprosy to borderline Tuberculoid leprosy (6%)

Table 3: Age wise distribution of leprosy cases

Age	TT	BT	BB	BL	LL	INDT	LL TOBT	TYPE 1	TYPE2	ENL	TOTAL PERCENTAGE
0-10 YRS						10YR					6%
11-20YR						18YR 20 YR					11%
21-3OYR	22YR	29YR			23YR						17%
31-40YR	40YR	37YR			38YR 35YR					35YR	28%
41-50YR		45YR 50YR				44YR 45YR		45 YR 50YR,70YR		45YR	28%
51-60YR											
61-70YR		62 YR									6%
>70YR											

The most common sites involved were upper limbs and the lower limbs (50%), followed by face (28%), the back (22%), trunk (17%), buttocks and waist (12%). Out of all 18 cases, 78%(14 cases) were paucibacillary whereas 22%(4cases) were multibacillary. Nerve involvement was seen in 3 out of 18 patients (24% cases). They showed ulnar nerve, auricular nerve and posterior tibial nerve involvement. No case of pure neuritic leprosy was observed in this study. The most common presentation on clinical examination was the presence of single or multiple well-defined hypopigmented patches (56%) with loss of sensations. The other types of skin lesions found were erythematous lesions (28%), hypopigmented nodules, xerotic patches (12%), macules (6%) and papules (6%). Fite-Faraco staining to identify acid-fast bacilli (AFB) was done in all 18 cases. It was positive in 5 (28%) of cases. No bacilli were noted in all cases of TT leprosy, whereas all cases of LL, BL, BT and indeterminate leprosy types showed presence of acid-fast bacilli.

Table 4: Percentage of various type of skin lesions on clinical examination.

Type of skin lesion	percentage
Hypopigmented patches	56%
Erythematous lesion	28%
Xerotic patches	12%
macules	6%
papules	6%
nodules	6%

On histopathological examination, epidermal and dermal changes were noted in the skin biopsies. Epidermal changes noted were presence or absence of atrophy, hyperplasia, hyperkeratosis, ulceration, orthokeratosis, spongiosis and acanthosis. Dermal changes noted were presence or absence of Grenz zone, perineural and perivascular inflammatory infiltrate, well formed or ill-formed epithelioid cell granulomas, Langhans giant cells and foamy histiocytes. 9 (50%) cases showed epidermal atrophy, and 9 cases (50%) showed other epidermal changes like orthokeratosis /hyperkeratosis/spongiosis. 7(39%) cases showed presence of granulomas in the dermis. Out of 6 cases clinically diagnosed Erythema Nodosum Leprosum two cases showed histopathological agreement. One case of borderline lepromatous and borderline tuberculoid correlated with histopathological diagnosis. In histopathological diagnosis one case of indeterminate turned out to be lepromatous leprosy, two cases of Boderline tuberculoid and one case of borderline lepromatous were diagnosed as indeterminate leprosy.

TABLE 5: Histopathology of dermis in various types of leprosy

Histological feature	Type							
	TT	BT	BB	BL	LL	IL	ENL	Type lepra reac
Epithelioid granulomas	1	6		1				
Giant cells (langhans /foreign body type)	1	6						
Lymphocytes around (Arrector pilorum Appendages ,Neurovascular bundle)	1	6		1	2	4		1
Macrophages (periadenexal , perineural , arrector pilli muscle)		6		1	2	3	2	1
Grenz zone				1				
Fibrinoid necrosis		1		1				

Table 6: Clinical versus histopathological diagnosis

Clinical diagnosis	Histopathological diagnosis
Erythema nodosum leprosum/lepra reaction	Borderline Tuberculoid ,Type I reversal reaction
Erythema nodosum leprosum	Erythema nodosum leprosum
Hansen's disease	Tuberculoid leprosy
Erythema nodosum leprosum	Erythema nodosum leprosum
Borderline tuberculoid Hansens	Indeterminate leprosy
Midboderline/borderline lepromatous leprosy	Borderline lepromatous leprosy
Erythema nodosum leprosum	Borderline tuberculoid leprosy with type-I Reaction
Borderline Hansen's	Indeterminate leprosy
Hansen's	Boderline tuberculoid leprosy
Hansen's	Lepromatous leprosy
Borderline tuberculoid	Indeterminate leprosy
Hansen's	Borderline tuberculoid
Erythema nodosum leprosum	Borderline tuberculoid
Borderline lepromatous Hansen's	Indeterminate leprosy
Borderline tuberculoid /actinic keratosis	Borderline tuberculoid
Erythema nodosum leprosum/indeterminate leprosy	Lepromatous leprosy
Hansen's disease	Indeterminate leprosy
Hansen's disease	Borderline tuberculoid leprosy

DISCUSSION

A total of two hundred skin biopsies were received in our department during Jan 2018 to Dec 2019.Out of these, 18 cases were diagnosed as Leprosy (9%). This was a retrospective study of 18 skin biopsies diagnosed as leprosy on histopathological examination in a tertiary care hospital, Asram medical college, Eluru. Our study showed male predominance with 1.57:1 being the male to female ratio. Similar findings have been observed in other studies as well [1-4,6-11] Vasaikar et al have noted a slightly higher number of females in their study, with male to female ratio being 0.8:1. [12] Mathur et al[11] in 1978 , showed male preponderance of cases (3:1) in his study . The male majority has been attributed to more chance of contact in males due to occupation, social inhibition and occupational factors regarding less reporting of cases in females in India. [1,8] The age of the patients in this study ranged between 10 and 70 years. Most of the cases occurred in the third and fourth decade, similar to other studies as well. [1, 2, 9-12] Kadam et al [7] found most of their cases to be between the ages of 35-55 years. In the study of Rao P.S.S. et al. [10], adults were found to be affected twice than children. Mathur et al[11] in 1978 found that majority of cases were in the age group of 21- 50 years. Incidence in younger age group could be due to the endemic nature of leprosy. [3] This emphasise that although Leprosy is borne at an early age, but because of relatively long incubation period the symptomatic cases appear at later age. As many of the lesions were present over exposed areas, this could also have led to noticing and reporting hence the concentration of cases in younger age group in this study. Hypopigmented plaque with loss of sensation was the most common clinical feature observed (56%) which is comparable to other studies [3, 9-11] followed by erythematous lesions (28%). A hypopigmented patch over skin with loss of temperature sense and numbness is a characteristic feature seen in leprosy. Nerve involvement was seen with the ulnar nerve being typically involved, as was also seen in other studies. [1,7] One patient presented with claw hand deformity in our study, who was diagnosed on microscopy to have indeterminate leprosy. No trophic ulcers were seen in our study. World

Health Organization (WHO) in 1994 advocated the clinical categorization of leprosy cases into paucibacillary and multibacillary based on the number of lesions counted in a patient. [13] More than 5 lesions counted is said to be multibacillary; a count of less than or equal to 5 lesions is typed as paucibacillary. According to this, 4 cases (22%) cases in our study were paucibacillary and 14 (78%) cases multibacillary. However, this method is unreliable as there may be miscounting and misreporting of cases. Thereby, histopathology is a crucial method of diagnosis. The biopsies were classified according to the Ridley-Jopling classification on histopathological examination. Maximum numbers of cases in our study were of Boderline Tuberculoid and indeterminate type; this is comparable to other studies.[1,4,7-12,14,15] Thapa et al [16] found the most common types to be both TT and BT (12 cases each) in their study. Khamankar et al [3] found LL to be the commonest histological type followed by BL. Pokhrel et al [17] found BT to be the least common (1 case) and TT to be the most common (14 cases) type. LL was the second commonest type in our study. Many patients exhibit a continuous shift over the immunological spectrum with progression and treatment of the disease. [1] This could be why a majority of patients were found to be of borderline type. With treatment, they move towards the tuberculoid pole and without it they tend to shift towards lepromatous pole. [1] Patients with good immune status usually are tuberculoid types and those with poor immunity usually tend to show lepromatous type lesions.

BT type (Figure 1, 1a) showed Granulomas and Langhans giant cells, with infiltration of lymphocytes around sweat gland and erector pili muscles, neurovascular bundles. AFB was demonstrated in two cases of Borderline Tuberculoid cases. TT type showed well formed epithelioid cell granulomas with infiltrate of lymphocytes around neurovascular bundles and no AFB. [18] In our study, 2 out of 5 cases of BT were positive for Fite-Faraco. None of the TT cases showed any lepra bacilli. 55% of BT cases showed unremarkable epidermis and the remaining showed areas of atrophy and hypertrophy. In a study done by Ravindranath S.[6] 55.55% of BT cases showed variable areas of epidermal atrophy and hypertrophy

Tuberculoid leprosy (TT): There were two cases (11%) of TT in our study which correlates well with study done by Sehgal VN et al. [7] The age involvement varied from 20 years to 40 years; with a peak incidence between 2nd - 4th decade. Male to female ratio was found to be 3:1, this finding correlates well with findings of Rao P.S.S. [10] The epidermis was unremarkable in both cases and showed stratification of epidermis with hyperkeratosis. The dermis showed well formed epithelioid granulomas, langhans giant cells located both in superficial and deeper dermis. Periadnexal dense infiltration of lymphocytes seen in both cases. Fite Faraco stain was negative in both the cases.

BL type (Figure 3A) showed poorly formed granulomas with lymphoid infiltrate around periadnexal and perivascular structures. A few Foamy macrophages, few epithelioid cells and globi (numerous bacilli clumped in macrophages) were not seen. LL type in our study showed the presence of a characteristic grenz zone (Figure 3B) which is a clear space of normal collagen without any cellular infiltrate just beneath the flattened epidermis. There was diffuse lymphoplasmacytic infiltrate and Virchow cells or globi extending into deeper dermis and no granulomas noticed. [18] All LL cases showed AFB positivity (Figure 3C).

IL type represents those cases that have histopathological and clinical features of leprosy but do not fit into the Ridley Jopling classification. This is an early, transitory lesion seen in patients with variable immunological status. [15] It may be difficult to elicit anaesthesia on facial patches, especially in children. These cases showed lymphocytic infiltration of the dermal adnexae, erector pili muscles, and perivascularly and no evidence of granulomas (Figure 3). In our study, a patient who presented with claw hand was diagnosed with IL. Only 1 out of 4 cases showed AFB positivity.

Histoid leprosy, coined by Wade in 1963, is an uncommon type of lepromatous leprosy showing spindle cells which are fusiform histiocytes arranged in storiform pattern that contain the AFB. There is no globus formation and a grenz zone is often seen. Patients on discontinuous dapsone therapy often show this type. [5] These often show high number of AFB, almost resembling sheaves of wheat. [18] We did not have any case of Histoid leprosy in our study. Epidermal atrophy was seen; this has been explained by dermal expansion due to underlying Delayed hypersensitivity reactions in type 1 and type 2 leprosy. Type 2 reactions (ENL) show dermal abscess formation, vasculitis and edema of dermis, endothelial cell proliferation along with neutrophils, foamy macrophages and numerous bacilli extending into subcutaneous tissue (figure 2). [18] Similar features were seen in both the cases of type 1 and type 2 lepra reactions in our study. These are associated with immune complex deposition and may be seen in untreated cases or LL patients on treatment. [1]

CONCLUSION Histopathological examination of skin lesions is a crucial method and the gold standard for accurate diagnosis and typing of leprosy. [9] Combined with Fite staining, it is very important in cases where insufficient clinical history is available, in paediatric cases and in early/ borderline/ indeterminate/histoid cases which may not have characteristic clinical signs and show overlapping. It is also helpful in cases where patients may not have anaesthetic patches, especially on the face, and those with vague erythematous nodules or papules where leprosy is suspected. Biopsy is a minimally invasive and easy method as well. Thus, histopathology and demonstration of acid fast lepra bacilli is recommended in all cases of leprosy for a good clinicopathological correlation and diagnostic accuracy, which would ultimately help in the prognosis and line of treatment of the patient.

ABBREVIATIONS BT- Boderline tuberculoid, TT- Tuberculoid leprosy, IL-Indeterminate leprosy, LL-Lepromatous leprosy, BL-Boderline lepromatous, BB-Midboderline, ENL- Erythema nodosum leprosum.

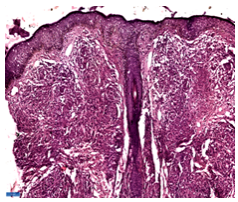

Fig 1: HPE Boderline tuberculoid leprosyH&E:Epitheliod granul omas,necrosis,langhan giant cells, lymphoid infiltrate.

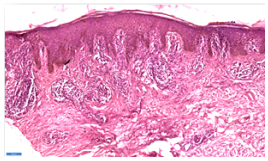

Fig 1 a: HPE Boderline tuberculoid leprosy granulomas perivascu arly around dermal adnexae

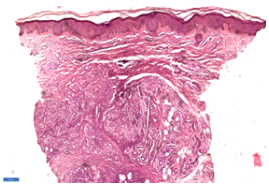

Fig 2: HPE Erythema nodosum leprosum H&E X10 foamy histioc ytes invading sweat glands

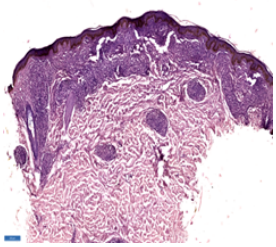

Fig 3: HPE Indeterminate leprosy H&E X10Foamy macrophages laden with lepra bacilli around dermal adnexae& erector pillae muscle, focal lymphocytic collections

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