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Dr. Archana
Postgraduate Resident,
Department of Pathology,
Father Muller Medical College,
Mangalore, Karnataka, India

Dr. Hilda Fernandes
Professor and Former HOD,
Department of Pathology,
Father Muller Medical College,
Mangalore, Karnataka, India

Corresponding Author:
Dr. Archana
Postgraduate Resident,
Department of Pathology,
Father Muller Medical College,
Mangalore, Karnataka, India

Clinico-Histopathological correlation in Hansen's disease: A retrospective study

Dr. Archana and Dr. Hilda Fernandes

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Abstract
Background: Hansen's disease is a chronic infectious disease with a wide range of clinical manifestations. The clinical diagnosis must be confirmed by histopathological and bacteriological studies in order to adequately manage the condition and prevent drug resistance.
Aim: To perform a clinico-histopathological correlation of skin lesions in all patients with a clinical suspicion of Hansen's disease.
Materials and methods: A retrospective, hospital based, cross-sectional study was conducted in the Department of Pathology, Father Muller Medical College, Mangalore.
Skin biopsies of all suspected cases of Hansen's disease received over a period of three and a half years were included in the study. Haematoxylin and eosin, Fite-Faraco stained sections of all cases were reviewed. The cases were classified according to Ridley–Jopling classification into TT, BT, BB, I, BL, and LL. Clinical details of the patient, including type and site of lesion were obtained from the patient's medical records. Clinico-histopathological correlation was done for all the cases. In addition, wherever available, the corresponding slit-skin smears were also included.
Results: A total of 76 cases were clinically diagnosed as Hansen's disease. Clinico- histopathological correlation was seen in 33/76 cases (43.42%). The most common histological subtype of Hansen's was Borderline Tuberculoid (BT) - 24/76 cases (31.58%). Maximum agreement was seen in Mid-borderline leprosy (92.11%). Fite Faraco stain was positive in 21 out of 76 cases. Slit skin smears were available for 55 cases and positive in 20 cases.
Conclusion: Due to clinical and morphological overlap, it is imperative to correlate the clinical, histopathological and bacteriological index results in order to accurately subtype the categories in Hansen's disease.

Keywords: Clinico-histopathological correlation, Fite-Faraco, Hansen's disease, slit-skin smear

Introduction

Hansen's disease is a chronic, infectious granulomatous disease caused by Mycobacterium leprae and poses a major public health problem in developing nations, such as India [1]. In 1873, Norwegian physician, Gerhard Armauer Hansen was instrumental in identifying *Mycobacterium leprae* as the causative organism and his name has been the premise in labelling this disease. The clinical presentation depends on the immune status of the host, with the skin and peripheral nerves being most commonly affected [1].

Hansen's disease has a high rate of prevalence in the tropics and subtropical regions. Since the 1960s, the WHO has strived to prevent and reduce the prevalence and eliminate this disease, especially in high risk areas [2].

Hansen's disease occurs across all age groups and both genders but is known to have a propensity among the adults with a male preponderance. A high risk of transmission with respect to contact, either through the skin or nasal mucosal droplets is a well-established factor. *M. leprae* is viable outside the human body for a minimum of 9 days at room temperature and for longer periods in moist soil [2]. Human beings are a major reservoir of *M. leprae*, however, wild forms of this organism have been isolated in armadillos [2].

In 1966, Ridley-Jopling classified leprosy according to the clinical, bacteriological, immunological and histological categories into Tuberculoid Tuberculoid (TT), Borderline Tuberculoid (BT), Borderline Borderline (BB), Borderline Lepromatous (BL) and Lepromatous Lepromatous (LL) [3]. Following this, WHO had proposed a classification of paucibacillary and multibacillary leprosy in 1982, this was based on clinical findings and the bacteriological index.

Indeterminate, TT and BT were classified under paucibacillary and the remaining entities were considered as multibacillary [4]. The purpose of the WHO classification was to aid in convenient diagnosis and treatment in the field by health workers [4]. By the year 1988, a positive slit skin smear at any site was sufficient to initiate multibacillary therapy [2].

The Ridley-Jopling classification system has found a convenience and acceptance in routine practice among pathologists and dermatologists. Sole dependence on clinical assessment of the skin lesions could lead to inadequate treatment and further result in multi-drug resistance which is an ongoing therapeutic problem.

Evaluation of skin biopsies based on histopathological findings and special stains help to arrive at a definitive diagnosis and this would in turn help the clinician to initiate adequate anti-microbial therapy [1].

The present study was undertaken to evaluate the concordance between clinical and histopathological diagnosis in clinically suspected cases of Hansen's disease.

Materials and Methods

A retrospective, hospital based, cross-sectional study was performed in the Department of Pathology in Father Muller medical College Hospital, which is a tertiary care centre with a specially dedicated unit for the treatment of Hansen's disease. Ethical clearance was obtained from the institutional ethics committee. Skin punch biopsies with a clinical suspicion of Hansen's disease in the study period from January 2016 up to June 2019 were included. Biopsies all age groups and both genders were included in the study. Patients with a previous history of Hansen's disease and on treatment for the same were excluded from the study. Relevant clinical history, such as, age, sex, nature and location of the lesion were noted. Skin biopsies were fixed in 10% buffered formalin, processed and sectioned as per the standard operating protocols in our institute. Haematoxylin and eosin stained sections and Fite-Faraco stained slides of all the cases were reviewed. A minimum of two tissue levels were seen for each case. Slit-skin smear was utilized, wherever available. The clinical classification by the dermatologist was documented. Histopathological classification of the cases was performed according to Ridley-Jopling classification. A clinico-histopathological correlation was performed. Statistical analysis to obtain an agreement percentage and analyze demographic data was performed using JASP 0.11.1.

Results

A total of 76 cases were clinically diagnosed as Hansen's disease in the study period. The age of the patients in this study ranged from 5 years to 80 years with a mean age of 39.39 years. Majority of the patients were in the age group of 21-30 years and 51-60 years [Table 1]. Males constituted a majority of the study population accounting for 67% and the male:female ratio was 2.03:1 [Table 2]. The most common clinical presentations were macules (42%) followed by plaques, hypopigmented patches and nodules [Table 3].

Out of the 76 clinically suspected cases in the study, 58 (76.31%) cases showed evidence of Hansen's disease. We obtained a clinico-histopathological correlation of 83.42%. The most common clinical and histopathological subtype was borderline tuberculoid leprosy. Based on the histopathological diagnosis, borderline tuberculoid (BT) constituted 31% of the cases, while, lepromatous leprosy (LL) was seen in 13% of the cases, tuberculoid (TT) was 11% and borderline lepromatous was 10%. Maximum clinico-histopathological correlation of 92.11% was observed in mid-borderline leprosy (BB) with least correlation of 68.42% in borderline tuberculoid (BT) [Table 4]. Major disagreement of difference of two or more groups was not observed in any of the categories.

Fite-Faraco stain was negative in all the cases of tuberculoid leprosy (TT) and mid-borderline leprosy (BB). Four cases (16%) of borderline tuberculoid leprosy were positive for Fite stain. All cases of lepromatous leprosy showed a positivity with Fite stain. The modified Fite-Faraco stain used in this study had a sensitivity of 84.2% and specificity of 88.9%. Slit skin smears were available for 55 cases and positive in 20 cases (36.63%). [Table 5]

Table 1: Age wise distribution of cases

Age group (years)	No. of patients
0-10	3
11-20	12
21-30	15
31-40	12
41-50	8
51-60	14
61-70	10
71-80	2

Table 2: Gender wise distribution of cases

Gender	Number of cases
Males	51
Females	25

Table 3: Clinical presentation of the cases studied

Clinical presentation	Frequency
Hypopigmented patch	10 (13%)
Macule	32 (42%)
Nerve thickening	2 (3%)
Nodule	10 (13%)
Papule	3 (4%)
Plaque	17 (22%)
Ulcer	2 (3%)

Table 4: Clinico-histopathological correlation of the cases studied

Type of Leprosy	Clinical diagnosis	Histological Diagnosis									Correlation (%)
		TT	BT	BB	BL	LL	Histioid	Indeterminate	OTHERS		
									No Evidence of Hansen's	Miscellaneous	
TT	14	5	1					2	4	2	82.89
BT	38	4	19	1	2			2	9	1	68.42
BB	6		2	1	2	1					92.11
BL	12		1		4	5			2		84.21
LL	6		1			4	1				89.47

Table 5: Correlation between histological diagnosis and slit skin smear

Histological diagnosis (Fite positive/Total number of cases)	SSS available	SSS results (Positive cases/Number of cases)
TT (0/9)	4	0/4
BT (4/24)	19	1/19
BB (0/2)	2	2/2
BL (6/8)	8	7/8
LL (10/10)	10	9/10
Histioid (1/1)	1	1/1
No Evidence Of Hansen's (0/15)	9	0/9

Table 6: Comparison of correlation among other studies with the present study

Various studies	Year of study	Clinico-pathological correlation (%)
Pandya *et al*. [9].	2008	58
Manandhar *et al*. [5].	2010	45.33
Mathur *et al*. [8].	2011	80.4
Giridhar *et al*. [10].	2012	60.23
Banushree CS *et al*. [6].	2016	79.44
Semwal *et al*. [1].	2018	62
Present study	2020	83.42

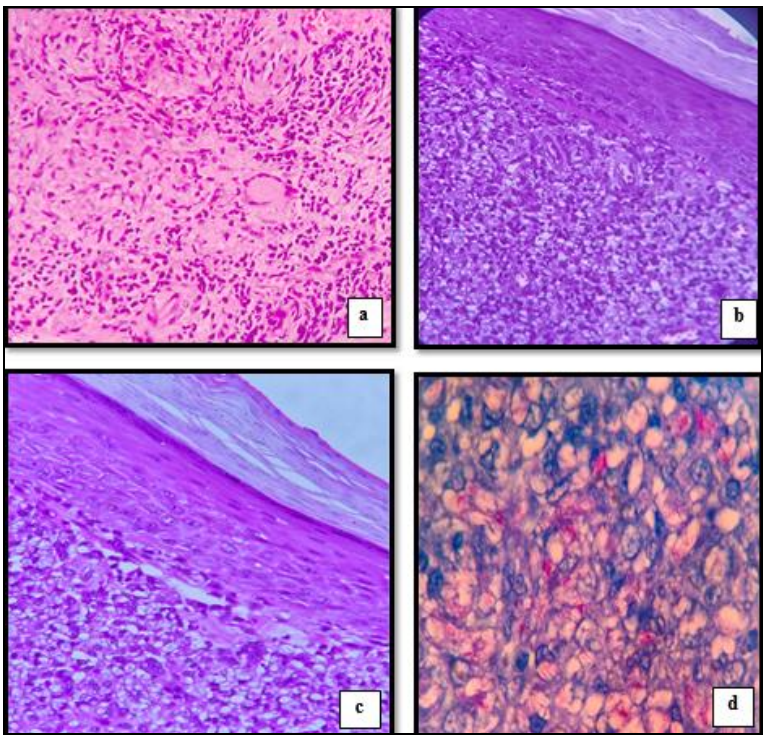

Fig 1: (a) High power, Well-formed granulomas with Langhans' type of giant cell in a case of Tuberculoid leprosy; (b) Low power, Dermis is filled with sheets of foamy macrophages in a case of Lepromatous Leprosy; (c) High power, Presence of Grenz zone in another case of Lepromatous Leprosy; (d) Oil immersion, Numerous solid acid fast bacilli within the macrophages demonstrated by modified Fite-Faraco stain

Discussion

Hansen's disease is an infectious disease with a complex pathogenesis dependent on the immune status of the host. The clinicopathologic manifestations are a consequence of immunopathology and accumulation of infected cells and the host response could range from almost none to a marked immune response at the polar opposite end of the spectrum. When the host response is minimal, progressive damage to the nerves, eyes and skin are potentially permanent and morbid.

The present study classified cases according to the Ridley-Jopling classification as mentioned above. Cases of indeterminate leprosy and one case of histioid leprosy were also included in the study.

Tuberculoid leprosy is a result of good immune response of the host and clinically presents as hypopigmented, anaesthetic, well-bordered lesions; lepromatous leprosy is a manifestation of poor immune status of the host where the patient presents with numerous ill-defined skin lesions and frequent involvement of peripheral nerves. On histopathology of the skin biopsies, tuberculoid leprosy exhibits numerous well-formed granulomas with erosion into the epidermis and absence of a Grenz zone. Lepromatous leprosy due to the high bacillary load has a characteristic histopathological appearance of sheets of foamy macrophages with the presence of a Grenz zone

[Figure 1]. Borderline tuberculoid form has more granulomas with fewer lymphocytes and no erosion of the dermis, mid-borderline cases have activated macrophages with scant granulomas and lymphocytes; borderline lepromatous, microscopically, is rich in foamy histiocytes with few epithelioid histiocytes.

The present study showed a male preponderance of 67%, similar to the results obtained by Manandhar *et al.* [5], Banushree CS *et al.* [6], Semwal *et al.* [1] and Vargas-Ocampo *et al.* [7]. This could be attributed to an increased risk of exposure as a result of job associated mobility. The most commonly affected age groups in this study were between 21-30 years, followed by 51-60 years; this age range was even observed by Banushree CS *et al.* [6]. Macules and plaques were the most frequently dermatologic lesions encountered in our study, while Manandhar *et al.* [5] noticed more plaques in their study.

Borderline tuberculoid leprosy was the most common clinical and histopathological subtype in our study accounting for 50% and 31%, respectively. Numerous published studies have found a similar distribution, Manandhar *et al.* [5] studied 75 cases, wherein 40% were borderline tuberculoid histologically, Banushree CS [6] studied 110 cases with 39% being histologically classified as borderline tuberculoid. The predominance of borderline tuberculoid leprosy could be due to earlier detection and increased accessibility to medical care.

The clinico-histopathological correlation we obtained was 83.42%, which was similar to the results obtained by Mathur *et al.* [8] with a correlation of 80.4% and Banushree CS *et al.* [6] with a correlation of 79.44 % [Table 6]. The high rate of correlation could possibly be attributed to the large caseloads of Hansen's disease in our centre, thereby resulting in an increased familiarity. Frequent inter-departmental communications could also play a key role to identify and deal with problematic cases.

The polar forms of the histological subtypes showed an excellent correlation; however, the correlation was a little lower for borderline tuberculoid and borderline lepromatous leprosy. Mid-borderline lesions showed maximum correlation. Contrasting results were seen by Semwal *et al.* [1] and Banushree CS *et al.* [6] where they obtained maximum histopathological correlation for the polar ends of the disease process. The variation in these results could possibly be due to the difference in the patient population studied by us.

The general disparity between clinical and histopathological findings can be due to the fact that clinical examination is observer dependant with a certain degree of lack in uniformity, whereas histopathological demarcation is almost accurately reproducible based on the characteristics being analyzed.

The modified Fite-Faraco stain was positive in 100% of the lepromatous leprosy cases, similar to the studies by Semwal *et al.* [1] and Banushree CS *et al.* [6]. The relationship between the bacterial load and cell mediated immunity is reflective in the bacteriological index which can be studied by analyzing Fite Faraco stained sections and calculating the presence of bacilli on a semi-logarithmic scale. The bacillary index in our study was evidently high in the lepromatous leprosy form of Hansen's disease and is similar to the results obtained by Banushree CS *et al.* [6].

Eighteen cases of clinically suspected Hansen's disease did not show any evidence of the same on histopathological analysis. In most of these cases (15/18), the histopathological findings were nonspecific. However, confirmed diagnosis of epidermal nevus, superficial perivascular dermatitis and pseudoepitheliomatous hyperplasia were established in one case each.

Although specific histopathological findings are in place for each category, an overlap is often observed in borderline cases with the least stability in mid-borderline Hansen's disease. A wholesome approach involving clinical, histopathological and microbiological parameters need to be considered for accurate classification in each case [11, 12]. This would help to initiate accurate therapy and further prevent the debilitating effects associated with this condition.

Conclusion

Clinical and morphological diagnosis are essential for all cases which arouse a suspicion of Hansen's disease. The histopathological features need to be interpreted in conjunction with clinical findings as early lesions tend to pose a diagnostic challenge. Newly diagnosed cases of Hansen's disease have a major epidemiological impact in our country. A due diligence is thus essential by both, the dermatologist and pathologist which can be achieved by a clinico-histopathological correlation, as observed by us.

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