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Original Research Article

A Histopathological Spectrum of Granulomatous Skin Lesions in a Tertiary Health Centre in Western Maharashtra

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Leprosy,
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Abstract

Background: Granulomatous disorders remain to be a major cause of morbidity and mortality amongst samples received in the histopathology department of a tertiary health center. Natural causes of deaths have certain medicolegal concerns in various sudden deaths. The present study was undertaken to assess the histopathological spectrum of various skin conditions that were characterized by a granulomatous reaction pattern on histopathology**. Material and Method:** A Total of 120 patients who presented with clinical features suggestive of granulomatous disorder of the skin, were enrolled during a period of one year prospectively were included in this study. **Statistical analysis and Results:** The mean age of patients was 38.09 years with male predominance (61.7%). 93.3% of cases within the state of Maharashtra. 68(59.16%) cases belong Kuppuswamy class 4. Infectious causes (78.07%) outnumbered non-infectious causes (21.93%). Among infections, leprosy (58.29%; 67 cases) and cutaneous Tuberculosis (14.2%; 17 cases) while among non-infectious causes, erythema nodosum (8.3%) was most common. **Conclusion:** The present study highlights the importance of the histopathological spectrum in arriving at a final diagnosis in cases of granulomatous disorders of the skin. Certain medicolegal concerns can be settled in better way with confirmation of natural causes of deaths.

1. Introduction

A granuloma is defined as a localized aggregation of inflammatory cells such as macrophages, epithelioid cells, giant cells, eosinophils, lymphocytes, plasma cells, etc. with connective tissue and blood vessels, and may contain ingested foreign material or pathogens.[1] Because of the focal and well-defined nature of this reaction, it is called a granuloma (Granul = granule or grain; oma = tumor).[2]

Depending on the pathophysiological stage at which the biopsy is taken, a granuloma can appear ill-defined or well- defined. However, granuloma formation can take place in any tissue depending on the site of the triggering agent, and

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immune mechanism activated by it. Formation of a granuloma begins primarily as an attempt by the body's immune system, to isolate any substance it recognizes as 'foreign' or 'non-self' and is unable to destroy as a whole (a poorly or partially soluble antigen). This process is termed as a granulomatous reaction.[3] It is a type IV Coombs and Gell hypersensitivity reaction.[4]

The cutaneous manifestations of the granuloma are polymorphic, and these dermatoses are diagnosed with a combination of a high index of suspicion based on presenting features and findings on histopathology. In many cases, the clinical or histopathological features do not align, and in such cases, additional investigations may be done. The final diagnosis in most cases, is always a product of histopathological correlation.[5] Hence the present study aims to document the varied presentations of these granulomatous skin lesion, to histological spectrum correlating the presenting skin lesions with their histopathology in order to arrive at the final diagnosis.

2. Materials and Methods:

After obtaining Institutional Ethical Committee approval, this open, prospective, hospital–based, cross-sectional study was conducted in 120 patients having granulomatous skin lesion sample were received in the Department of Pathology of a tertiary health center. All these included patients with skin lesions clinically diagnosed as granulomatous and suffering from tuberculosis, leprosy, sarcoidosis, syphilis, sporotrichosis, chromoblastomycosis, blastomycosis, histoplasmosis, mycetoma, leishmaniasis, atypical mycobacterial infections, botryomycosis, cat scratch disease, lymphogranuloma venereum, malakoplakia, pyoderma gangrenosum, halogenodermas, xanthogranulomas, granuloma annulare, necrobiosis lipoidica, rheumatoid nodule, vasculitis such as Wegener's granulomatosis, Churg-Strauss syndrome, Erythema Induratum, Erythema Nodosum, Takayasu disease, foreign body reactions, granulomatous mycosis fungoides and co-incidental detection of granulomatous reaction on histopathology (in patients who had come to seek advice for some other cutaneous problem).

A detailed history was taken, and sociodemographic data included education and occupations of head of the family, total monthly income of the family, Kuppuswamy`s socio-economic status scale 2021 were noted. Special staining techniques for histopathology were used in relevant cases, if required. For Fite-Faraco staining of tissue sections, sections were deparaffinized with two changes of 12 min each of xylene-peanut oil and stained in carbol fuchsin stain for 30 min, washed in running tap water, decolorized by 5% H_2SO_4 differentiated in 25% ethanol followed by washing again under running tap water. Slides were counterstained with Harris hematoxylin for 3 min. Excess hematoxylin was washed off, blotted, and kept for a few minutes for air dry and finally mounted with DPX (Dibutyl phthalate Polystyrene Xylene). Data recorded in the case record format and obtained via department records was organized in a master chart and was correlated with skin biopsy findings.

Data collected were, final diagnosis after histopathological correlation, proportion of cases where histopathological findings showed a positive correlation and uncommon presentation/ findings, if any were mentioned accordingly. At the end of the study, an analysis was done as to how many histopathologically diagnoses showed the histological features as mentioned in literature, and in how many, histological spectrum was essential in reaching a conclusive diagnosis.

3. Results and Observations:

Total 120 patient's samples were received during the study period. Most of the cases were in the age group of 18-64 years (93.96%) with mean age of 38.09 years and a male predominance (61.7%). Majority i.e., 68 (59.16%) cases belonged to the Kuppuswamy class 4 and 93.3% cases were from within the state of Maharashtra region.

Multiple complaints in a single case have been counted separately. As per our data, (59.62%) 68 cases had raised lesions, being the most common presenting complaint, followed by ulcers (18.42%), white spots (17.52%), swelling (15.78%) loss of sensation (12.28%), and discharge (purulent) (10.52%). Patients most commonly complained of lesions on upper limbs (59.2%), followed by lower limbs (28.3%), and face (0.8%). Exactly 66.9% cases had an insidious onset of lesions and remaining 34.41% reporting sudden onset of lesions. Gradual progressive lesion found in 76.7%, rapidly progressive in 18.3% and non-progressive (5.0%).

Number of infectious causes (78.07%) outnumbered the non-infectious causes (21.93%). Amongst infections, the commonest was leprosy

(58.29% - 67 cases), followed by cutaneous TB (14.2% - 17cases)

Hansen's disease (leprosy):

Out of 120 cases, 66 were clinically diagnosed to have Leprosy. Further this diagnosis was confirmed using SSS and Fite-Faraco staining in all cases. Using SSS sensitivity, specificity, positive predictive value, negative predictive value and accuracy were 48.48%, 100.0%, 100.0%, 66.0% and 74.24% respectively. Whereas using Fite-Faraco staining sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 22.58%, 100.0%, 100.0%, 59.32% and 63.64% respectively.

Histopathological features in Leprosy:

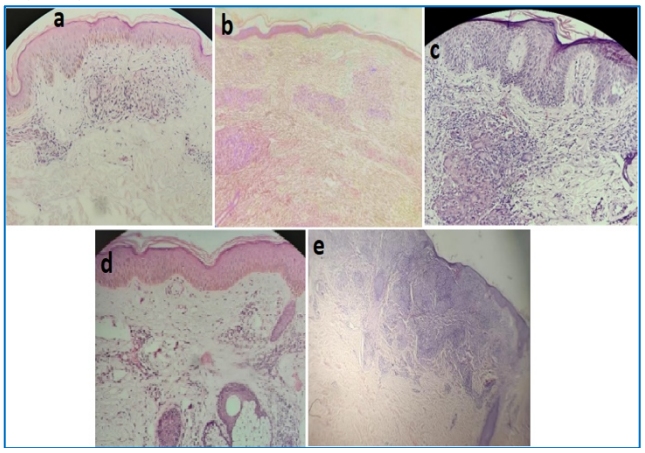
Overall, the most consistent epidermal feature was flattening or loss of rete ridges 42.42%), followed by hyperkeratosis (27.28%), unremarkable epidermal changes (22.3%), and increased basal layer pigment (13.28%). The least consistent features were acanthosis, orthokeratosis, and follicular plugging, each seen in only 3.3% of cases. Acanthosis was appreciated in only Pure Neuritic cases. In the dermis, the most consistent feature overall was a perivascular/ periadnexal / perineural inflammatory infiltrate, seen in 86.3% cases, the cellular components of which (in decreasing order of frequency), were lymphocytes (68.3%), macrophages (25.0%), foamy histiocytes (37.5%), epithelioid cells (13.3%), neutrophils (43.3%), Langhans giant cells (37.5%), and eosinophils (3.1%). Grenz zone was appreciated in only 1 case of type 1 reaction. Majority of biopsies showed unremarkable changes in the subcutaneous tissue.

Histopathological spectrum of Leprosy:

Histopathological spectrum was indispensable for the final diagnosis of Leprosy, and classification into its subtypes. The degree of agreement of histopathological diagnosis was maximum in Histoid and pure Neuritic Hansen's (50%), followed by type 2 reactions, Borderline Tuberculoid Hansen's (BTH), and Borderline Lepromatous Hansen's (BLH). Overall, the strength of histopathological spectrum in this study was found to be 76.754%. This is much higher than the strength of diagnosis after only histopathological examination (only 40.90% cases detected). All cases had Leprosy as a provisional diagnosis,

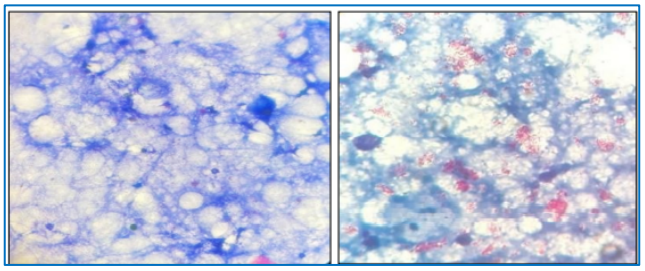
Borderline Lepromatous Hansen's- Microscopy showed a thin Grenz zone with diffuse inflammatory infiltrate and foamy macrophages [**Figure 1(a)**]; Histopathological findings of **Lepromatous Leprosy** showed diffuse lymphocytic infiltration with foamy macrophages with several ill-formed granulomas in mid-dermis [**Figure 1(b)**]; Histopathological findings of **Tuberculoid Hansen's** showed sparse perivascular and periadnexal inflammatory infiltrate comprised of epithelioid cells, lymphocytes and occasional giant cells [**Figure 1(c)**]; Histopathological findings of **Erythema Nodosum Leprosum** showed diffuse and focal granulomatous infiltrate with foam cells and a dense lobular and septal panniculitis [**Figure 1(d)**]; Histopathological findings of **Histoid leprosy** showed upper and mid-dermal granulomas with dermal oedema [**Figure 1(e)**].

Figure 1 (a-e): Histopathological findings of Lepromatous Leprosy



Slit skin smear shown in **figure 2(a)** in a case of BTH with a bacillary index of 2+, compared to **Figure 2(b)** (right), showing a bacillary index of 5+ in a case of LL Hansen's. Abundant acid-fast bacilli with globi or cigar-bundle appearance can be seen in **Fig.2(b)**- signifying a high bacillary load. Modified ZN stain, 40x.

Figure 2 (a-b): Histopathological findings of Borderline tuberculoid Hansen's disease.



Cutaneous tuberculosis:

Cutaneous TB was found more likely to present as a single lesion (63.636%), and in case of multiple lesions, monomorphic (81.818%). A strong association was found to exist between the

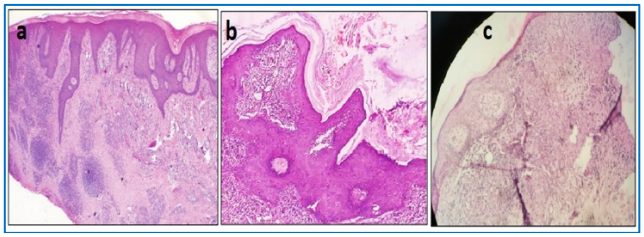
occurrence of cutaneous TB and active/past Tuberculosis or a close contact with Tuberculosis (54.545% cases). Clinical presentations of cutaneous Tuberculosis (TB): The most common skin lesion was a plaque (63.636%), followed by scars (36.364%), ulcers (36.364%). Scarring was a feature seen in both Scrofuloderma and Lupus Vulgaris but absent in TBVC. Lupus vulgaris had the most variable lesions, showing papules, plaques, nodules, ulcers, and scarring. The commonest site of involvement was extremities (54.545%), Lips (1.7%) and face (0.8%) (in decreasing order of frequency).

Histopathology features of cutaneous TB:

In the epidermis, the commonest feature seen was hyperkeratosis (81.818%), followed by acanthosis (54.54%) while dermal features in order of decreasing frequency were an inflammatory infiltrate (100%) (which comprised of lymphocytes (100%), neutrophils (100%), and epithelioid cells forming granulomas (90.909%)

On histopathology, the epidermis was unremarkable, but the dermis showed perivascular and periadnexal lymphoplasmacytic inflammatory infiltrate, areas of haemorrhage and haemosiderin-laden macrophages with extracellular brown pigment. However, there was a strongly positive correlation between clinical and histopathological features in both cases of Scrofuloderma, 100% agreement between clinical and histopathological diagnosis. Histopathological findings of **Lupus vulgaris** showed acanthosis with diffuse mixed inflammatory infiltrate [Figure 3(a)]; Histopathological findings of **Tuberculosis Verrucosa Cutis** showed pseudoepitheliomatous hyperplasia and mixed inflammatory infiltrate with extravasation of RBCs [**Figure 3(b)**]; Histopathological findings of **Scrofulderma** showed dense inflammatory infiltrate with acanthosis, areas of caseation necrosis and dilatation of blood vessels [**Figure 3(c)].**

Figure 3 (a-c): Histopathological findings of Lupus vulgaris



Non-infectious granulomatous disorders of the skin:

The commonest clinical lesion was a papule (56%), followed by plaque (52%), nodule (32%), and the least common lesion was a sinus (4%). On histopathology, the commonest epidermal features were hyperkeratosis (52%) followed by acanthosis (48%). In the dermis, a mixed inflammatory infiltrate was most commonly seen (84%) which showed lymphocytes (84%), plasma cells (32%), neutrophils (20%), eosinophils (20%) and histiocytes (32%) in varying proportions

Histopathological findings of **Cutaneous Malakoplakia** showed epidermal breach (focal ulceration) with areas of hyperkeratosis, and a dermal inflammatory infiltrate of neutrophils, lymphocytes, dilated blood vessels [**Figure 4(a)**]; Histopathological findings of **Pyoderma Gangrenosum** showed ulcerated epidermis with mixed inflammatory infiltrate, no granulomas were seen [**Figure 4(b)**]; Histopathological findings of **Granuloma Annulare** showed hyperkeratosis and Hypergranulosis, with a lymphohistiocytic infiltrate in the dermis, and areas of mucin deposition [**Figure 4(c)**]; Histopathological findings of **Granulomatous Cheilitis** showed multiple well-formed epithelioid cells granulomas with lymphocytic inflammatory infiltrate [**Figure 4(d)**]; Histopathological findings of **Tattoo Granuloma** showed mounds of hyperkeratosis with mixed inflammatory infiltrate in upper dermis [**Figure 4(e)**]; Histopathological findings of **Erythema Nodosum** showed dense lymphocytic inflammatory infiltrate in the dermis and subcutaneous tissue [**Figure 4(f)**]; Histopathological findings of **Hidradenitis Suppurative** showed periadnexal lymphocytic inflammatory infiltrate [**Figure 4(g)**]; Histopathological findings of **Wegeren's Granulomatosis** showed mixed inflammatory infiltrate with abundant neutrophils, no eosinophils and many lymphocytes [**Figure 4(h)**].

Figure 4 (a-h): Histopathological findings of Cutaneous Malakoplakia

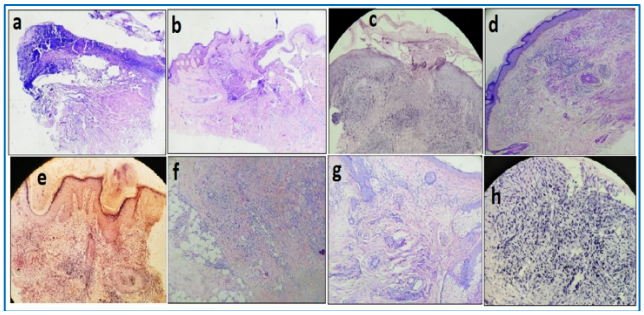


Table 1 represents the percentage of clinical and histopathological agreement in each diagnosis encountered in this study. The overall

histopathological concordance in this study was found to be 87.24%.

Table 1: Histopathological correlation and degree of agreement

Diagnosis	% of Histopathological concordance
Leprosy	86.38
Cutaneous TB	87.87
Granuloma annulare	71.42
Erythema Nodosum	100
Granulomatous cheilitis	100
Cutaneous malakoplakia	100
Wegener's granulomatosis	100
Pyoderma Gangrenosum	54.54
Hidradenitis suppurativa	100
Foreign body (tattoo) granuloma	100
Average value	87.24

4. Discussion:

In the present study, highest number of cases were in the third and fourth decade of life, which are the periods of maximum physical exertion, active social and professional life and greater personal or professional stress. These factors may be contributory to the occurrence of these disorders in this age-group. The incidence among males was twice that of females. Males being more likely to work outdoors, suffer trauma, migrate, or travel to different regions, have been known to be more commonly affected with infectious diseases.[6,7]

Maximum cases (59.16%) belonged to Kuppuswamy class IV. The lack of sanitation, frequent overcrowding, and poor hygiene prevalent in this socio-economic stratum play a major role in the spread of infectious diseases. Majority of cases (93.3%) were from within the state of Maharashtra region. The large proportion of migrants in the city of Mumbai and the poor living conditions may play a large role in the concentration of infectious cases in this city and active spread of such diseases.[8,9]

The number of infectious causes outnumbered the non-infectious causes which is compared with the other studies.[8,10] Among the infectious causes, Hansen's disease (Leprosy) was the largest etiological condition with 57 cases, followed by cutaneous tuberculosis with 6 cases which is in accordance with the study done by Bal et al, Chakrabarti S et al and Gautam K et al.[10,11,12] This reflects the high burden of these infectious diseases in the community, and calls for stronger preventive measures, mass education and better access to healthcare, as infectious diseases are associated with poor sanitation, lack of awareness and health infrastructure. Among non-infectious causes, most cases were erythema nodosum (18.3%) followed by granuloma annulare (4.2%).

Leprosy:

Amongst leprosy cases, there was 36 (30%) of borderline tuberculoid, 14.2% cases of tuberculoid and 6 (5.0%) cases of pure neuritic leprosy. 4 (3.3%) cases of leprosy in reaction. Skin lesions in leprosy were more common in males which is comparable with the Gautam K et al.[12] We did not come across any case of indeterminate leprosy, but there were three cases where histopathology showed features of indeterminate leprosy. On histopathology, granulomatous inflammation was seen in most cases of leprosy. Well-formed granulomas could be appreciated in 23 cases of BTH, 4 case of BLH in type 1 reaction, (total 23.49%). In the remaining cases, dense inflammatory infiltrate with poorly formed granulomas could be seen. Langhans giant cells were seen in 5 cases of BTH and 2 case of BTH in type 1 reaction (total – 6.09%). Similar results are reported in previous studies.[12,13]

Special stains (slit skin smear and Fite-Faraco) showed more consistent results in the lepromatous pole of the disease (Leprosy). Hence their utility is limited in the diagnosis and management of leprosyas their sensitivity was 44.8% for SSS and 28.5% for Fite-Faraco staining which is correlated with the other studies.[8,14] Histopathological spectrum was highest in cases of tuberculoid (TT), Borderline Lepromatous Hansen's in type 1 or 2 reaction, and Pure Neuritic Hansen's (100%) followed by Borderline Tuberculoid Hansen's (79%), BTH in type 1 reaction (68%). The mean histopathological spectrum was 86.38%. It can be seen that the histopathological spectrum of Hansen's disease was higher in current study than most other studies.[12,15,16] This highlights the importance of histopathological correlation in the diagnosis and management of Hansen's disease.

Cutaneous tuberculosis:

Out of 11 patients of cutaneous TB, a majority of patients had active/past history of pulmonary TB or a close contact with TB. Among cutaneous tuberculosis, we had 6 cases (3.3%) of lupus vulgaris, 1 case (0.87%) of scrofuloderma and 1 case (0.87%) of tuberculosis verrucosa cutis (TBVC) which is similar to Bal et al and Grover et al [10,17] study. In all cases, the tuberculin test was strongly positive, which is in

agreement with the fact that Lupus vulgaris occurs in immunocompetent individuals.[13,14]

The presentation was that of a hyperpigmented plaque with central scarring and atrophy over the right hand, similar to the common presentation described in previous studies.[8,13,14] We could not find any case reports of HIV coexisting with cutaneous TB. Histopathological concordance was present in 4 cases of lupus vulgaris (63.636%) and in 100% cases of Scrofuloderma and TBVC. Hence the overall clinicopathological concordance was 87.87% in cutaneous TB. In 1 case of Atypical mycobacterial infection, there was a 100% clinicopathological concordance. However, the limiting factor was the lack of comparability as there were single cases of each condition.

Non-infectious granulomatous dermatitis:

The various non-infectious granulomatous dermatoses seen in current study were Granuloma Annulare, Erythema Nodosum, Granulomatous Cheilitis, Cutaneous Malakoplakia, Wegener's Granulomatosis, Pyoderma Gangrenosum, Hidradenitis Suppurativa, Granulomatous Rosacea, and Tattoo Granuloma. Majority of the patients were young with a female predominance, similar to the study conducted by Friedman-Birnbaun et al and Mohan et al.[18,19] On histopathological examination there was dominance of an interstitial pattern. Palisading pattern of presentation was seen in 5 of the total 5 cases. Similar findings have been seen in studies done by Gautam K et al and Friedman-Birnbaun et al.[12,18]

All 10 cases of erythema nodosum were non-infectious in nature, and there was no history of TB or TB contact in these cases. All presented with tender nodules and plaques, which were located over upper limbs. They all showed septal panniculitis on histopathology, which has classically been described in literature.[12,20] None of the 2 cases of granulomatous cheilitis had any nerve palsy, only isolated lip swelling was seen. There were no systemic symptoms or findings. Histopathology in all 2 cases showed well-formed epithelioid granulomas with dermal Oedema and inflammation. Amongst non-infectious causes of granulomatous reaction, a strong positive correlation between clinical and histopathological features was noted in 3 out of 5 cases of Granuloma annulare (71.429%), all 10 (100%) cases of Erythema nodosum, all 2 (100%) cases of Granulomatous cheilitis, as well as 1 case (100%) each of cutaneous malakoplakia, Wegener's granulomatosis. We had 11 cases of Pyoderma gangrenosum, out of which clinicopathological concordance was noted in only 6 case (54.54%). 1 case each, of Hidradenitis suppurativa, and 3 cases of foreign body (tattoo) granuloma, showed the classical clinical and histopathological features with a clinicopathological concordance of 100% as similar to the previous studies.[7,11,12,15]

5. Conclusion:

The present study highlights the importance of histopathological spectrum in the process of arriving at a final diagnosis in cases of granulomatous disorders of the skin. Granulomatous skin lesions have various modes of presentation. A classical clinical picture may not always be present. Skin biopsies still remain to be the gold standard as they help in confirming diagnosis, provided a proper history is taken and clinical correlation utilized.

Special stains play a supporting role in infectious granulomas, but most of them have a low sensitivity. In the end, it depends on the clinical acumen of the treating doctor and the diagnostic accuracy of the pathologist to correlate the findings and arrive at a final diagnosis, which is the major factor affecting patient outcomes in this group of disorders. From medicolegal point of view, correct diagnosis of these lesions is of prime importance which can be misinterpreted with the injuries in various stages of healing over the body.

Ethical Clearance: IEC approval is taken from the Institutional Ethical committee.

Contributor ship of Author: All authors equally contributed.

Conflict of interest: None to declare.

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