



Original Article

Histopathological study of cutaneous granulomas

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ABSTRACT

Background: Cutaneous granulomas comprise a wide spectrum of diseases that are frequently encountered. Since clinical assessment alone is insufficient in most of the cases, skin biopsies are a basic requisite in evaluating these lesions. Histopathological examination, although helpful in deciding the nature of granulomas and etiology in most of the cases, maybe noncontributory in some cases, thus requiring further ancillary tests such as microbial culture, polymerase chain reaction.

Materials and Methods: This prospective cross sectional study enrolled 109 cases of skin biopsies after histopathological confirmation of granulomatous lesions. The specimens were received at the Department of Pathology from 14th April 2017 to 13th April 2018.

Results: Out of 650 skin biopsies, 109 cases (16.8%) were diagnosed as granulomatous lesions on histology. Male predilection was noted and age group of 31 to 40 years was the commonest affected. Upper extremities were more commonly involved. Leprosy was the commonest etiological agent and tuberculoid granulomas were the commonest type based on their histology.

Conclusion: Leprosy was the most common cause of cutaneous granuloma followed by Tuberculosis, fungal infection and foreign body reaction. Among the cases of leprosy, borderline tuberculoid leprosy and tuberculoid leprosy were the commonest subtype.

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INTRODUCTION

Granulomas are focal chronic inflammatory response characterized by a collection of activated histiocytes and multinucleate giant cells that may or may not have a cuff of surrounding lymphocytes or show necrosis. Granulomas occurring in the skin have numerous etiologies and accordingly variable clinico-pathological presentations. The etiologies range from infections like tuberculosis, leprosy, fungal infections to other causes like foreign body, sarcoidosis, necrobiosis and drug reactions. Thus, an etiological classification is unsatisfactory.

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Based on the histology, granulomas can be classified into seven types, namely Sarcoidal, Tuberculoid, Suppurative, Necrobiotic (Palisaded), Foreign body, Xanthogranuloma and Miscellaneous.¹ Many conditions described within this group may show only non-specific changes in the early or late resolving stage.¹ The histological appearances will also depend on the stage of the disease process and treatment status. Fully developed granulomas with sheets of epithelioid histiocytes and giant cells are easily recognized, but more subtle lesions containing a few epithelioid histiocytes still qualify as granulomatous lesions.

The occurrence of different types of granulomatous lesions of the skin varies according to the geographical location.² It is necessary in any granulomatous dermatitis to exclude an infectious cause. Leprosy constitutes majority of the cases of granulomatous skin lesions in our region.

Skin biopsies are mandatory in suspected cases to confirm the presence of granulomatous reaction and to identify the etiology. In many cases, the clinical and pathological appearances overlap, making definitive diagnosis of the lesions difficult. Special stains, culture for organisms, and molecular techniques may be required to reach a diagnosis.³ But since all of these investigative approaches were not available in our laboratory setting, a definite diagnosis was not obtained in some of the cases.

MATERIALS AND METHODS

This prospective cross sectional study was carried out from 14th April 2017 to 13th April 2018 at the Department of Pathology, of TUTH. Permission from ethical review committee was taken. The study enrolled 109 cases of skin biopsies after they were histopathologically confirmed to be granulomatous lesions. Granulomatous lesion of anogenital region, nasal cavity and ocular adnexa were excluded because these sites include mucosal surfaces and can deviate the study from being purely cutaneous lesions.

All skin biopsies received in the department were fixed in 10% formalin and subjected for tissue processing. The sections were then stained with Hematoxylin & Eosin and examined under the microscope. Cases that showed

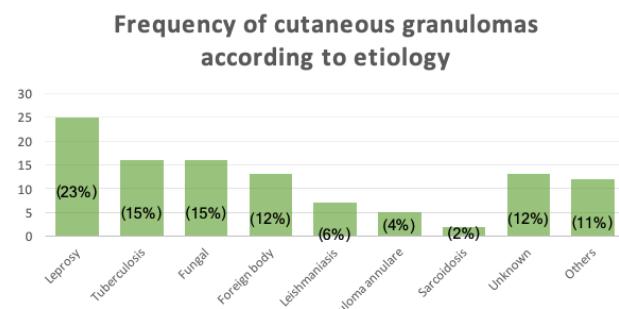


Figure 1: Distribution of cutaneous granulomas according to etiology

granulomatous reaction pattern were chosen for the study. Informed consent was obtained from the patients and their relevant clinical findings and other investigation findings were collected in a predesigned proforma. Data entry and analysis was done by using SPSS 24 version. Frequency and cross-tabulations were used to determine the frequency of various lesions. Age, sex, clinical feature, anatomical site of lesion, clinical diagnosis and histological diagnosis were the variables studied.

RESULTS

Within the study period, skin biopsies comprised of 650 cases, out of which 109 cases were histologically diagnosed as granulomatous lesions. Granulomatous diseases frequented among 31 to 40 years age group with a mean age of 39.3 years. Males were affected more with a Male: Female ratio of 1.3:1. Upper extremities were involved in majority of cases (32%) followed by head and neck region (28%). Most common clinical presentation was as plaques (40.3%). Commonest cause of cutaneous granulomas was Leprosy (n=25; 23%), followed by Tuberculosis (n=16; 15%). Other etiologies are shown in figure 1. Definite etiology was not determined in 12% cases.

Histologically, most common type of granuloma was tuberculoid granuloma (n=47; 43%), followed by suppurative granulomas (n=25; 23%). Equal incidence of xanthogranulomatous and foreign body type granulomas were noted (fig. 2).

Sarcoidal granulomas comprised of 3 cases, 2 (66%) of which were of Sarcoidosis and 1 (33%) case of Cutaneous Crohn's disease. The case of Cutaneous Crohn's disease had colonoscopic findings suggestive of Crohn's disease with skin lesion in the buttock showing multiple draining sinuses and histologically sarcoidal granuloma closely apposing the epithelium.

Among 47 cases of tuberculoid granulomas, 17 cases were leprosy (36%) followed by 15 Tuberculosis (32%). Six cases of tuberculoid granulomas were of unknown etiology (13%) (fig.3).

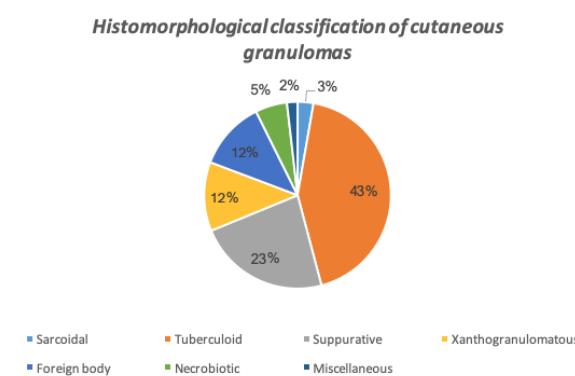


Figure 2: Histomorphological classification of cutaneous granulomas

Etiologies of tuberculoid granulomas

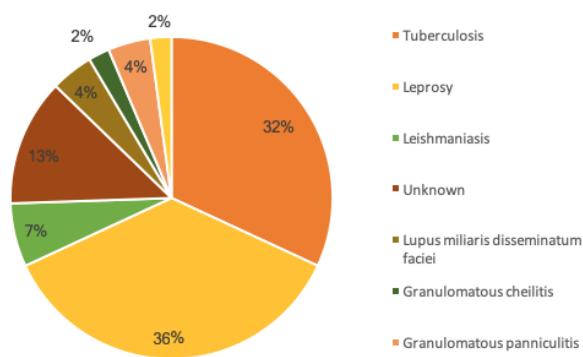


Figure 3: Pie chart showing etiologies of tuberculoid granulomas

Among the 17 cases of leprosy, tuberculoid leprosy and borderline tuberculoid leprosy comprised of 8 cases each and 1 case was of Mid-borderline leprosy.

Out of 15 cases of cutaneous tuberculosis with epithelioid granulomas, 12 cases were Lupus vulgaris (79%) and 2 cases were of Scrofuloderma (21%). One case of scrofuloderma showed suppurative granuloma. Acid fast bacilli were detected in all cases of Scrofuloderma and one case of Lupus vulgaris.

Most common causes of suppurative granulomatous diseases was fungal infection (n=15), followed by Leishmaniasis (n=2; fig. 4). All the causes of suppurative granulomatous conditions are shown in fig.⁴ Among the fungal

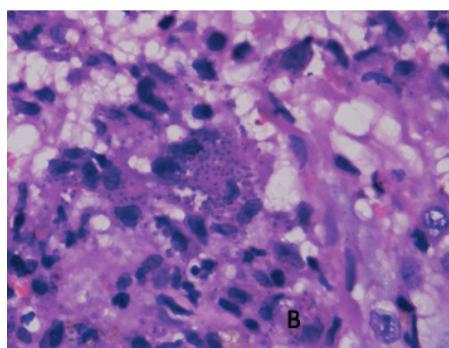
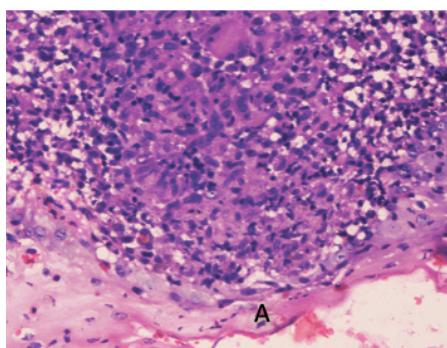


Figure 4A: Cutaneous leishmaniasis showing thinned out epidermis with multiple tuberculoid granulomas in the dermis (HE stain; X200). **4B:** High power magnification showing intracytoplasmic trophozoites of Leishmania (HE stain; X1000).

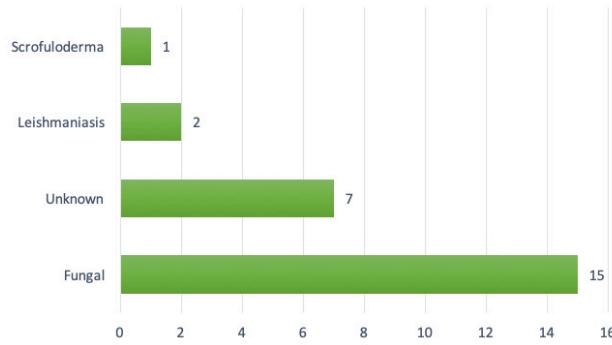


Figure 5: Etiologies of suppurative granulomatous lesions

infections, Sporotrichosis (n=4; 25%), Histoplasmosis, Chromoblastomycosis and Cryptococcosis (n=1; 6.3%) were identified one each. Rest of the cases did not yield any organisms but clinically and histologically favored fungal infection.

Xanthogranulomatous lesion was commonest in Leprosy (n=8; 61%) comprising of 4 cases each of Lepromatous leprosy (16%) and Borderline lepromatous leprosy (16%). This was followed by Leishmaniasis (n=2; 15%), Cryptococcus (n=1; 8%) and atypical mycobacterial

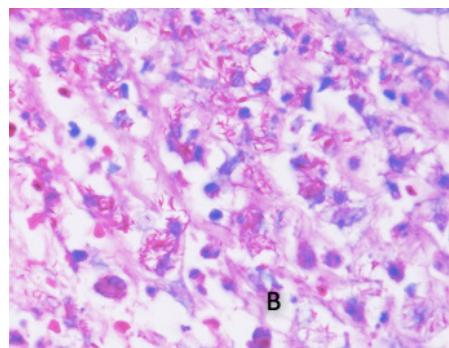
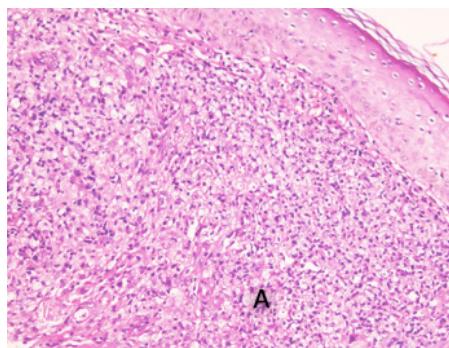


Figure 6A: Atypical mycobacterial infection showing focal epidermis with xantho-granulomatous lesion in the dermis (HE stain; X100). **6B:** High power showing clumps of acid fast bacilli (Fite stain, X1000).

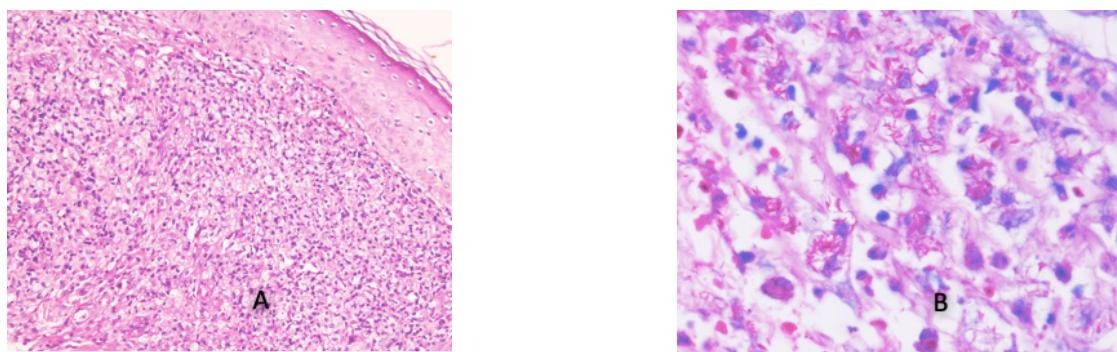


Figure 6A: Atypical mycobacterial infection showing focal epidermis with xantho-granulomatous lesion in the dermis (HE stain; 100). **6B:** High power showing clumps of acid fast bacilli (Fite stain, X1000).

infection (n=1; 8%, fig. 6A,B). Necrobiotic granulomas were seen in Granuloma annulare (n=5; 83%) and rheumatoid nodule (n=1; 16%).

Special stains were performed in 95 cases and the results are shown in Table 2. Out of the total 109 cases of cutaneous granulomas diagnosed on histology, 69 cases correlated with clinical diagnosis (63%). Granulomatous lesion was not suspected clinically in rest of the cases.

DISCUSSION

Cutaneous granulomas are commonly encountered in skin clinics and pose considerable amount of diagnostic dilemma to the dermatologist. Skin biopsy helps confirm a granulomatous reaction and further may point towards a diagnosis in many cases. However, histology alone may also not be sufficient in many cases and other adjunctive tests may be essential to come to a final diagnosis.

In the current study, granulomatous skin lesions constituted 16.7% of total skin biopsies and 1.32% of all the biopsy specimens received in our department. The values are higher than studies conducted in India, Srilanka and Pakistan. A study in Kolkata, India⁴, showed 14.53% of skin biopsies comprising of granulomatous lesions while another in Kandy, Srilanka⁵ showed 8.3% and 4.6% in Pakistan.⁶ This discrepancy maybe due to the lower number of total skin biopsies compared to the other studies where the number of skin biopsies exceeded 1500. Also, although leprosy has been said to be eradicated from Nepal since 2010, department of health services of the government of Nepal has reported an increasing incidence of new cases of leprosy exceeding 3000 new cases each year.⁷ This may also have contributed to the increased incidence of cutaneous granulomas in this region.

The commonest cause of cutaneous granuloma was Leprosy followed by Tuberculosis and fungal infection in the current study. This was similar to the study done by Chakrabarti et al.⁴ however, fungal infections were not as common in current study. In the study by Dutta et al.⁸ leprosy was the commonest followed by fungal infections and then by

Tuberculosis.

Granulomatous lesions affected people from 4 to 85 years in current study and the most common age group affected was 31 to 40 years of age. In the study by Gupta et al.⁹, maximum number of cases occurred in the third decade. Studies by Gautam², Chakrabarti⁷ and Gupta⁹ showed a male predominance which correlated with the present study but female predominance was noted by Kumbar et al.¹⁰

Majority of the lesion were affecting upper extremity in our study which was similar to Dutta's study⁷ and contrary to Zafar's study⁶ where head and neck were commonly affected.

Classifying the granulomas histologically, tuberculoid granulomas were the commonest type, similar to that in other studies.^{2,4,6} Among the tuberculoid granulomas, Leprosy was the commonest cause in the current study, which is in concordance with other studies^{5,11} but contrasting from Zafar's study⁶ in which tuberculosis was commonest. Males were more commonly affected by leprosy with a ratio of 1.5:1, similar to that seen in Bal's study¹¹ showing ratio of 1.5:1. Majority of the cases of leprosy were borderline tuberculoid and tuberculoid leprosy according to Ridley Jopling classification which had equal incidence (32% each, 8 cases each). Most of the studies showed borderline tuberculoid leprosy to be the commonest^{2,4,11} including one done previously in our institute.¹² However, few studies also showed Tuberculoid leprosy to be more common.^{13,14} The granulomas were similar to the non-caseating granulomas in Tuberculosis. Modified Fite stain revealed lepra bacilli in 1 case of Borderline Tuberculoid type (BT). To differentiate the rest of the lesions from Tuberculosis, location of granulomas around neurovascular bundles and skin adnexa with proper clinical presentation were useful. Ten cases had loss of sensation clinically and all the cases had periadnexal and perineural granulomatous inflammation, thus diagnosed as leprosy.

After leprosy, the second commonest cause of tuberculoid granulomas was cutaneous tuberculosis, which comprised of 12 cases of lupus vulgaris and 3 of scrofuloderma. These

findings are in concordance with the other studies.^{6,8,9} Female preponderance with a ratio of 1.2:1 was noted similar to that in the study by Yasmeen et al.¹⁴ Common site of involvement was head and neck which is also in concordance with other studies.^{2,15} On histology, epithelioid granulomas in the dermis along with necrosis was noted in 4 cases (36%) of Lupus vulgaris and all 3 cases (100%) of scrofuloderma, comparable to the study by Dutta et al.⁸ One case of Scrofuloderma showed suppurative granulomatous reaction. Acid fast bacilli was detected in 1 case of lupus vulgaris and 3 cases of Scrofuloderma, similar to that in other studies.^{6,8}

Cutaneous leishmaniasis accounted for 6% of total cases. This is similar to that in the study by Zafar⁶ done in Pakistan (7.3%) and Jayawardhana⁵ in Srilanka (8.6%) but higher than those in the studies by Gautam² in Mangalore, India (3.7%) and Bal¹¹ in Chandigarh, India (1.16%). The variable values maybe due to regional variation in endemicity of Leishmaniasis. Four out of seven cases were female in contrast to other studies showing male predominance.^{2,4} Most lesions were nodules like in the study by Chakrabarti et al.⁴ Out of these 3 cases showed epithelioid morphology, 2 were xanthogranulomatous and 2 were suppurative with the organism staining for Giemsa stain in all the cases. This was similar to findings in Zafar's study⁶ where 3 cases had epithelioid granuloma and 6 cases has non epithelioid granulomas. The suppurative lesions were secondary to ulceration in both the cases.

Other miscellaneous causes of epithelioid granulomas included two cases of nodular vasculitis/lobular granulomatous panniculitis and granulomatous rosacea. The case of granulomatous rosacea was not suspected clinically. On histology there were dilated follicular infundibulum with follicular plugging and epithelioid granulomas in the dermis some of them surrounding the hair follicles. Occasional cases of granulomatous rosacea were noted in other studies as well.^{6,9} The two cases of nodular vasculitis showed epithelioid granulomas infiltrating the fat lobules along with multinucleated giant cells and features of vasculitis. Stain for acid fast bacillus was negative in both cases.

Suppurative granulomas comprised of 23% cases, which was much higher than those in other studies ranging from 1.9% to 10.5%.^{2,9} Sixteen cases were of fungal infection, out of which 4 cases were of Sporotrichosis and one each of Cryptococcus and Histoplasma, all of which were positive on PAS staining. Remaining ten cases were reported as fungal infections based on clinico-histomorphological findings. The suspected histoplasma organism on H and E stain was further grown on fungal culture media and was morphologically consistent with Histoplasma. One case of Chromoblastomycosis showed suppurative granulomatous reaction with copper pennies like thick walled brown spores within giant cells and extracellularly. The patient with Cryptococcosis had disseminated cutaneous lesions

without any known co-morbidities and on histology showed xanthogranulomatous reaction pattern with encapsulated round to oval organism positive on PAS and Alcian blue stain. Histoplasmosis, Chromoblastomycosis and Cryptococcosis were also noted in Gupta's study.⁹ Sporotrichosis and Chromoblastomycosis were seen in the study by Dutta⁸ and only the latter in Chakrabarti's study.⁴

Xanthogranulomatous reaction was noted in 13 cases (12%), higher than that in Chakrabarti's⁴ study (6.9%). This comprised of 4 cases of Lepromatous leprosy, 4 cases of Borderline lepromatous leprosy, 2 cases of cutaneous leishmaniasis and 1 each of Cryptococcus and Atypical mycobacteria. The cases of multibacillary leprosy showed collections of foamy histiocytes in the dermis which on Fite stain revealed high bacillary load. The case of atypical mycobacteria histologically revealed xanthogranulomatous reaction in the dermis which on Z-N stain revealed plenty of acid fast bacilli.

Foreign body granulomas comprised of 12% cases, similar to Mohan's study¹⁶ showing 14%. The values were much lower in other studies.^{6,8} Majority of the cases were epidermal/dermoid cysts, secondary to rupture of the cyst and release of keratin against which granulomatous reaction ensued. Cysticercus, melanocytic nevus, pilonidal sinus, suture and unknown foreign bodies were other causes of foreign body granulomatous reaction.

Among the necrobiotic granulomas, 5 cases were of Granuloma annulare (4%), similar to that in other studies.^{2,17,18,19} Among the 5 cases, 3 were male. Similar male preponderance was noted in Mohan's study¹⁶ but rest of the studies showed female preponderance. Morphologically, all cases showed necrobiotic foci with palisading histiocytes, similar to that in Mohan's study¹⁶ with central mucin positive for Alcian blue. This is in contrast to Gautam's study² showing predominantly interstitial pattern.

Sarcoidal granulomas were seen in 3 cases comprising of 2.7% of the total cases. This was similar to that in the study by Bal et al¹¹ which showed the finding in 2.6% of the cases. Other studies showed 1.6% and 1.9% incidence.⁶ Among the 3 cases of sarcoidal granuloma in this study, two cases were diagnosed as Sarcoidosis. Among these 2 cases, one case had mediastinal lymphadenopathy with raised serum calcium levels. The other case, however, lost to follow up so no clinical history could be evaluated. Both cases, on histology, revealed non-caseating epithelioid granuloma devoid of inflammatory cells. One case of sarcoidal granuloma was diagnosed as Cutaneous Crohn's disease. The patient had colonoscopic findings suggestive of Crohn's disease with plaques in the buttock showing multiple draining sinuses. On histological examination, sarcoidal granulomas were noted in the dermis that was closely apposing the epidermis. No foreign body was detected.

Table 2: Special stains positivity in different diseases.

Etiology	Special stain							
	Modified Fite positive	Giemsa positive	PAS positive	AFB positive	Ver-hoeff positive	Alcian blue positive	None	Total
Leprosy	9	-	-	-	-	-	16	25
Tuberculosis	-	-	-	4	-	-	12	16
Fungal	-	-	6	-	-	-	10	16
Leishmaniasis	-	7	-	-	-	-	-	7
Sarcoidosis	-	-	-	-	-	-	2	2
Granuloma annulare	-	-	-	-	-	5	-	5
Others	-	-	-	1	1	-	9	11
Unknown	-	-	-	-	-	-	13	13
Total	9	7	6	5	1	5	62	95

There were 2 cases under the miscellaneous category that included one case of granulomatous vasculitis and one of annular elastolytic giant cell granuloma. In case of granulomatous vasculitis, vasculitis was suspected clinically, however, no further clinical data was available, thus a diagnosis of granulomatous vasculitis was given. Granulomatous vasculitis was noted in Zafar's study⁶ as well. The second case was annular elastolytic giant cell granuloma. There have been case reports of this rare entity and female predominance was noted in some of the reports²⁰ with occurrence on both sun exposed and non-sun exposed sites. Our case was female with lesion on the upper back. The diagnosis was not suspected clinically, however, on histology, there was a central zone devoid of elastic fibres surrounded by increased amount of thick elastotic material. This was further surrounded by histiocytes and occasional giant cells. The elastic fibres were demonstrated by elastin stain (Verhoeff-van Gieson stain).

Definite etiological agent could not be determined in 13 cases (12%). This is higher than Permi's study²¹ showing 8.7% and lower than Adhikari's study²² showing 28.9% cases of unknown etiology. Further workup with other ancillary tests like PCR studies, in situ hybridization, immunofluorescence maybe helpful, however, these were not availability at our institute.

Special stains were performed in 95 cases. Foreign body granulomas were not subjected to special stain. Ziehl-Neelsen stain for acid fast bacilli was positive in 4 cases of all epithelioid granulomas. Among the cases of tuberculosis, this comprises of 25% cases showing AFB positivity. Out of these, 9 cases had caseating necrosis with 3 cases showing acid fast bacilli. Only one case of non caseating granuloma yielded acid fast bacilli. Thus acid fast bacilli was noted in 33% of caseating granulomas and 2.6% of non-caseating granulomas. This is similar to the study by Zafar et al⁶ and Gautam et al², both showing 25% positivity in caseating and 2.8% in non caseating granulomas. 75% of

Scrofuloderma yielded the bacilli and both cases of LMDF were negative for bacilli. This is in concordance to Gupta's and Bal's study.^{9,11}

Lepra bacilli were noted in 9 cases of leprosy, 1 of them was borderline tuberculoid and 4 cases each of lepromatous leprosy and borderline lepromatous leprosy. Thus, acid fast bacilli was seen in 36% of all leprosy cases, similar to that in Bal's study¹¹ showing 36.4% and slightly higher than Permi's study²¹ showing 25%. In cases of suppurative granulomas, fungal organisms were noted in 6 cases (37%) and copper penny like organism was noted in one case of Chromoblastomycosis. PAS positivity was 24% in one study²³ which is slightly lower than that in this study. Leishmania organism was identified in all the 7 cases similar to Chakrabarti's study⁴ but in contrast to Bal's study¹¹ where Leishmania was seen in 50% cases. Mucin was noted in all cases of Granuloma annulare which was highlighted by Alcian blue stain. This finding was close to that in another study by Cheng et al²⁴ showing mucin in 93.2%.

Clinical correlation was noted in 69 out of 109 cases (63%). This is in concordance to Gautam's study² showing 61.3% and lower than that in Permi's study²¹ showing 92% concordance. Among the 25 cases of leprosy, 5 were clinically discordant and maximum correlation was noted in lepromatous and borderline tuberculoid leprosy. This is in concordance to Manandhar's study.¹² Overall concordance was noted in 80% cases of leprosy, similar to that in Nadkarni's study²⁵ with 82% correlation and Chhabra's study²⁶ with 78.8% correlation. Tuberculosis cases showed 68.7% concordance, similar to that in the study by Soli et al²⁷ showing 68.4% concordance. Similarly among the fungal infections, 68.8% were concordant clinically, similar to study by Sivayogana R et al²⁸ showing 77% correlation. Cutaneous leishmaniasis showed 43% clinico-pathological correlation. This is in concordance with Bari's study²⁸ in Pakistan showing 56.6% clinico-pathological correlation.

Ten out of thirteen cases of granulomatous inflammation that were of unknown etiology were clinically suspected to be granulomatous lesion, thus showing 77% clinicopathological correlation.

CONCLUSIONS

Biopsies for granulomatous skin lesions constituted 16.7% of total skin biopsies. Patients were more common in fourth to fifth decade with male predominance. The most common cause for cutaneous granulomas was Leprosy. Histologically, the commonest form of granulomas was tuberculoid granuloma. Sixty three percent cases showed clinico-pathological correlation. Therefore, skin biopsies are an integral part of evaluating cutaneous granulomatous lesions and correlation with clinical findings and special stains can help in approaching the diagnosis in about two-thirds of the cases.

Conflict of interest: None

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