IJPRP

Indian Journal of Pathology: Research and Practice
Volume 9 Number 2 (Part II), May – August 2020
DOI: http://dx.doi.org/10.21088/ijprp.2278.148X.9220.22

Original Research Article

Histopathological Study of Granulomatous Lesions of the Skin at Tertiary Care Hospital

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How to cite this article:

Ahilya Balaso Dhadas, Dilip Sarate, Pradeep Umap, Pradeep Male. Histopathological Study of Granulomatous Lesions of the Skin at Tertiary Care Hospital. Indian J Pathol Res Pract 2020;9(2 Part II): 137–144.

Abstract

Granulomas are organized aggregates of macrophages and other immune cells often with characteristic morphological changes. Granulomas evolved as protective responses to destroy or sequester particles but are frequently pathological in the context of foreign bodies, infections, and inflammatory diseases. Cutaneous diseases occur in 60% to 70% of cases of granulomatous lesions. Present study aimed to study the morphology of cutaneous granulomatous lesions. Total 170 patients with clinical suspicion of granulomatous skin lesions were subjected for punch biopsy from skin lesion. Histopathological examination was done to study the morphology of lesion. We found 148 cases of Leprosy, 11 cases of tuberculous of skin, 03 cases of actinomycosis and 8 cases were non infectious granulomatous lesions. Age group of the study population varies from 9 year to 69 years and had mean age 35.57 year. 106 were male and 64 were female. Upper limb (41%) followed by lower limb (19%) was the most common site of biopsy. Clinically, hypopigmented patch (34%) followed by plaque (27%) was the most common presentation. Of the leprosy cases, borderline tuberculoid leprosy (BT- 45%) followed by tuberculoid leprosy (TT – 14%) was the predominant lesion. Lupus vulgaris (56%) was the predominant tuberculous skin lesion.

Keywords: Actinomycosis; Biopsy; Borderline Tuberculoid; Granuloma; Leprosy; Lupus Vulgaris; Skin; Tuberculosis; Tuberculoid Leprosy.

Introduction

Granulomas are organized aggregates of macrophages and other immune cells often with characteristic morphological changes. Granulomas evolved as protective responses to destroy or sequester particles but are frequently pathological in the context of foreign bodies, infections, and inflammatory diseases.[1] Chronic granulomatous disease represents a group of genetic disorders in which impaired intracellular microbial killing by phagocytes leads to recurrent bacterial and fungal infections and granuloma formation.[2] Cutaneous disease occurs in 60% to 70% of cases. The granulomatous reaction can be defined as a distinctive inflammatory response characterized by the presence of granuloma, which are relatively discrete collections of epithelioid histiocytes with variable numbers of admixed multinucleated giant cells and chronic inflammatory cells.[2]

Granulomatous inflammations are a common and intriguing problem. Six histological types of granulomas can be identified on the basis of constituent cells and other changes within the granulomas: Tuberculoid, Necrobiotic, Sarcoidal, Foreign body, Suppurative and

Miscellaneous.[3] Granulomatous reaction is a type IV hypersensitivity reaction evoked by poorly soluble reactive substances. Incidence and prevalence of different types of granulomatous dermatitis depends on geographic location. Many granulomatous skin lesions have identical histomorphology and conversely a single pathology can produce varied histological features. They often lead to diagnostic confusion among Dermatologist and Pathologist due to variable morphology.[4] Because of overlapping features and still a diverse histopathological spectrum, these lesions pose a diagnostic difficulty to naïve and even expert dermatologists and pathologists need a clinicopathological correlation.[5] The occurrence of different types of granulomatous lesions of the skin varies according to the geographical location.[2] The arrival at a proper diagnosis is mandatory, so that the appropriate treatment can be meted out. Good clinical history, a close histological examination and a clinicopathological correlation are essential in making a diagnosis. It is important to know the infectious etiology in any granulomatous lesion.[3] So, this study was conducted to know the etiology and morphology of different granulomatous lesions of skin in our geographical location.

Aims

1. To study the morphology of different granulomatous lesions of skin.
2. To find out the aetiology of all the granulomatous lesions.
3. To correlate granulomatous lesions with their clinical findings.

Methodology

Study place: Tertiary care teaching hospital in Maharashtra

Study design: Cross sectional study

Study duration: 2016 to 2018 (2 Years)

Inclusion Criteria

1. Clinically suspected granulomatous lesions of skin.
2. Skin biopsies showing granulomatous lesions on histology.

Exclusion Criteria

1. Skin biopsies with non-granulomatous lesions on clinical and histopathology examination.

Study was approved by institutional ethical committee. Skin biopsy was done in all patients attending to dermatology outpatient department with high suspicious of granulomatous lesions. The biopsies were received in 10% formalin. They were routinely processed in the histopathology section and paraffin blocks were prepared. 3-5 µ sections were taken on the appropriately labelled slides and stained with haematoxylin and eosin. The slides were dried and mounted with DPX for microscopic examination. Special stains were performed wherever necessary. Before proceeding to the biopsy, the total procedure was explained to the patients and after obtaining the written consent from the patients; biopsy was performed from the site of lesion. Punch biopsies were obtained using the punch of sizes 3–5 mm.

Results

Punch biopsies were obtained from total 220 patients. Of these, 170 cases found to be granulomatous on histology. Hence, further observations and discussion is confined to 170 cases only.

Demographic data of the study population showed sex ratio of 1.65:1 with 106 (62.35%) male and 64 (37.65%) female. Youngest case was of 09 years old and oldest of 69 years with mean age was 35.57 year with standard deviation 11.62. Majority of the cases were lying in the third decade of life accounting for 55 (32.35%) cases followed by fourth and fifth decade of life accounting for 48 (28.24%) and 38 (22.35%) cases respectively.

Site of biopsy (lesion) was noted among the study population. It was found that upper limb was the predominant site of biopsy contributing for 69 (40.59%) cases followed by lower limb 32 (18.82%), Head-Neck-Face 29 (17.06%) and chest and back 28 (16.46%) cases. Abdomen was the least common site of biopsy found among 12 (07.06%) cases. Status of pigmentation at the site of lesions was noted. It was labelled as hyperpigmentated lesion among 21 (12.35%) cases, hypo pigmented lesions among 142 (83.53%) and normal skin colored lesions among 07 (04.12%) cases.

Clinicopathological correlation of these granulomatous lesions was done. Considering the clinical diagnosis, leprosy was the predominant entity comprising of 148 (87.06%) cases. Clinical diagnosis of the study population was correlated with

histopathological findings. The clinicopathological correlation of the granulomatous skin lesions is shown in Table 1.

Among the leprosy cases, clinical diagnosis was well correlated with the histopathological diagnosis among 64.86% cases. Considering the tuberculosis, 55.56% cases had good clinicopathological correlation.

In the present study, the number of the leprosy cases was sub-typed as per Ridley Jopling classification. It was found that borderline tuberculoid leprosy (BT) was the predominant histological entity accounting for 85 (57.43%) cases. It was followed by tuberculoid leprosy (TT) 20 (13.51%), borderline Lepromatous (BL) 18 (57.43%), lepromatous leprosy (LL) 11 (7.43%).

Histoid leprosy comprises of 04 (2.70%) cases, erythema nodosum leprosum (ENL – type 2 lepra reaction) and borderline tuberculoid leprosy (BT) with type 1 upgrading reaction was found in 03 (2.03%) cases of each. Inderminate leprosy (IL) and mid borderline leprosy (BB) accounting 02 (1.35%) cases of each.

All 3 cases diagnosed as Mycetoma clinically were consistent on histopathology. We found 06 cases of lupus vulgaris, 03 cases of tuberculosis verrucosa cutis (TBVC) and 1 case each of erythema induratum and tuberculosis cutis orificialis. Among non-infectious group we found 3 cases each of foreign body granuloma and granuloma annulare and 1 case each of Sarcoidosis and nodular Vasculitis.

Granulomatous skin lesions were presented with variety of clinical presentations like cystic lesion, macule and papule etc. The details about the clinical presentations of various granulomatous skin lesions are shown in Table 2. Patchy lesions followed by plaque were the predominant clinical presentation among leprosy cases. Among the tuberculosis cases, papule followed by plaque lesion was the common presentation.

On histopathology along with granuloma different changes are seen in epidermis. Most of the leprosy cases (132 cases, 89.18%) showed atrophy of epidermis. In tuberculosis on histopathology 4 cases showed hypertrophy, 5 cases showed hyperkeratosis and 6 cases showed atrophy. Most of the cases of actinomycosis (3 cases, 100%) showed abscess. In non-infectious cases 3 cases

Table 1: Clinico-Pathological Correlation of Granulomatous Lesions (N=170).

Clinical Diagnosis		No. of patients	HP Diagnosis	
			Consistent with clinical diagnosis	Non consistent with clinical diagnosis
Leprosy (148)	Tuberculoid Leprosy	21	11	6BT, 1BB, 2BL, 1IL
	Borderline Tuberculoid	76	67	6TT, 1BB, 1BL, 1BT with Type 1 reaction
	Borderline Lepromatous	15	06	3BT, 4LL, 1TT, 1BT with Type 1 reaction
	Lepromatous Leprosy	18	07	4BL, 3BT, 1ENL, 1HL, 1IL, 1BT with Type 1 reaction
	BT With Type 1 Reaction	01	00	1 BT
	ENL	03	02	1 TT
	Histoid Leprosy	07	03	4 BL
	Indeterminate Leprosy	02	00	1 TT, 1BT
	Relapse of Hansen	05	00	4 BT, 1BL
Tuberculosis (9)	Lupus Vulgaris	04	03	1 TBVC
	TBVC	04	02	2 Lupus Vulgaris
	Lichen Scrofulosum	01	00	1 Lupus Vulgaris
Actinomycosis (3)	Mycetoma	03	03	–
Other (10)	Foreign Body Granuloma	04	03	1 Erythema Induratum
	Granuloma Annulare	04	03	1 Tuberculosis cutis orificialis
	Nodular Vasculitis	01	01	–
	Sarcoidosis	01	01	–
	Total	170	112	58

Table 2: Clinical Presentation of Granulomatous Skin Lesions (n=170).

Condition	Clinical Presentation							
	Cyst	Macule	Nodule	Papule	Patch	Plaque	Ulcer	Total
TT	–	01	01	01	13	04	–	20
BT	–	11	03	05	34	32	–	85
BB	–	01	–	–	–	01	–	02
BL	–	03	03	01	09	02	–	18
LL	–	03	05	–	02	01	–	11
BT type 1 Reaction	–	02	–	–	–	01	–	03
ENL	–	–	01	–	–	–	02	03
IL	–	02	–	–	–	–	–	02
HL	–	–	03	–	–	01	–	04
TB	–	–	01	06	–	04	–	11
Mycetoma	01	–	02	–	–	–	–	03
Non infectious	02	01	–	04	–	–	01	08
Total	03	24	19	17	58	46	03	170

Abbreviations : BT: Borderline Tuberculoid Leprosy, TT: Tuberculoid Leprosy, BL: Borderline Lepromatous Leprosy, BB: Midborderline, LL: Lepromatous Leprosy, IL: Indeterminate Leprosy, HL: Histoid Leprosy, ENL: Erythema Nodosum Leprosum, TB: Tuberculosis, TBVC: Tuberculosis Verrucosa Cutis

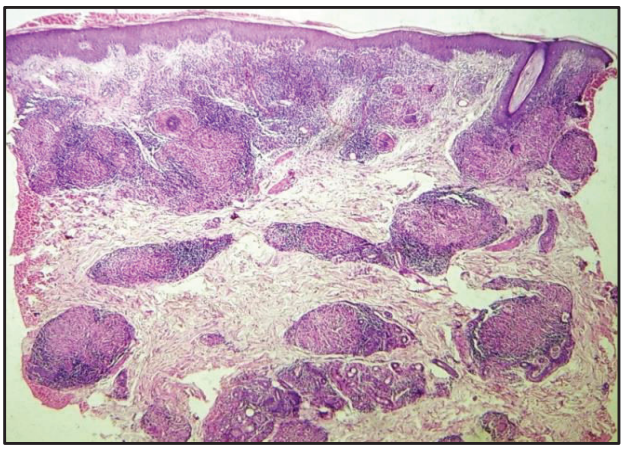

Fig. 1: Tuberculoid Leprosy (TT) showing multiple granulomas in upper and mid dermis, around adnexa and nerve bundles. Granuloma erodes the epidermis. [4X,HandE stain]

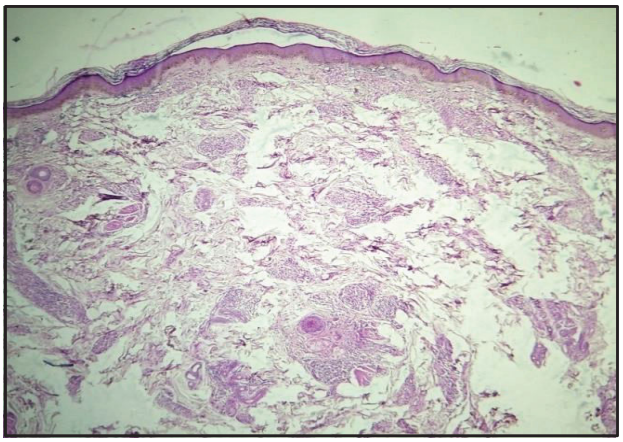

Fig. 3: Borderline Lepromatous Leprosy (BL) is showing atrophic epidermis below which there is grenz zone and well formed macrophagic granuloma in upper dermis. [4x view, HandE stain]

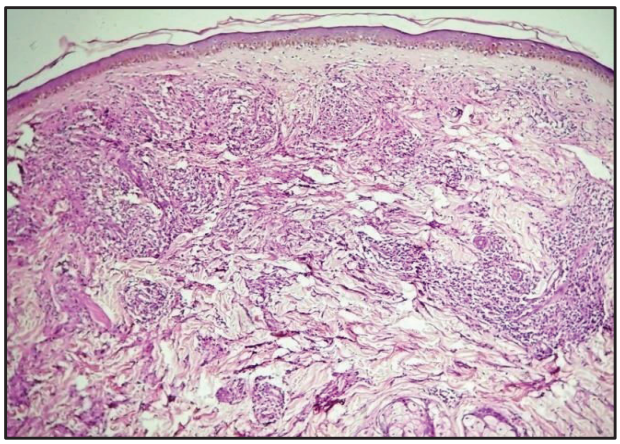

Fig. 2: Borderline Tuberculoid Leprosy (BT) showing atrophic epidermis well formed grenz zone beneath epidermis and well formed granuloma in upper dermis. [10X,HandE stain]

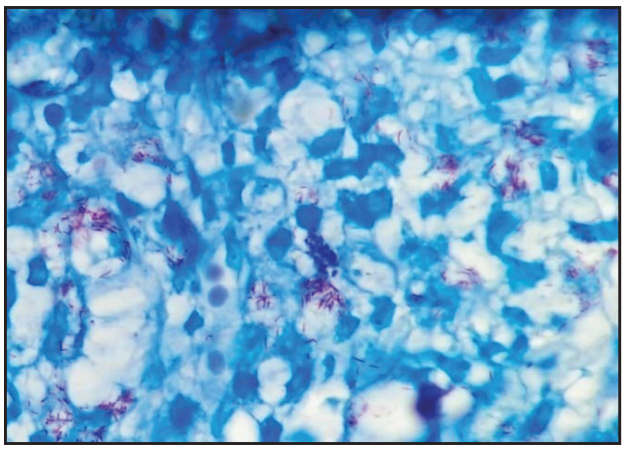

Fig. 4: Borderline Lepromatous (BL) showing Acid-Fast Bacilli showing positive Fite Faraco stain. Bacteriological index 4+[100x, Fite Faraco stain]

showed abscess and 2 cases showed hyperkeratosis. Destruction of basal layer was seen in 20 cases of leprosy and these 20 cases were of tuberculoid leprosy.

The morphology of the granuloma was studied. Out of total 170 cases, 121 cases showed nodular granuloma while 49 cases showed diffuse granuloma. Nodular granuloma was seen in 18 (90%) cases of TT, 77 (90.59%) cases of BT, 2 (100%) cases of BB, 2 (100%) cases of indeterminate leprosy, 6 (100%) cases of lupus vulgaris, 3 (100%) cases of TBVC, 1 (100%) case of Tuberculosis Cutis Orificialis, 3 (100%) cases of actinomycosis and 7 (87.50%) cases of non-infectious cases. Whereas 17 (94.44%) cases of BL, 2 (66.67%) cases of BT type 1 reaction,11 (100%) cases of LL, 3 (100%) cases of ENL and 1 (100%) case of Erythema Induratum had diffuse morphology of granuloma.

In the present study, the location of the granuloma in the different lesions was noted. Most of the cases 111 cases (65.29%) showed granuloma at upper dermis. Mid dermis granuloma was noted among 65 (38.24%) cases and 44 (25.88%) cases had granuloma at lower dermis.

Of the 148 leprosy cases, perineural involvement was most frequently seen among 96 (65%) cases while 69 (43%) cases had periadnexal and 57 (39%) cases had perivascular involvement. Among the tuberculous cases, only one case of erythema induratum showed perivascular involvement and all 06 cases of lupus vulgaris had periadnexal involvement. Out of 148 cases of leprosy 65 (43.92%) cases showed positive Fite Faraco stain. Most common bacillary index was 1+ seen among 37% cases followed by 3+ (22% cases) and 4+ (15% cases).

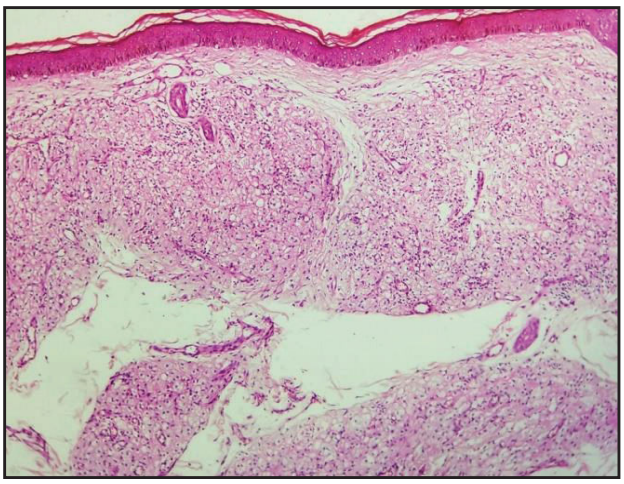

Fig. 5: Lepromatous Leprosy (LL) showing atrophic epidermis, grenz zone below epidermis and granuloma made up of macrophages/Lepra cells in upper dermis. [10x view, HandE stain]

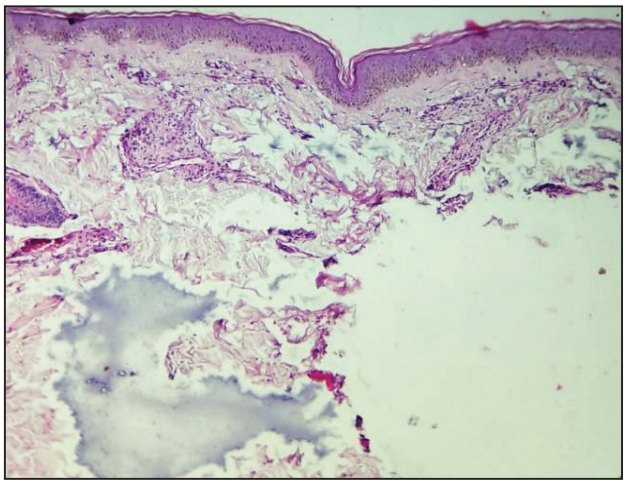

Fig. 7: BT Type 1 reaction showing granuloma in upper dermis and oedema within dermis.
[10x view, HandE stain]

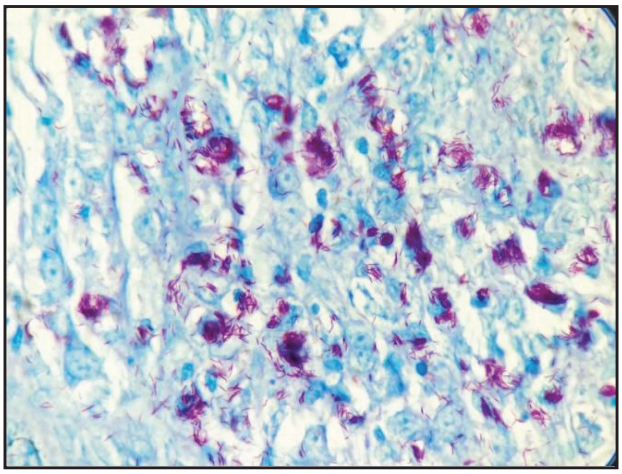

Fig. 6: Lepromatous Leprosy (LL) showing globi made up of acid-fast bacilli (AFB) ,6+ bacillary index. [100x, Fite Faraco stain]

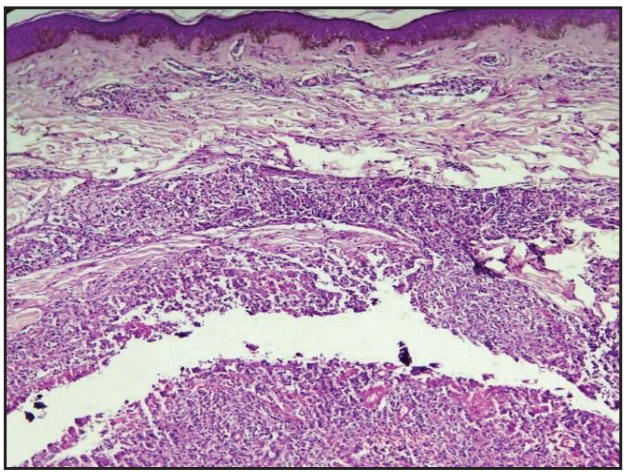

Fig. 8: Histoid Leprosy showing atrophic epidermis, grenz zone and collection histiocytes within dermis. [10x view, HandE stain]

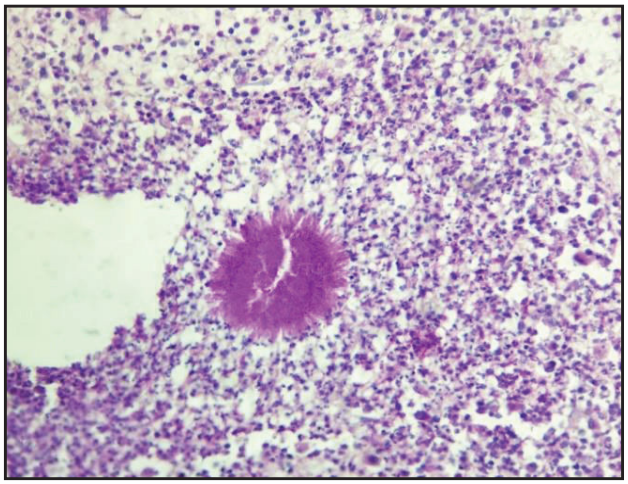

Fig. 9: Actinomycosis is showing central colony of actinomycosis with surrounding granuloma. [40x view, PAS stain]

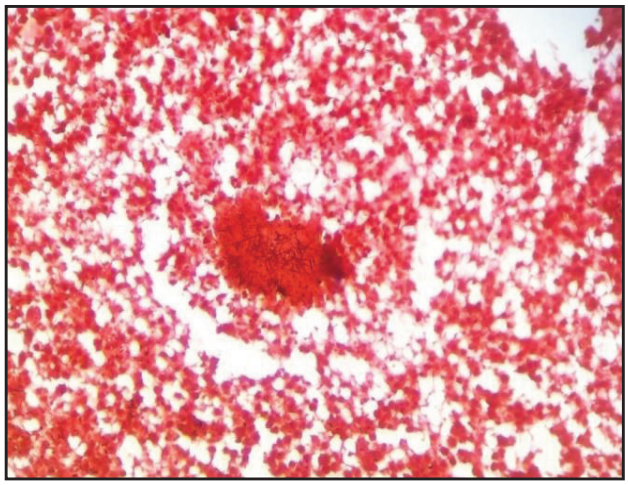

Fig. 10: Actinomycosis showing colony of actionmycosis in centre of granuloma. [100x view, Gram stain]

Zeihl Neelsen (ZN) stain was done in 11 cases of tuberculosis out of that 2 (18%) cases showed positive result. All 03 cases of Mycetoma showed PAS positivity.

Discussion

This prospective study was carried out from 2016 to 2018 for period of 2 years at our tertiary care hospital. Patients coming to skin OPD were examined and history was taken. Out of them clinically suspected cases of granulomatous lesions were selected, and biopsy was done in them. There were total 220 cases which clinically suspected as granulomatous lesions. Out of these 220 cases 170 cases histopathologically proved as granulomatous lesions.

In our study, male was predominate in the study population with male to female ratio was 1.6:1. Similar male predominance was noted in the study by Chakrabarti S. et. al.[4],Gautam et. Al.[6], Agarwal D. et. al.[7] and Potekar RM. et. al.[8]

In the present study, among the leprosy cases, hypopigmented patch was the most common clinical presentation found among 58 (34.12%) cases. Our findings are well correlated with the findings of Khamankar ST. et. al.[9] where she found 79 cases (75.96%) cases presented with hypopigmented patch among 104 leprosy cases.

In present study most of the cases of TT (17 cases, 11.49%) had only one lesion. Most of the cases of BT (72 cases, 48.65%) had 2-3 numbers of lesions.

Most of the cases of BL (12 cases, 8.11%) had 4-5 numbers of lesions. All cases of BT type 1 reaction had 2-3 numbers of lesions. In LL 9 cases had greater than 5 lesions and 2 cases had 4-5 numbers of lesions. All indeterminate leprosy cases presented with single lesion.

All cases of ENL had 4-5 numbers of lesions. In histoid leprosy 2 cases had 2-3 numbers of lesions and 2 cases had 4-5 numbers of lesions.

Tiwari M. et. al.[10], studied 53 cases of leprosy, all cases of lepromatous spectrum had multiple skin lesions while all cases of IL and TL had single lesion. In case of BT, 2 (10%) cases had multiple lesion, 13 (59%) had single and in 8 (31%) cases, number of lesions was not mentioned.

In our study most of the TT (17 cases, 11.49%) patient's and all indeterminate leprosy cases showed only one lesion similar to the study by Tiwari M. et.al.[10]

More than 5 lesions were seen in most of the cases of lepromatous leprosy (9 cases) in our study which is also seen similar to study by Tiwari M. et.al.[10]

In our study, upper limb was the most common site of biopsy accounting for 69 (40.59%) cases. Zafar UZ et. al.[11] found that out of 123 cases of granulomatous skin lesions, 29 (23.57%) biopsies were from head and neck region followed by lower limb 20 (16.2%), upper limb 13 (10.5%), from chest and abdomen and pelvis region 9 (7.3%) and back 8 (6.5%).

Gautam K et. al.6, studied granulomatous lesions of the skin with wide age distribution occurring predominantly on the head - neck and the trunk area. Khatib Y. et. al.[12] studied clinicopathological correlation of infectious granulomatous dermatoses, in this study upper limb (33.33%) was the most common site followed by trunk (22.22%) and face (11.11%).

Jayawardhana et. al.[13], studied 128 patients of granulomatous inflammation, out of those patients 32.03% had biopsy from face, 46.88% had biopsy from limbs, 3.91% had multiple sites of biopsy. Thus, site affected by granulomatous skin diseases showed wide geographical variation. However, findings in our study are fairly matched with the findings of Khatib Y. et. al.[12]

In the present study, out of total 170 cases, 148 (87.06%) cases were of leprosy. There were 11 (6.47%) cases of tuberculosis, 3 (1.76%) cases were of actinomycosis and 8 (4.71%) cases were of non-infectious aetiology. In the study of Singh R et. al.[14], 26 out of 112 (23.2%) skin biopsies, was found to have a granulomatous reaction pattern. The commonest aetiology of granuloma was found to be leprosy accounting for 12 (46.16%) cases followed by 11 (42.31%) cases of tuberculosis. Less common causes (3 cases, 11.53%) of granulomatous reaction included erythema nodosum and granuloma annulare. Thus, our findings are in accordance with findings of Singh R et. al.[14]

In the present study, 64.86% cases of leprosy were well correlated both clinically and histologically. Among the leprosy cases, highest clinicopathological correlation was found in the 88.16% cases of borderline tuberculoid leprosy (BT). 52.38% cases of TT, 40% cases of BL, 38.89% cases of LL showed good clinicopathological correlation.

In the study of Tiwari M. et. al.[10] related to clinic –histopathological correlation of leprosy, maximum clinico-histopathological correlation was seen in BL (87.5%) followed by BT (68.1%), TL (66 %) and LL (50%). Only 28% of IL was correlated with clinical diagnosis and 50% cases of IL were clinically diagnosed as BT. Khamanakar S. et. al.[9] studied recent trends in leprosy, in this study clinico-histopathological correlation was seen in LL (85.71%), TT (80%), followed by BL (75%) IL (50%) and BT (42.85%). Least correlation was seen with BB (0%). Overall concordance of diagnosis was seen in 74.04% cases. Manandhar U et. al.[15] studied clinic-histopathological correlation of skin biopsies in leprosy. In this study Clinical and histopathological correlation was seen in 34 cases (45.33%). The correlation was highest in borderline tuberculoid (63.15%) followed by borderline lepromatous (57.14%) and lepromatous leprosy (57.14%). In our study overall clinico-histopathological correlation in leprosy patients is 64.86% which is similar to the study by Khamanakar S. et.al.[9] and Tiwari M. et. al.[10] There is maximum concordance in borderline tuberculoid cases (88.16%) similar to study by Manandhar U.et. al.[15]

In present study total correlation between clinical and histopathological diagnosis for tuberculosis was 55.56%. Highest correlation was seen among the cases of lupus vulgaris (75% cases). Similar correlation was noted by Subhra dhar and Sandipan dhar.[16]

In present study in TT patients 18 (90%), 13 (65%) and 16(80%) patients had nerve, blood vessels and adnexal involvement respectively. In LL patients 4 (36.36%) patients had adnexal and one patient had blood vessels involvement. In ENL patients 1 patient had blood vessel and one patient had adnexal involvement.

In tuberculosis cases, one patient of Erythema Induratum (one case) had blood vessels involvement and all 6 patients of lupus vulgaris had adnexal involvement. No nerve involvement is seen in Tuberculosis. These findings are similar to the findings of Singh A. and Ramesh.[17]

In present study out of 148 cases of leprosy 65 (43.92%) cases had positive Fite Faraco stain. Among the leprosy cases Fite Faraco positivity was seen in 34.55% cases by Potekar RM et. al.[8], 25.74% cases by Permi HS et. al.[18]

In present study, 24 (36.92%) patients had 1+ bacillary index, 4 (6.15%) patients showed 2+ bacillary index, 14 (21.54%) patients had 3+ bacillary index, 10 (15.38%) patients had 4+ bacillary index, 3 (4.62%) patients had 5+ bacillary index and 9 (13.85%) patients had 6+ bacillary index.

In the study of Tiwari M et. al.[10] out of 53 leprosy patients 4 (7.55%) patients had 1+ bacillary index, 2 (3.77%) patients had 2+ bacillary index, 2 (3.77%) patients had 3+ bacillary index and 3 (5.66%) patients had 4+ bacillary index. Thus, findings of our study are correlated with findings of Tiwari M. et. al.[10]

In the present study, all 3 cases of actinomycosis showed PAS and Gram stain positivity. Gupta K. et. al.[3] found that all 4 cases of actinomycosis were PAS and Gram stain positive.

In present study Zeihl Neelsen stain (ZN) was done in 11 cases of tuberculous skin lesions. Out of them, only 2 cases (18.18%) show positivity for acid-fast bacilli. Permi HS et. al.[18] found 27 (20.74%) cases out of 130, had ZN positivity. Pawale J. et. al. found positive ZN stain in 19 (22.62%) cases out of 84.

Conclusion

To achieve the maximum clinicopathological correlation, the dermatologist should have high

suspicion about granulomatous lesion as well as the pathologist must be aware about the technique and interpretation of skin biopsies of granulomatous lesion. National Leprosy and Tuberculosis eradication programs are being implemented by Government of India. Though the effective measures are there, the prevalence of leprosy is still high in our society. In the present study, prevalence of leprosy was found to be 87 %. So, in order to reduce or eliminate the prevalence of leprosy, more exaggerated efforts are needed.

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