Original Article

Etiological and Histopathological Spectrum of Granulomatous Skin Diseases: A Retrospective Descriptive Study from a Tertiary Care Hospital in Pakistan

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Abstract

Background Granulomatous skin diseases include diverse groups of disorders, and they pose a diagnostic difficulty because of their overlapping clinical features. Although they have a wide etiological spectrum, from infectious diseases like tuberculosis to noninfectious diseases like sarcoidosis. Due to high prevalence of these infections in Pakistan, accurate histopathological evaluation is needed to guide proper treatment.

Objective To find out the etiological spectrum, prevalence, and histopathological patterns of granulomatous diseases and to evaluate their regional distribution and clinical significance.

Methods This retrospective descriptive cross-sectional study was carried out between January 2021 and December 2023 at Khyber Teaching Hospital, Peshawar. Among them, 60 cases (16.7%) with confirmed histopathological granulomatous inflammation were included. Immunohistochemistry, and special stains were used to confirm the specific aetiology where needed. Data were analyzed using SPSS 22.0.

Results Infectious etiologies were most common, led by cutaneous tuberculosis (38.4%, n=23) followed by cutaneous leishmaniasis (33.4%; n=20), leprosy (10%; n=6) and syphilis (5%; n=3). Among the noninfectious cases, sarcoidosis was on top (8.3%; n=5) followed by foreign body granuloma (5%; n=3). Lupus vulgaris was the most predominant subtype of cutaneous tuberculosis (65.2%; n=15) followed by scrofuloderma (26%; n=6) and Tuberculosis verrucosa cutis (8.69%; n=2). Lepromatous Leprosy was the most frequently observed form of leprosy.

Conclusion Granulomatous diseases represent a significant health burden in Pakistan, particularly cutaneous tuberculosis and cutaneous leishmaniasis which account for over 70% of cases. Early skin biopsies with a clinicopathological correlation and aided by special stains and immunohistochemistry where needed is essential for accurate diagnosis, proper treatment, and improved patient outcome.

Keywords Granulomatous skin lesions; Cutaneous tuberculosis; Leishmaniasis; Sarcoidosis, Leprosy.

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Introduction

Granulomatous inflammation is a chronic inflammatory response that occurs when the body cannot eliminate a persistent organic or inorganic antigen.[1] Granulomatous inflammation is a type IV cell mediated hypersensitivity reaction and is characterised by collection of epitheloid histiocytes admixed with other inflammatory cells and multinucleated giant cells on histology.[2] These infiltrates exhibit a nodular, palisading, or interstitial pattern.[3,4] Granulomatous skin diseases include both

infectious and non-infectious etiologies.[5-7] Non-infectious granulomatous conditions include granuloma annulare, necrobiosis lipoidica, cutaneous sarcoidosis, foreign body granuloma, and interstitial granulomatous dermatitis. Infectious granulomas are caused by organisms like mycobacterium, fungi, spirochetes and parasites.[3,5]

During granuloma formation, an antigen, which is a foreign substance, is taken up by macrophages or dendritic cells, which are antigen-presenting cells. These antigens are presented via major histocompatibility complex (MHC) class II molecules to the CD4+ helper T cells. This triggers a cascade and various cytokines are released. The CD4+ helper T cell changes to the TH1 subtype. When TH1 cells accumulate at the inflammation site, they release more cytokines and chemokines. The antigen-presenting cells also release tumor necrosis factor alpha (TNF-α), attracting more inflammatory cells, resulting in granuloma formation by driving the differentiation of macrophages into epithelioid cells and fusion into giant cells.[8-10]

Cutaneous Tuberculosis comprises a major portion of granulomatous skin diseases in endemic regions such as Pakistan. Cutaneous leishmaniasis remains a major health cate concern with approximately 600,000 to 1 million cases reported annually worldwide. Pakistan continues to report new cases of leprosy. Sarcoidosis is less commonly reported in South Asia as compared w/o western countries.[10-12]

Accurate histopathological diagnosis is important for appropriate treatment. Most previous studies from Pakistan and the region have focused on single granulomatous entities. Our study provides a comprehensive, up-to-date etiological and histopathological spectrum of all granulomatous skin lesions diagnosed at a major tertiary care centre in Khyber Pakhtunkhwa over a three-year period, thereby filling an important gap in recent regional data.

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Methods

This retrospective cross-sectional study was conducted at the Departments of Pathology and Dermatology, Khyber Teaching Hospital, Peshawar. Ethical approval was obtained from the hospital's ethics and scientific committee (Approval No. 762/DME/KMC dated 10.01.2023).

All biopsy records of patients presented with skin diseases between 1st January 2021 to December 2023 were reviewed. All cases with granulomatous inflammation on histology were included. No prior sample size calculation was performed, and a total population sample size technique was applied. Biopsies with incomplete record and inconclusive diagnosis were excluded. In total, 340 cases were analysed Histopathological analysis were performed on routinely processed eosin-hematoxylin-stained sections and special stains were applied, such as Ziehl-Neelsen to look for Mycobacterium tuberculosis and Giemsa stain to identify Leishmania species were deployed based initial findings.

Sixty cases with confirmed granulomatous skin lesions were included in the final analysis. SPSS version 22.0 was used for data analysis. Numerical variables were reported as mean ± standard deviation. Categorical variables (age, gender, etiological frequency, histopathological subtypes) were presented as frequencies and percentages.

Operational definitions

Granulomatous disease: Inflammatory disorder characterised by aggregates of epithelioid histiocytes with or without giant cells.

Etiological spectrum: Distribution and frequency of different infectious and noninfectious causes of granulomatous skin lesions.

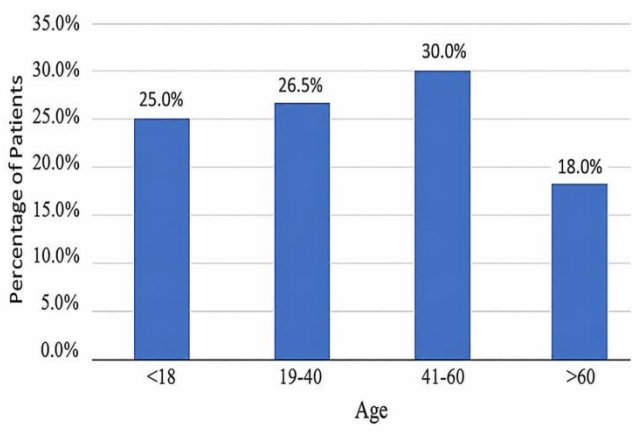


Figure 1 Age-wise Distribution of Patients with Granulomatous Skin Lesions (n=60).

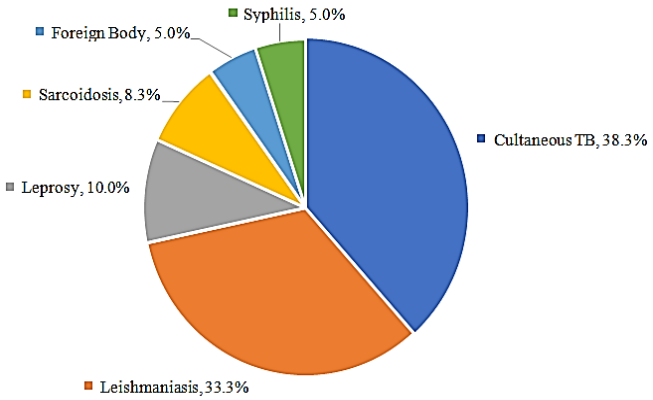


Figure 2 Prevalence of different granulomatous skin diseases in the study population.

Patterns of granulomatous skin diseases: Histopathological patterns of granuloma formation such as tuberculoid, sarcoid, suppurative, foreign body and mix.

Regional Distribution: Frequency of granulomatous skin diseases in patients presented to Khyber teaching hospital, Peshawar.

Clinical Significance: The practical application of study findings for patient management.

Result

A total of 340 skin biopsies were reviewed, of which 60 (16.7%) were confirmed as granulomatous skin lesions. The study cohort comprised 34 male patients (56.7%) and 26 female patients (43.3%), with a male-to-female ratio of 1.3:1.

The mean age of patients was 36.57 years (SD: 11.23 years), and the highest prevalence was observed in the 41 to 60-year age group (29.96%) **(Figure 1)**.

Cutaneous tuberculosis was the most prevalent etiology (38.4%, 23 cases), followed by cutaneous leishmaniasis (33.4%, 20 cases), leprosy (10%, 6 cases), and sarcoidosis (8.3%; 5 cases) **(Figure 2)**. Syphilis and Foreign body granuloma were diagnosed in 5% each.

Among cases of cutaneous tuberculosis (CTB), Lupus Vulgaris was the most common form (65.2%, 15 cases), followed by Scrofuloderma (26%, 6 cases) and Tuberculous Verrucosa Cutis (8.69%, 2 cases) **(Figure 3)**.

Leprosy cases are predominantly of the lepromatous type (50%; 3 cases), while the remaining cases included borderline leprosy (16.6%; 1 case) and tuberculoid leprosy (33.4%, 2 cases).

Discussion

Granulomatous skin disease poses diagnostic difficulties because of their overlapping clinical features and histomorphologies. A single etiological agent can produce varied histological feature. In the present study, wide spectrum of histopathological features were observed.

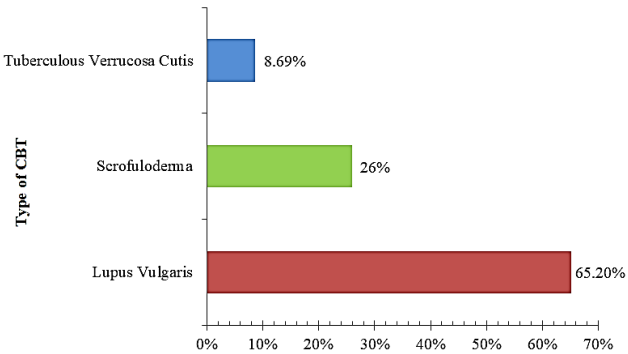


Figure 3 Morphological variants of cutaneous tuberculosis in patients with granulomatous skin diseases.

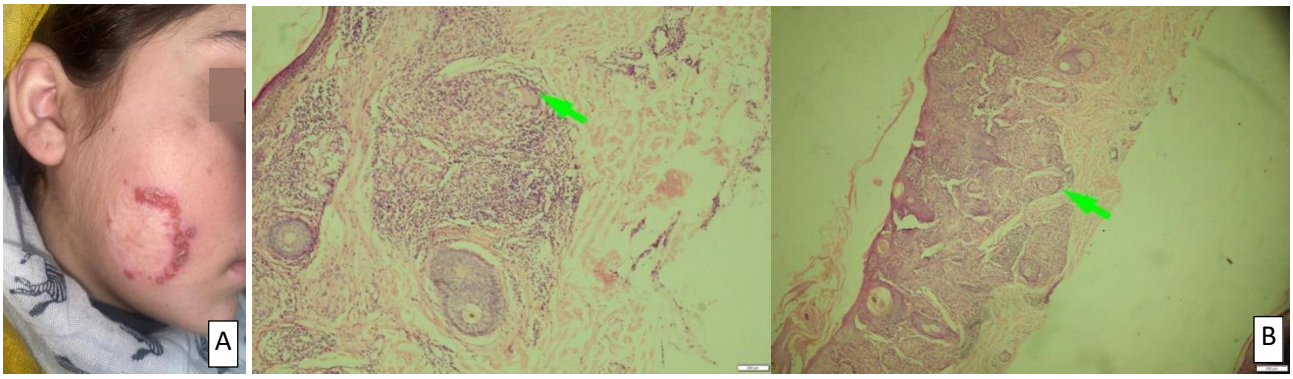


Figure 4 A) Clinical photograph of a patient diagnosed with Lupus Vulgaris. The lesion, localized on the face, had been gradually progressing over a 6-month period. It appears as an erythematous plaque with central atrophy and peripheral infiltration. Diagnosis was confirmed by histopathological examination and Z-N staining, consistent with cutaneous tuberculosis. B) Histopathological analysis showing features of Lupus Vulgaris on 10x and 40x magnification showing well-formed tuberculoid granulomas composed of epithelioid histiocytes and a surrounding rim of lymphocytes in the dermis (H&E).

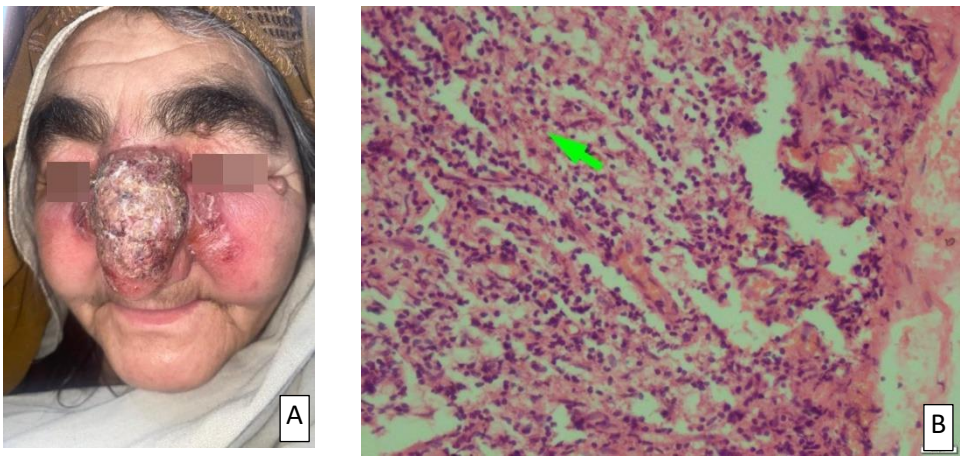


Figure 5 A) A case of suspected cutaneous leishmaniasis with 3 months history of slowly progressive indurated crusted plaque on the dorsum of the nose. Diagnosis confirmed on histopathological analysis. B) Histopathological section showing features of cutaneous leishmaniasis. The dermis reveals a dense inflammatory infiltrate composed predominantly of histiocytes containing intracellular amastigote forms of Leishmania (Leishman-Donovan bodies), surrounded by lymphocytes and plasma cells. Staining was performed with hematoxylin and eosin (H&E, 40x).

In our study prevalence of granulomatous lesions was (16.7%) and a male predominance (male-to-female ratio of 1.3:1) was observed, consistent with prior studies.[12-16]

The histopathological evaluation demonstrated a broad range of granuloma morphology, reflecting the diversity of granulomatous skin diseases.

The most prevalent pattern was tuberculoid granulomas **(Figure 4)**. Caseating granulomas with neutrophilic aggregates in the centre were seen in infectious aetiologies. In some non-infectious granulomatous diseases such as sarcoidal granulomas, compact, "naked" granulomas with little surrounding inflammation were found.

Histopathology played a central role in diagnosing and differentiating granulomatous skin diseases with overlapping clinical features by assessing granuloma structure and inflammatory pattern.

Global estimates suggest that cutaneous tuberculosis accounts for 0.1% to 1% of all skin lesions, making our findings notable for their regional relevance.[12] Cutaneous Tuberculosis comprises approximately 1-2%, represents an important cause of granulomatous skin diseases in tuberculosis endemic regions such as Pakistan.[17,18] Ting *et al*. and Chakrabarti *et al*. also mentioned in their study the significance of cutaneous tuberculosis as a manifestation of extrapulmonary. TB in South Asia, the second most frequent infectious granulomatous skin disease.[16]

In Pakistan, specific data on the national prevalence of CTB is limited. However, as one of the studies carried out in Larkana noted, several cases of CTB have been quite evident, with the highest incidence in the area.[20] Overall, while CTB remains uncommon, its occurrence is more notable in regions with higher rates of tuberculosis, such as in South Asia.

Cutaneous leishmaniasis was the second most common etiology in our study (33.4%). Several types of granulomas were seen on histopathology **(Figure 5)**, more commonly non-caseating, but caseating granulomas were also reported, like the study findings of Siyab *et al*.[21] This finding highlights the endemic nature of leishmaniasis in the region, needing ongoing public health interventions.

Leprosy, as compared to leishmania, is less common in our study (10%) but is still important because of the serious disability it can cause. From the study it has been observed that most prevelant was lepromatous leprosy. Balaram G. also found lepromatous leprosy to be the most common form in his thesis, while Gautam *et al*. reported borderline leprosy as the most frequent, which is followed by the tuberculoid type.[15,22] Clinically, leprosy can present like other dermatoses. Therefore, early skin biopsy is crucial to make early diagnosis and treated before complications develop.[23]

In our study, sarcoidosis was identified in 8.3% of the cases, and Syphilis and Foreign body granuloma was diagnosed in 5% each indicating a relatively low frequency of these diseases. Although less common but it should be considered in routine clinical and histopathological evaluation.

Conclusion

Our study shows that both infectious and noninfectious skin diseases can be seen in our area as granulomatous skin lesions on different parts of body. Recognizing specific histopathological patterns together with clinicopathological correlation help in the diagnosis of the relevant condition and its management. Diagnosing the disease and hence a multidisciplinary approach may help in a better outcome

Limitations of this study were that it was single-cantered, retrospective design and relatively small numbers of cases were included so the results may not be considered generalized. As it was a retrospective study, some information and records may be missed during data collection. Still, the study helps us understand the prevalence of these skin diseases in our area and highlighted that skin biopsy is the gold standard for diagnosis and proper management.

Recommendations Although it was a single-centered study, more such studies are recommended to see the exact distribution across different areas. Timely diagnosis and hence in-time treatment of the disease may help in reducing the burden of the disease.

Declaration of patient consent Authors certify that they have obtained all appropriate patient consent.

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Conflict of interest No conflict of interest.

Author's contribution

PK, IU, WZK: Substantial contribution to conception, study design, critical review of the manuscript.

SP: Substantial contribution to acquisition, analysis and interpretation of data and drafting the manuscript.

MK: Substantial contribution conception and design and critical review of the manuscript.

MR: Substantial contribution acquisition of data, analysis and drafting the manuscript.

Every author has given final approval of the manuscript version to be published and agreed to be accountable for all aspects of the work.

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