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TO ASSESS THE BURDEN OF AND TRENDS OF HANSENS DISEASE -MAINLY BY ASSESSING THE HISTOMORPHOLOGICAL SPECTRUM AND CLINICOPATHOLOGICAL CORRELATION, AT A TERTIARY CARE HOSPITAL IN TELANGANA STATE, INDIA

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ABSTRACT

Introduction: Context: Leprosy an important public health problem which needs to be addressed. **Aims:** We study the histopathological features of leprosy in skin biopsies and categorize them into various types based on microscopic features. Clinico pathological correlation was done in all cases. **Materials and Methods:** Skin biopsies after adequate fixation in 10% of formalin, were routinely processed and paraffin embedded sections of 5 µ thickness were stained with H and E and fite -faraco stain and were studied microscopically. **Results:** A total of 1200 skin biopsies were obtained from patients of skin department during a period of two years from May 2016 to May 2018,out of which 136 cases were clinically diagnosed as Hansens and among them 116 were confirmed as Hansens histologically . Among them - Lepromatous leprosy 61 cases,- Borderline lepromatous leprosy 18 cases, Tuberculoid leprosy-11 cases, Borderline tuberculoid leprosy- 19 cases and lepra reaction[ENL]-7 cases, rest 20 cases included indeterminate leprosy and other d/ds. With an age range of 11 -68 years, majority were in 2nd decade, with male to female ratio of 2.5:1. LL was the most common type of leprosy (%). Majority of biopsies were of multibacillary type (52.5%). Clinicopathological correlation was observed in all cases. **Conclusions:** For diagnosis, correlation of clinical and histopathological features along with special stain [fite faraco] appears to be more useful than considering any of the single parameters alone.

KEYWORDS: Leprosy, Hansens, H & E stain, Fite Faraco stain.

INTRODUCTION

Leprosy, also known as **Hansen's disease** (**HD**), is a long-term infection by the bacterium *Mycobacterium leprae* or *Mycobacterium lepromatosis*.[3,4] Initially, infections are without symptoms and typically remain this way for 5 to 20 years.[3] Symptoms that develop include granulomas of the nerves, respiratory tract, skin, and eyes.[3] This may result in a lack of ability to feel pain, which can lead to the loss of parts of extremities due to repeated injuries or infection due to unnoticed wounds.[2] Weakness and poor eyesight may also be present.[2]

Pathogenesis of leprosy is complex and its clinicopathological manifestations are the result of host-parasite interactions.

In 2015, the number of cases of leprosy was about 175,000 and the number of new cases was 210,000.[57]

As of 2013, 14 countries contain 95% of the globally reported leprosy cases.[58] Of these, India has the greatest number of cases (59%), followed by Brazil (14%) and Indonesia (8%).[58] Although the number of cases worldwide continues to fall, pockets of high prevalence remain in certain areas such as Brazil, South Asia (India, Nepal, Bhutan), some parts of Africa (Tanzania, Madagascar, Mozambique), and the western Pacific.

Leprosy is spread between people.[7] This is thought to occur through a cough or contact with fluid from the nose of an infected person.[7] Leprosy occurs more commonly among those living in poverty.[2] Contrary to popular belief, it is not highly contagious.[2] The two main types of disease are based on the number of bacteria present: paucibacillary and multibacillary.[2]

MATERIALS AND METHODS

Skin biopsies after adequate fixation in 10% of formalin, were routinely processed and paraffin embedded sections of 5 µ thickness were stained with H and E and fite - faraco stain and were studied microscopically.

The demographic data, clinical findings and clinical diagnosis were recorded from the requisition slip forwarded along with the biopsy material for histopathological diagnosis. Particularly in reference to skin, nerves and sensory disturbances, a detailed clinical examination was carried out including general, local and systemic examination with relevant past and family history was asked.

The biopsies were taken from the most active lesions (margin of the lesion) and were sent in 10% formalin bulbs to pathology department. The biopsy specimens of leprosy were processed and serial sections were stained using the routine Hematoxylin and Eosin stained sections in relation to clinical findings and modified Fite-Faraco stain for detection of acid-fast bacilli. The histopathological diagnosis was based on the scheme put forth by Ridley and Jopling.[8,9]

Immunopathogenesis of Leprosy

Leprosy is the classical example of the disease with an immunopathologic spectrum wherein the host immune reaction to the infective agent ranges from none to marked with a consequent range of clinicopathologic manifestations. Tuberculoid leprosy (TT) shows a high cellular response characterized by T-cell and macrophage activation and very few bacilli in the tissues. Lepromatous leprosy (LL) on the opposite pole shows an absent cellular immune response to *M. leprae* antigens with no macrophage activation and abundant bacilli in the tissues. The immunopathologic spectrum is a dynamic continuum, in which the patients move in either direction according to the host immune response and treatment. The standard delineation follows the classification of Ridley and Jopling [8] with categories defined along this spectrum by a combination of clinical, microbiological, and histopathological indices: Tuberculoid (TT), borderline tuberculoid (BT), midborderline (BB), borderline lepromatous (BL), and lepromatous leprosy (LL). The TT and LL group of patients are stable, the former often self-healing and the latter remaining heavily infected unless given chemotherapy. The central point of the spectrum BB is most unstable with patients quickly downgrading to LL if not treated. Apart from these, there are some patients who are labeled as 'indeterminate' leprosy and these are the patients with the earliest identifiable skin lesions that cannot be categorized definitely in any immunopathologic spectrum.

Histopathology of Leprosy

Histopathological examination of the skin biopsy from a leprosy patient helps to; (a) confirm the diagnosis of leprosy; (b) classify the disease in the leprosy spectrum; (c) identify the bacillary load in the tissue; (d) assess disease activity and response to treatment; (e) confirm and classify lepra reactions.

Biopsy from a well-developed cutaneous lesion is an important procedure for diagnosis and classification of leprosy. Standard histopathological examination of the formalin-fixed paraffin-embedded skin tissue can provide information regarding cellular morphology, presence of acid fast bacilli (AFB), and can be enhanced by techniques like immunohistochemistry and molecular studies.

Indeterminate leprosy

Indeterminate leprosy is the earliest detectable skin lesion comprising one or few hypopigmented macules with no clear sensory changes. The skin biopsy may show mild accumulation of lymphocytes and macrophages and an occasional AFB either in the non-inflamed nerve, arrector pili or in the sub-epidermal zone in the very early stages. It may show neuritis evidenced by Schwann cell proliferation and infiltration of the nerve fibers with lymphocytes. Nerve infiltration is the most significant feature of leprosy when the rest of the skin shows non-specific changes. Moreover, the histological changes are known to precede the clinical manifestations by at least few months.[12] Most indeterminate leprosy cases are known to heal spontaneously,[6] but since it is not possible to predict which indeterminate cases will evolve into well-known forms, it is ethical to treat all the patients.

Tuberculoid leprosy

Primary polar tuberculoid leprosy has large and compact epithelioid cell granulomas along the neurovascular bundles with lymphocytes. Langhans giant cells are typically scanty or absent, and AFB are rare to find. Epithelioid cell granulomas always erode into the basal layer of the epidermis. The dermal nerves may be either obliterated and completely effaced or eroded by lymphocytes.[fig. 5,6].

Borderline tuberculoid leprosy

The epithelioid granulomas of BT do not invade into the epidermis and have less lymphocytes in comparison to TT. The granulomas are arranged in a curvilinear pattern along the neurovascular bundle. Nerve erosion by the granuloma is typical, and AFB are scanty and are more readily detected in the Schwann cells of the nerves. In addition to nerves, the granuloma can also involve the sweat glands and the arrector pili muscle.[fig .7,8].

Mid-borderline leprosy

The histopathology in BB shows almost equal admixture of epithelioid cells and macrophages forming a distinct granuloma. The lymphocytes are scant and scattered and multinucleate giant cells are absent, a feature that helps it to be distinguished from BT. AFB may be frequent.

Borderline lepromatous leprosy
The predominant cells in the granulomas are macrophages with occasional epithelioid cells arranged in patches. Lymphocytes are sparse, AFB are abundant but usually not present as globi. Perineural fibroblast proliferation forming 'onion-skin' in cross section is a typical feature. Foamy histiocytes are frequently seen. [fig.3,4].

Lepromatous leprosy
The typical features consist of a flattened epidermis separated from the dermal infiltrate by a grenz zone of normal collagen also called as band of Unna. The macrophage granuloma of is large and expansile one consisting of sheets of histiocytes with only few lymphocytes. The histiocytes harbor abundant AFB. The solid bacilli are stacked like cigars and appear as globi d. Such an appearance is the rule rather than an exception. In contrast to tuberculoid leprosy, the nerves in the skin of LL patients may contain considerable AFB; however, the morphological features of the nerve are fairly well preserved in the earlier phase of the disease before eventually becoming fibrotic. Presence of foamy change in LL suggests regression[fig .1,2].

Pure neuritic leprosy
Pure neuritic leprosy is characterized by neural involvement in the absence dermal lesions. The histopathological examination of a nerve reveals a granuloma or infiltrate characteristic of leprosy.

Histoid leprosy
This is another variant of LL, which shows the highest load of solid staining AFB arranged in clumps and sheaves. The macrophage reaction is unusual in the sense that the macrophages become spindle-shaped and oriented in a storiform pattern reminiscent of a fibrohistiocytoma.

Histopathological Differential Diagnosis
Tuberculoid leprosy needs to be differentiated from other granulomatous dermatitides. Cutaneous tuberculosis is the most important differential diagnosis, which has to be excluded. The epidermis in tuberculoid leprosy is usually flat and not hyperplastic as in tuberculosis. The arrangement of the granulomas in leprosy is along the neurovascular bundles giving an oblong pattern to the granuloma unlike tuberculosis where there is intense and sometimes lichenoid pattern of the chronic granulomatous infiltrate. The dermal nerve twigs when seen are spared by the infiltrate in tuberculosis. The presence of granuloma or AFB in the nerve is a conclusive proof of leprosy. Cutaneous sarcoidosis may sometimes be confused with tuberculoid leprosy as fibrinoid necrosis may be found in both these entities. The granulomas of sarcoidosis show paucity of lymphocytes and are more confluent and show fibrosis around the granuloma. Other granulomatous lesions like leishmaniasis or granulomatous post-kala-azar dermal leishmaniasis also need to be excluded by demonstration of Leishman-Donovan bodies and frequent presence of plasma cells. Borderline lepromatous and pure lepromatous leprosy may be confused with histiocyte-rich lesions like xanthomas; however, demonstration of AFB in these lesions usually solves the diagnostic dilemma.

Histopathology of Reactions in Leprosy
Leprosy reactions are periodic episodes of acute inflammation caused by immune responses to *M. leprae* or its antigens superimposed on the chronic course of the disease. There are two main types of leprosy reactions depending on the immunological mechanism, i.e. type 1 lepra or reversal reaction and type 2 lepra reaction, which is an immune complex manifestation. In type 1 lepra reaction, the biopsy will show invasion of the epidermis by the granulomatous infiltrate and edema in the superficial dermis. The granuloma becomes more epithelioid, shows infiltration of lymphocytes within and around them, and the Langhans giant cells become increased in number and bigger in size and may also show bizarre shapes. The granulomas also erode into the epidermis representing the upgrading reaction. In addition, caseous necrosis and acid-fast bacilli may be seen in the nerves. The skin and nerves are infiltrated by an influx of CD4 lymphocytes and macrophages that secrete an array of cytokines of Th1 class like interferon-γ and tumor necrosis factor-α and are responsible for the inflammation and tissue damage. These changes of epidermal erosion, dermal edema, intragranuloma edema, and lymphocytes within the granuloma are clues favoring a diagnosis of leprosy type 1 reaction.

Type 2 lepra reaction is characterized by varying degree of polymorphonuclear infiltration superimposed on the already existing granuloma. Edema is frequently present in the dermis. Deposition of immune complexes in the small cutaneous capillaries, arterioles, and venules results in necrotizing vasculitis. This type of reaction is also called as erythema nodosum leprosum and is reflected by deeper infiltration of foamy histiocytes into the subcutaneous fat and presence of neutrophils. The influx of neutrophils can be intense so as to form neutrophilic microabscess. The AFB are fragmented and granular. Superficial ulceration, bulla formation, and necrosis may sometimes supervene.[fig 9,10].

OBSERVATIONS

136 cases were clinically diagnosed as Hansens and among them 116 were confirmed as Hansens histologically. Rest of the cases included other common causes of hypopigmentation. Among them - Lepromatous leprosy 61 cases,- Borderline lepromatous leprosy 18 cases, Tuberculoid leprosy-11 cases, Borderline tuberculoid leprosy-19 cases and lepra reaction[ENL]-7 cases, rest 20 cases included indeterminate leprosy, vitiligo, lichen sclerosus, pitryriasis alba, pityriasis versicolor and uncommon causes like hypopigmented MF, hypopigmented sarcoidosis .Age range of 11 -68 years, majority were in

2rd decade, with male to female ratio of 2.5:1. LL was the most common type of leprosy (52.5%). Most common clinical feature was loss of sensation. Atrophic epidermis and grenz zone was more common in lepromatous leprosy and borderline leprosy. There were 7 biopsies with lepra reaction. Majority of biopsies were of multibacillary type (52.5%) and rest [47.5%) were of paucibacillary type. Fite faraco stain also affirmed the diagnosis in majority of cases .Clinicopathological correlation was observed in all cases.

Table-1.

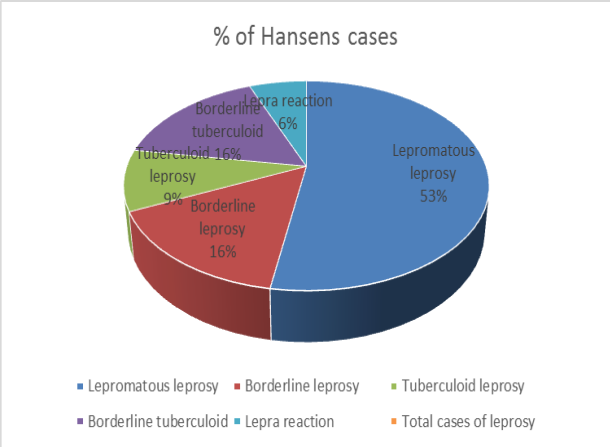
Total skin biopsies	Clinically s/o Hansens	Clinically Non Hansens
1200	136 [11.33%]	1064 [88.66%]

Table-2.

Total cases clinically s/o Hansens	Confirmed Hansens on histopathology	Others [including Indeterminate hansens]
136	116 [85.29%]	20 [14,7%]

Table-3.

Types of Hansens	No. of cases	% of cases
Lepromatous leprosy	61	52.5
Borderlinelepromatous	18	15.5
Tuberculoid leprosy	11	9.4
Borderline tuberculoid	19	16.3
Lepra reaction[Erythema Nodosum leprosum]	07	6.03
Total cases of leprosy	116	



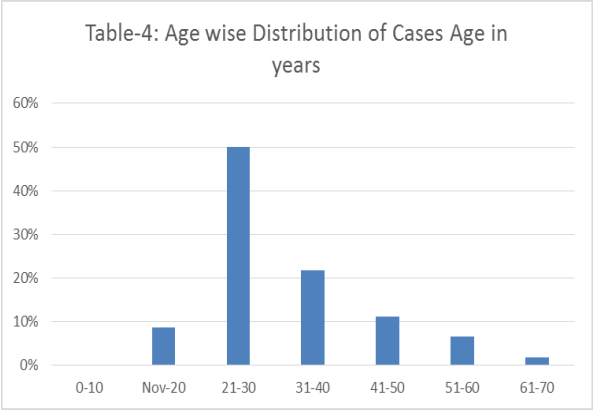


Table-4: Age wise Distribution of Cases Age in years.

Age group	Percentage of cases
0-10	0%
11-20	8.69%
21-30	50%
31-40	21.7%
41-50	11.09%
51-60	6.52%
61-70	1.82%

Table-5: Sex wise Distribution of cases.

No of cases	Males	Females
116	83 [71.5%]	33 [28.4%]

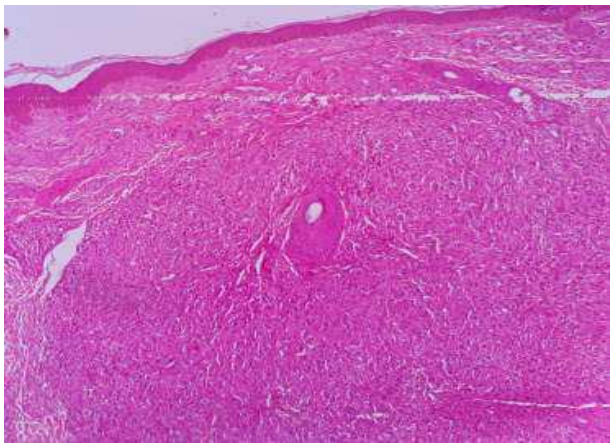


Fig 1: Lepromatous leprosy H & E section.

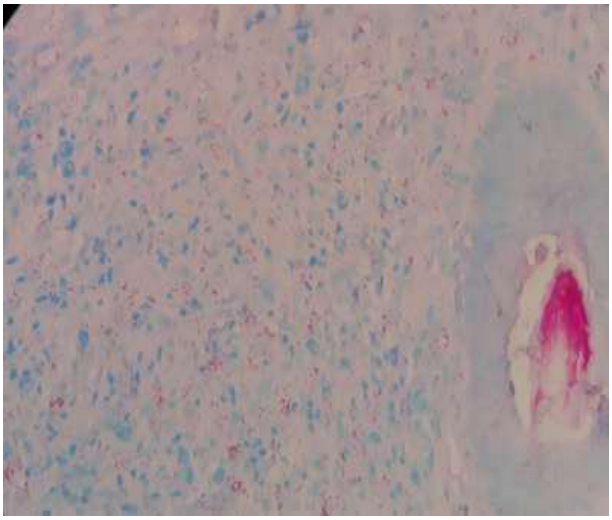


Fig 2: Lepromatous Leprosy fite faraco stain.

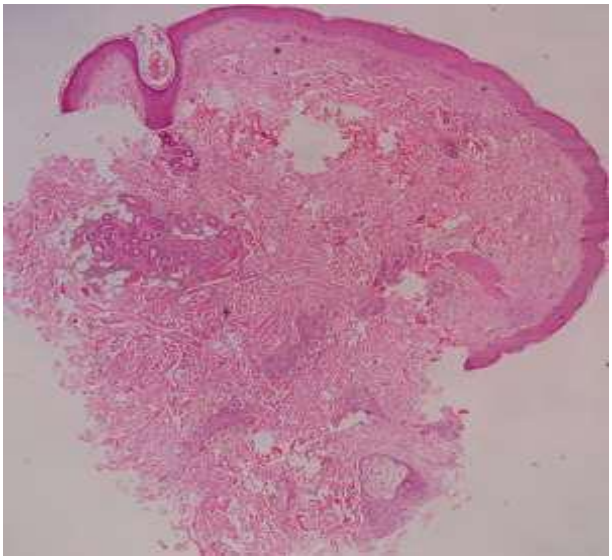


Fig 3: Borderline lepromatous H&E section.

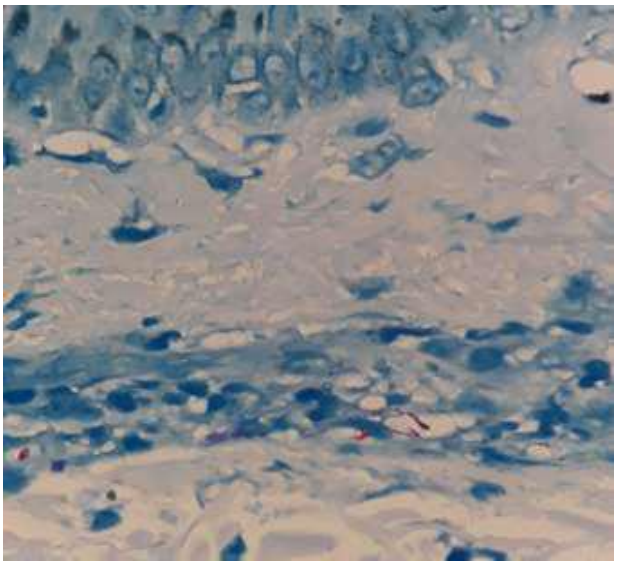


Fig 4: Borderline Lepromatous fite faraco stain.

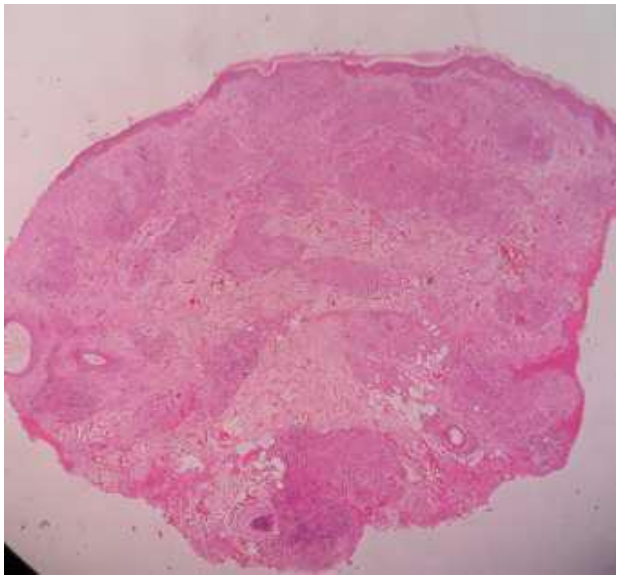


Fig 5: Tuberculoid leprosy H&E section.

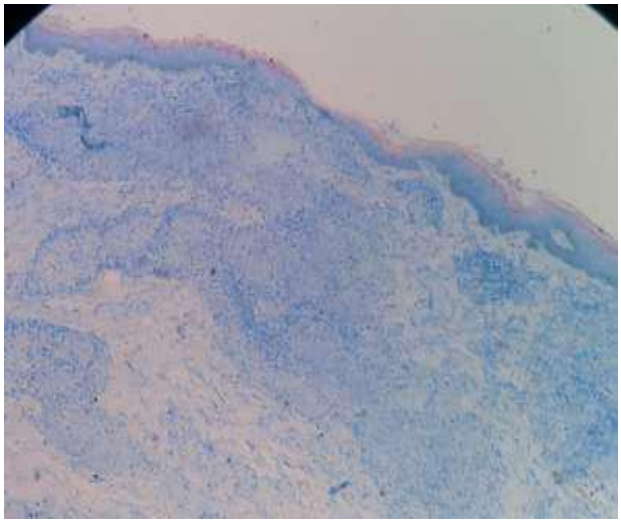


Fig 6: Tuberculoid Leprosy fite faraco stain.

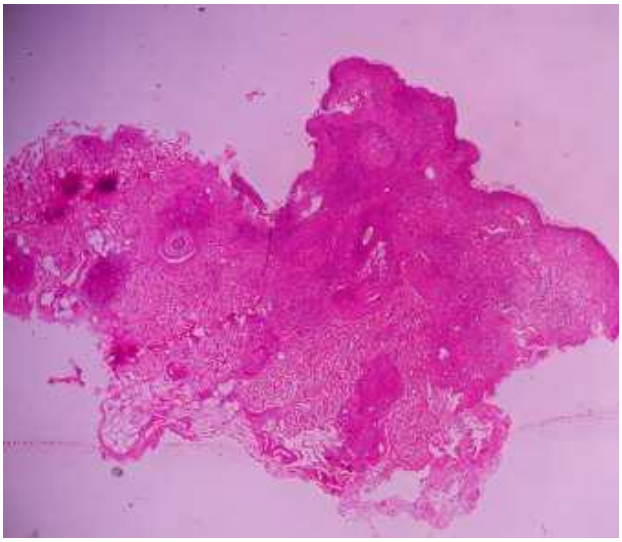


Fig 7: Borderline Tuberculoid leprosy H & E section.

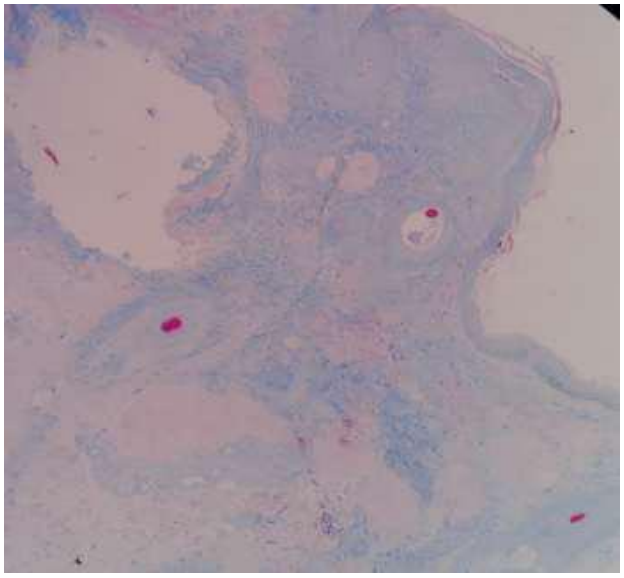


Fig 8: Borderline Tuberculoid leprosy fite faraco stain.

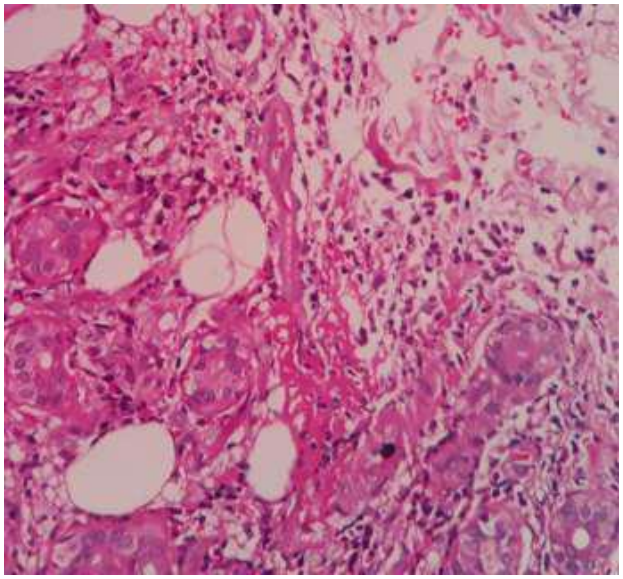


Fig 9: Erythema Nodosum leprosum H & E section.

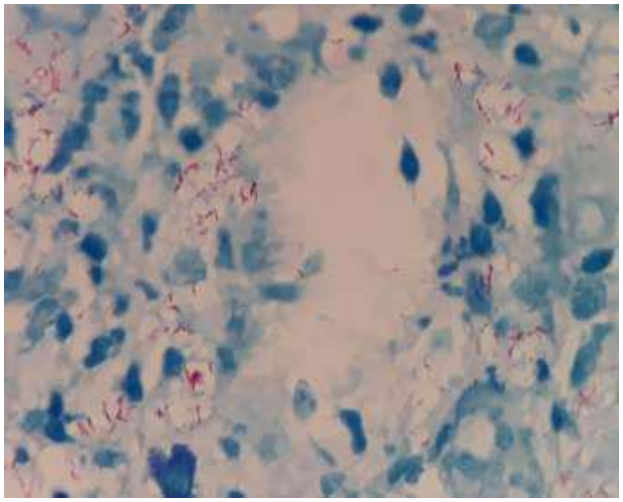


Fig 10: Erythema Nodosum leprosum fite faraco stain.

DISCUSSION

Educational status of leprosy cases shows that most cases are illiterate, showing unawareness and lack of information among common people about leprosy and its common symptoms, disabilities and the need for early diagnosis and treatment. The present study showed the highest number of cases in LL type and the least number of cases in TL type. The age and sex distribution of cases reveal that all cases were seen in age group 11-68,majority [50%]in the age group 21-30years and [71.5%] were males, M: F ratio-2.5:1. This age difference may be due to differences in exposure, opportunities for infection and immunological differences in children and adults. The study shows male preponderance. Similar findings were recorded by the National Leprosy Eradication Programme (NLEP) in 2007.[18] The socioeconomic status reflects that Leprosy is a disease of the poor and overcrowding of homes.

CONCLUSION

To conclude, histopathological examination is integral to the understanding of leprosy, its causative organism and for monitoring relapse and drug resistance. Diagnosis of leprosy has been based on classical cardinal signs, characteristic histopathological findings, and demonstration of acid-fast bacilli both from the skin biopsies of these lesions. The current primary goal is early diagnosis of this disease in order to interrupt the transmission by treating it early. Histopathological examination remains an integral tool for diagnosis and classification.

CONSENT

An informed oral consent was collected from all the subjects in the study prior to testing.

ETHICAL APPROVAL

Prior permission was obtained from institutional ethics committee.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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