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Histopathological Evaluation of Granulomatous Skin Lesions: A Study from North India

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ABSTRACT

Background and objectives: Granulomatous disorders of the skin are frequently encountered in clinical practice and require histopathological confirmation due to a considerable etiological and clinical overlap. A single histopathological pattern may be produced by many causative agents and at the same time, a single cause can present with varied histopathological patterns. The present study was performed to evaluate the histomorphological patterns of granulomas in various granulomatous skin lesions and to identify the causative agents.

Methods: The study (both prospective and retrospective) was carried out in the department of pathology over 5 years. All skin biopsies were evaluated for the presence of granulomas. Detailed analysis of the histopathological pattern of granulomas was performed and categorization was made according to the type and etiology. Special stains were also used when required. A clinicopathological correlation was established with the Kappa statistic.

Results: Of 1,150 skin biopsies, granulomatous skin lesions were observed in 325 cases. Histiocytic granuloma pattern was the most common subtype (55.7%). The predominant etiology of granulomatous inflammation was leprosy (93.5%), followed by cutaneous tuberculosis (2.7%). The cases of Hansen's disease showed a maximum clinicopathological correlation (58.5%).

Conclusion: Histopathological examination is the gold standard for the diagnosis and subtyping of granulomatous skin lesions. Varied morphologies of granuloma patterns were observed in our study, and infectious diseases were the causative agents in the majority of cutaneous granulomatous disorders.

Keywords: Antibodies, Antinuclear, Lupus Erythematosus, Systemic, ELISA, Diagnosis.

INTRODUCTION

Granulomatous inflammation is a chronic inflammation in which confluent granulomas are formed in response to insoluble, nondigestible, or gradually released antigens with varying degrees of necrosis and differing cell components (1, 2). Inflammation is considered to be granulomatous if at least 50% of the infiltrate is made up of histiocytes or macrophages (3). Granulomatous inflammation is classified as a type of intravenous hypersensitivity reaction and may be induced by various kinds of infections, autoimmune, toxic, allergic, and neoplastic conditions (4). There is considerable difficulty and ambiguity in the classification of granulomatous skin diseases since a single histopathological pattern is produced by many causative agents, while a single cause may present various histopathological patterns (5). Therefore, the present study was carried out to determine the frequency and histomorphological patterns of different granulomatous skin lesions and to identify the various causative agents.

MATERIALS AND METHODS

The present study was conducted at the Department of Pathology of a tertiary care institute. The study was approved by the local institutional ethics committee (approval number: IEC/GMC/2019/822, Dated: 19.12.2019) and was conducted in two parts with a retrospective analysis for four years (November 2014 - October 2018) and a prospective analysis for one year (November 2018 - October 2019). After obtaining a detailed clinical history, record of relevant data, and clinical findings from the histopathology requisition form, skin biopsy specimens were grossed. After routine tissue processing, sections were sliced and stained with hematoxylin and eosin (H&E). Special stains such as acid-fast bacilli, periodic acid-Schiff, and Giemsa were also used when required. Follow-up cases as well as inadequate, non-cutaneous, and poorly preserved biopsies were excluded from the study.

In cases where slides were not available, fresh sections from the available paraffin blocks were sliced, stained, and then reviewed. All biopsy specimens with histological evidence of granulomas were included in the study. All granulomas were examined under polarized light to detect or exclude birefringent foreign material.

Quantitative data were expressed using mean and standard deviation. Qualitative data were expressed using frequency and percentage. All analyzes were carried out in SPSS (version 21) and Microsoft Excel 2016.

RESULTS

Of 1,150 skin biopsies, 576 cases (50.09%) were either clinically diagnosed or suspected cases of cutaneous granulomatous lesions. Of these cases, the clinical diagnosis of infectious granulomatous disorders was made in 560 cases (97.22%). The histopathological diagnosis of infectious granulomatous disorders was made in 361 cases (62.67%) comprising 343 leprosy cases (95.01%), nine cutaneous tuberculosis cases (2.49%), five sporotrichosis cases (1.39%), and four cutaneous leishmaniasis cases (1.11%).

Cutaneous granulomatous lesions were detected in 325 cases (28.3%) (Table 1).

Table 1- Etiology of various cutaneous granulomatous lesions on histopathology (n=325)

Disease	Number	Percentage
Leprosy	304	93.5
Tuberculosis:		
Lupus Vulgaris	5	1.5
Scrofuloderma	3	0.9
Tuberculosis cutis orificialis	1	0.3
Leishmaniasis	3	0.9
Sporotrichosis	5	1.5
Foreign Body Reaction	1	0.3
Xanthoma	1	0.3
Granuloma Annulare	1	0.3
Sarcoidosis	1	0.3
Total	325	100

Table 2- Patterns of granulomas on histopathological examination (n=325)

Patterns of granulomas	Etiology	Number of cases		Percentage
Histiocytic	Leprosy	180	181	55.7
	Leishmaniasis	1		
Tuberculoid	Leprosy	103	109	33.5
	Tuberculosis	6		
Sarcoidal	Leprosy	6	7	2.2
	Sarcoidosis	1		
Necrobiotic	Leprosy	6	7	2.2
	Granuloma annulare	1		
Suppurative	Leprosy	9	19	5.8
	Tuberculosis	3		
	Leishmaniasis	2		
	Sporotrichosis	5		
Foreign body type		2	2	0.6
Total			325	100

Table 3- Histopathological patterns of granulomas in subtypes of leprosy (n=304)

Subtypes of leprosy	Histopathological patterns	Number of cases	Percentage
Lepromatous leprosy	Histiocytic	75	Histiocytic (59.2%)
Borderline lepromatous	Histiocytic	57	
Histoid leprosy	Histiocytic	17	
Borderline	Histiocytic	31	
Borderline tuberculoid	Tuberculoid	67	Tuberculoid (33.9%)
	Sarcoidal	4	Sarcoidal (1.97%)
Tuberculoid tuberculoid	Tuberculoid	36	
	Sarcoidal	2	
Erythema nodosum leprosum	Suppurative	9	Suppurative (2.95%)
	Necrobiotic	6	Necrobiotic (1.97%)

The age of the patients ranged between 1 and 80 years (mean age: 44.2 years). The frequency of patients was highest in the 21-40 years age group (n=146, 44.92%). In addition, 264 cases (81.2%) were male and 61 cases (18.8%) were female.

On the histopathological examination, various etiologies of cutaneous granulomatous lesions were observed. Infectious etiology was observed in 321 cases. Granulomatous lesions were classified into six histological patterns: histiocytic, tuberculoid, sarcoidal, necrobiotic, suppurative, and foreign-body granulomas. Different granuloma patterns and their respective etiologies are depicted in table 2. The most common granuloma patterns were the histiocytic (55.7%) and tuberculoid (33.5%) types. Borderline, tubercular tuberculoid, erythema nodosum, and histoid leprosy were excluded from the analysis due to negligible mean and variance (<10) (Table 2).

Leprosy was the most common etiology observed in our study (93.5%). It was further categorized according to the Ridley–Jopling.

Lepromatous leprosy (LL) was the most common subtype (24.7%), followed by borderline tuberculoid (BT) (23.4%) (Table 3). The second most common causative agent of

granulomatous skin lesions was cutaneous tuberculosis (2.77%). It was further subcategorized into five cases of lupus vulgaris, three cases of scrofuloderma, and one case of tuberculosis cutis orificialis. The tuberculoid pattern was seen in 66.7% of the cases, while the suppurative type was seen in 33.3% of the cases. The tuberculoid caseating pattern comprised one lupus vulgaris and one tuberculosis cutis orificialis case in which granulomas were found with giant cells and lymphocytic cuffs (Figure 1).

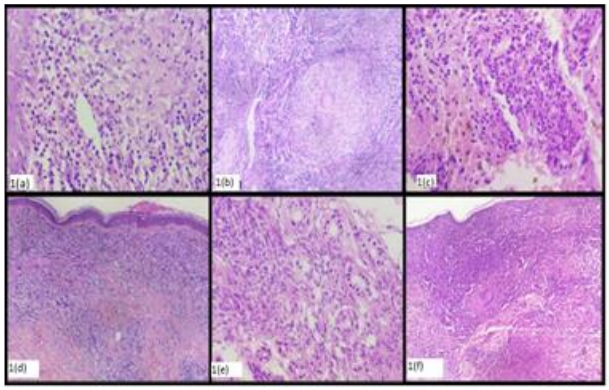

Figure 1. A) Epitheloid granulomas (tuberculoid type) and Langhans type giant cells in the dermis in a case of lupus vulgaris (H&E stain; 40× magnification). B) Tuberculoid granuloma in tuberculosis cutis orificialis (H&E stain; 10× magnification). C) Lepromatous leprosy showing the atrophic epidermis, and large expansile histiocytic granulomas in the dermis (H&E stain; 10× magnification). D) Histiocytic granulomas around appendages in a case of borderline lepromatous leprosy (H&E stain; 40× magnification). E) Tuberculoid leprosy showing epithelioid cell granulomas (tuberculoid type) with a moderate number of lymphocytes and giant cells (H&E stain; 10× magnification). F) Suppurative granuloma with caseous necrosis seen with multinucleated giant cells in a case of scrofuloderma (H&E stain; 40× magnification).

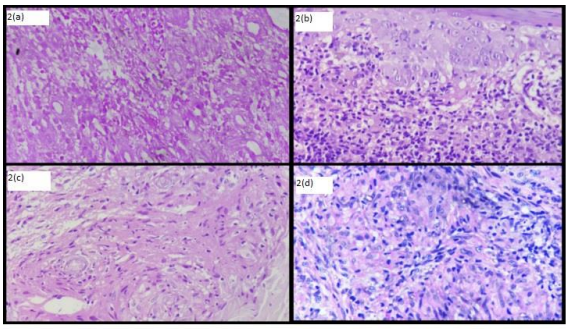

Figure 2- Noninfectious granulomatous dermatoses. A) Suppurative granuloma with neutophillic abscesses in a case of sporotrichosis (PAS stain, 10× magnification). B) Suppurative granulomas along with plasma cells in a case of leishmaniasis (H&E stain; 40× magnification). Inset showing Leishman-Donovan bodies within macrophages (H&E stain; 100× magnification). C) Granuloma annulare showing a palisade of elongated epithelioid histiocytes surrounding degenerated collagen showing fibriniod necrosis (H&E stain; 40× magnification). D) Sarcoidal granulomas in a case of sarcoidosis containing circumscribed epitheloid histiocytes forming circumscribed nodules without necrosis and scant mononuclear cells (H&E stain; 40× magnification)

There were five cases (1.5%) of sporotrichosis, all of which showed the suppurative type of granulomas. Cutaneous leishmaniasis was observed in three cases (0.9%), with the presence of suppurative granulomas in two cases and histiocytic granulomas in one case.

The clinical diagnosis of Hansen's disease (HD) without further categorization was the most common clinical diagnosis in 335 cases (66.73%) out of 502 leprosy cases. The most common subtype was LL (14.02%), followed by BL (11.34%). In 125 cases (37.31%), descriptive reports were given.

The clinical diagnosis of HD was in agreement with the histopathological diagnosis in 210 cases (62.69%). When the clinical diagnosis was made, the most concordant subtype of leprosy was BT leprosy (n=64), in which histopathological diagnosis was made in 30 cases (52.63%). In the rest of the cases, the sample size was not big enough to show any significance.

A normal distribution was seen in the concordant cases of BT, HD, and total leprosy cases. At a 95% confidence interval, histological concordance of all cases

with the clinical diagnosis of BT, HD, and all leprosy cases was 34.6%-59%, 54.8%-65.2%, and 69.1%-76.9%, respectively.
Although a high rate of concordance was calculated for LL and BL, confidence interval calculation was not justifiable due to the small sample size and variance <10.

DISCUSSION

Granulomatous dermatitis refers to an inflammatory skin disorder, which involves the activation of histiocytes. It is commonly observed in North India with overlapping clinical presentations (4). It is difficult to present a complete satisfactory classification of granulomatous dermatoses despite several attempts made in previous literature. Histopathology is the gold standard tool for establishing an accurate diagnosis of various granulomatous skin lesions (5).
In our study, the age of the patients ranged between 1 and 80 years, and the majority of cases were in the 21-40 years age group. These results are similar to the results of some previous studies (4-7). Several factors influence the sex predominance in endemic areas, mainly the opportunity for contact, industrialization, and urbanization as well as social customs and socio-economic barriers, which are rampant in lower and middle strata in all the communities and regions in India.
In the present study, the granulomatous lesions were observed in 325 cases including 321 cases with infectious and four cases with non-infectious etiology. Leprosy was the commonest etiology (93.5%), followed by cutaneous tuberculosis (2.77%). These results are in line with the findings of studies by Grover et al. and Bal et al. (8,9).
Leprosy or HD is a chronic infectious disease caused by *Mycobacterium leprae* and primarily affects the skin and peripheral nerves. It can express itself in different clinic-pathological forms depending on the cell-mediated immunity of the host. In the present study, a majority of cases comprised leprosy, which was subcategorized into five groups according to the Ridley-Jopling classification. Based on the results, LL (24.7%), followed by BT (23.4%), and borderline lepromatous (18.8%). In a study by Jindal et al., LL was the most common subtype of leprosy (10). In our study, of 304 cases of leprosy, AFB was positive in 162 cases (53.3%) including 75 cases of LL and 55 cases of BL. Other studies also found AFB positivity in 36.4% (9) and 28.03% (11) of the cases.
In the present study, nine cases of cutaneous tuberculosis were seen including 5 cases (55.6%) of lupus vulgaris, three cases (33.3%) of scrofuloderma, and a single case (11.1%) of TCO. These results are in agreement with previous studies (8, 11). The wide clinical spectrum of cutaneous tuberculosis relies on the route of infection (endogenous or exogenous), the immune status of the patient, and previous sensitization with tuberculosis. In the present study, four cases (44.44%) were found positive for AFB. Although the demonstration of AFB by Zeihl Neelson stain is specific, the most accurate diagnosis is made by polymerase chain reaction by detecting the mycobacterial DNA in the tissues (12).
In the present study, the granulomatous lesions were classified into six histological patterns (histiocytic, tuberculoid, sarcoidal, necrobiotic, suppurative, and foreign body granuloma) based on the morphology of granulomas, the nature of inflammation, types of necrosis, cellular constituents, and associated changes.
The most common granuloma pattern was the histiocytic pattern (55.7%), including 180 cases of leprosy and a case of leishmaniasis. These were found with a predominant population of histiocytes or macrophages present in dense clusters and sheets. Among 180 cases of leprosy with the histiocytic pattern, 75 cases of LL, 57 cases of BL, 31 cases of borderline, and 17 cases of the histoid variant of LL were observed. Chakrabarti et al. also observed that all LL and most BL cases had histiocytic granulomas (11).
Tuberculoid granulomas constituted the second largest group of granulomas in which infiltrates of lymphocytes were arranged around the aggregates of histiocytes as cuffs. Tuberculoid granulomas were observed in 109 cases (33.5%), including 103 cases of leprosy and six cases of cutaneous tuberculosis. Among the leprosy subtypes, tuberculoid granulomas were observed in 67 cases of BT and 36 cases of tuberculoid tuberculoid (TT). The results are inconsistent with the results of studies by Chakrabarti et al. and Gautam et al.
that reported BT as the most frequent subtype of leprosy (11, 13).
In TT and BT cases, the location of the granulomas around the differentiate them from

sarcoidal and non-caseating tuberculoid granulomas (14).

The third most common granuloma pattern in our study was the sarcoidal pattern (2.2%), comprising six cases of leprosy and a case of sarcoidosis. Among the leprosy subtypes, four cases of BT and two cases of tubercular tuberculoid showed the sarcoidal granulomas where the cuff of lymphocytes was sparse.

Necrobiotic granulomas were seen in six cases of erythema nodosum leprosum and a single case of granuloma annulare. In these cases, histiocytes surrounded fewer cellular areas with fibrinoid necrosis and pale staining collagen fibers. The suppurative (or "mixed cell") granuloma is a common and important pattern of granulomatous inflammation, especially in the Indian population as it is seen in several tropical diseases. It is characterized by a collection of epithelioid histiocytes with scattered multinucleated giant cells, which surround both intact and degenerating neutrophils. In the present study, suppurative granulomas were seen in 19 cases, including nine cases of erythema nodosum leprosum, five cases of sporotrichosis, three cases of tuberculosis, and two cases of leishmaniasis.

Sporotrichosis is caused by *Sporothrix schenckii*, a dimorphic fungus that is found in soil and decomposing material. In our study, five cases (1.5%) of sporotrichosis were diagnosed. The fungal elements were seen as globose, oval to round bodies in all cases and confirmed by periodic acid–Schiff stain. In the study by Chakrabarti et al., seven cases of fungal granuloma were found all of which were typed as suppurative granuloma (11).

Cutaneous leishmaniasis is a protozoan infection caused by various species of the genus *Leishmania*. In the present study, leishmaniasis was observed in three cases (0.9%) with the suppurative type of granuloma in two cases and histiocytic type granuloma in a single case. These findings are consistent with the results of previous studies (9,11). On histopathological examination of LD bodies, the amastigote form of the protozoa was found within macrophages. It may be sometimes difficult to detect LD bodies in paraffin sections, but plasma cell histiocytic infiltrate can suggest the diagnosis (Figure 2).

Non-infectious granulomatous dermatoses (NGDS) are a challenging group of diseases in terms of diagnosis in terms of counseling the patients regarding their prognosis and the possible systemic comorbidities. In our study, amongst the non-infectious group, the foreign body granuloma pattern was found in two cases (0.62%). In addition, a single case of granuloma annulare (0.3%) was found in our study. Gautam et al. and Grover et al. found granuloma annulare in 3.7% and 3.98% of biopsies, respectively (13,15). The granuloma pattern was necrobiotic with the presence of degenerated collagen, perivascular histiocytes, a few scattered fibroblasts, and fibrinoid necrosis.

Sarcoidosis is a chronic inflammatory disease that can affect several organs. In our study, a solitary case of sarcoidosis (0.3%) was observed which showed sarcoidal granulomas, with sparse lymphocytic cuffs arranged around the hard core of epithelioid cells and without caseation necrosis. The initial diagnosis of sarcoidosis was made on skin biopsy and further substantiated by ancillary techniques.

Our study had some limitations. Firstly, only five cases of NGDS were seen. Limited incidence and prevalence of NGDS have precluded the researchers from providing a more varied spectrum, and only a few studies are available in the literature comparing the incidence, demographic factors, and histomorphological variations in different patients and regions. Secondly, our study was performed on a limited sample size. It is recommended to conduct future studies with a multicentric approach to further validate the findings of our study.

CONCLUSION

Histopathological examination is the gold standard for the diagnosis and subtyping of granulomatous skin lesions. Varied morphologies of granuloma patterns were observed in our study, and infectious diseases were the causative agents in the majority of cutaneous granulomatous disorders. A better comprehension of these disorders is required based on the clinical findings, laboratory workup, patterns and morphology of granulomas, and special stains to determine an etiological diagnosis for the proper clinical management.

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DECLARATIONS

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Ethics approvals and consent to participate

The study was approved by the local institutional ethics committee (approval number: IEC/GMC/2019/822, Dated: 19.12.2019).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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