Clinicohistopathological Concordance of Cutaneous Granulomatous Disorders at a Tertiary Care Hospital in Northern India: A Cross-sectional Study

PRIYANKA SHARMA¹, SUBHASH BHARDWAJ¹, POONAM SHARMA¹

ABSTRACT
Introduction: Granulomatous inflammatory pattern is a chronic inflammation with a limited number of possible conditions that cause it. Therefore, for treatment purposes, its diagnosis is mandatory. The overlapping clinical and histological features of granulomatous dermatitis demand a proper system of classification. The aetiology, histopathological granuloma patterns, and the morphology of various skin lesions can be informative and supportive towards their diagnosis.

Aim: To determine the distribution of various cutaneous granulomatous disorders in the demographical region and their causative agents.

Materials and Methods: This cross-sectional study was conducted in the Histopathology section of the Department of Pathology, Government Medical College, Jammu and Kashmir, India over a period of five years (1st November 2014-31st October 2019) involving a prospective and retrospective analysis of 1,150 skin biopsies. A clinical diagnosis of Infectious Cutaneous Granulomatous Disorders (IGDS) was made in 560 cases included in the study. Out of 560 cases, the histopathological diagnosis of IGDS was confirmed in 361 cases. The aetiology and granuloma histology were studied. A clinicopathological agreement was established with the kappa test.

INTRODUCTION
A granuloma is defined as a focal chronic inflammatory response to tissue injury, characterised by a collection of histiocytes, epithelioid cells, and multinucleated giant cells that may or may not be surrounded by lymphocytes and exhibit central necrosis [1]. The cutaneous granulomatous inflammatory response is a manifestation of many infective, toxic, allergic, autoimmune, and neoplastic conditions of unknown aetiology [2]. India is among the tropical countries that have endemicity for IGDSs. There are limited studies in the literature in this geographical region of Northern India determining the frequency, histology, and aetiology of different prevalent granulomatous skin lesions [3-5]. Therefore, the study was conducted to substantiate the data in the literature, enhance further management, and assess how histology is successful in achieving a proper diagnosis.

MATERIALS AND METHODS
The present cross-sectional study was conducted in the histopathology section of the Department of Pathology, Government Medical College, Jammu and Kashmir, India. The study was approved by the Institutional Ethics Committee (Approval number: IEC/GMC/2019/822, Dated: 19.12.2019) and was conducted in two parts: a retrospective analysis for a period of four years (31st October 2014 to 1st November 2018) and a prospective analysis for a period of one year (1st November 2018 to 31st October 2019), during which 1,150 skin biopsies were evaluated.

Inclusion criteria: All new and follow-up cases of clinically suspected and histopathologically diagnosed cases of cutaneous granulomatous disorders were included in the study, respectively, from the archives of the histopathology division of the Department of Pathology.

Exclusion criteria: Inadequate, non cutaneous, poorly preserved biopsies without demis, and those of non infectious origin were excluded from the study.

Study Procedure
Relevant clinical history, including age, sex, duration of the disease, and treatment received, was considered. The cases were studied for histopathological features of granuloma, its location, and associated epidermal changes. The most common infective aetiology, leprosy, was categorised according to Ridley-Jopling’s classification of 1966, and the second common aetiology of cutaneous tuberculosis was classified using the Tappeiner and Wolff classification system [6,7].

Results: Leprosy was the most common histopathological diagnosis, with 343 out of 361 cases (95.01%), followed by tuberculosis with 9 out of 361 cases (2.49%). Leprosy subtypes included Lepromatous Leprosy (LL) in 75 cases (21.87%), followed by Borderline Tuberculoid (BT) in 71 cases (20.70%). Among the nine cases of cutaneous tuberculosis, Lupus Vulgaris (LV) was found in five cases (55.56%), followed by Scrofuloderma (SD) in three cases (33.33%), and Tuberculosis Cutis Orificialis (TCO) in one case (11.11%). The cases of leprosy showed maximum clinicopathological concordance in 343 cases (68.33%), with the BT type being the most concordant with the clinical diagnosis at 30 out of 64 cases (46.88%). A statistical analysis of kappa was applied to the subtypes of leprosy, and the observed kappa value was 0.3439, indicating agreement between histology and clinical diagnosis.

Conclusion: Histopathological examination is the gold standard for diagnosing, categorising, and determining clinicopathological concordance of cutaneous granulomatous lesions. The wide spectrum of clinical differentials can be narrowed down. Although the importance of clinical examination and ancillary techniques for confirming the diagnosis cannot be denied, considering all aspects together can lead to a final conclusive diagnosis.

Keywords: Histopathological examination, Leprosy, Tuberculosis
detailed microscopic examination of Haematoxylin and Eosin (H&E), Periodic Acid Schiff, Acid-Fast Bacilli, and Giemsa stained sections was performed.

**STATISTICAL ANALYSIS**

Statistical analysis was conducted using Microsoft Excel, Statistical Package for the Social Sciences (SPSS) version 21.0, and the Kappa calculator. Data were represented in charts and tables, and the clinicopathological proportion of agreement of the cases studied was assessed using the Kappa test.

**RESULTS**

Out of a total of 1,150 skin biopsies received in the department, 576 (50.09%) cases had a clinical suspicion of cutaneous granulomatous lesions. The clinical diagnosis of infectious aetiology was made in 560 out of 576 cases (97.22%), which were included in the study. Leprosy was clinically suspected in 502 (89.64%) cases, followed by cutaneous tuberculosis in 24 (4.29%) cases, dermal leishmaniasis in 16 (2.86%) cases, and deep fungal infections in 18 (3.21%) cases. The clinical diagnosis of non infectious granulomatous disorders was made in 16 out of 576 cases (2.77%), which were excluded from the study.

The histological diagnosis of infectious cutaneous granulomatous dermatitis was made based on the granuloma, its location, along with associated epidermal changes in 361 out of 560 cases (64.46%) [Table/Fig-1,2].

**Table/Fig-1**: Microscopic findings in leprosy subtypes (n=343).

<table>
<thead>
<tr>
<th>Histopathological diagnosis leprosy</th>
<th>Perineural infiltrate</th>
<th>Inflammatory infiltrate</th>
<th>Scattered epitheloid cells</th>
<th>Giant cells</th>
<th>Total no. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lepromatous</td>
<td>Present n (%)</td>
<td>Dermal infiltrate n (%)</td>
<td>Present in no. of cases</td>
<td>Present in no. of cases</td>
<td></td>
</tr>
<tr>
<td></td>
<td>31 (41.33)</td>
<td>47 (58.67)</td>
<td>31 (41.33)</td>
<td>5</td>
<td>75</td>
</tr>
<tr>
<td>Borderle lepromatous</td>
<td>42 (73.68)</td>
<td>55 (96.49)</td>
<td>2 (3.51)</td>
<td>14 (24.56%)</td>
<td>57</td>
</tr>
<tr>
<td>Borderline borderline</td>
<td>26 (83.37)</td>
<td>31 (100)</td>
<td>0</td>
<td>20 (64.5%)</td>
<td>31</td>
</tr>
<tr>
<td>Borderline tuberculoid (BT)</td>
<td>42 (59.15)</td>
<td>69 (97.18)</td>
<td>2 (2.82)</td>
<td>14 (19.72%)</td>
<td>71</td>
</tr>
<tr>
<td>Tuberculoid tuberculoid</td>
<td>22 (57.89)</td>
<td>36 (92.3)</td>
<td>3 (7.7)</td>
<td>2</td>
<td>38</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>19 (48.7)</td>
<td>39 (100)</td>
<td>0</td>
<td>0</td>
<td>39</td>
</tr>
<tr>
<td>Histoid leprosy</td>
<td>4 (23.52)</td>
<td>9 (52.94)</td>
<td>8 (47.06)</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>Erythema nodosum lepromosum</td>
<td>5 (33.33)</td>
<td>15 (100)</td>
<td>0</td>
<td>2</td>
<td>15</td>
</tr>
</tbody>
</table>

**Table/Fig-2**: Microscopic findings in subtypes of cutaneous tuberculosis.

Out of the 361 cases, there were 301 male cases, accounting for 83.38% with a mean age of 56.14 years, and 60 female cases, representing 16.62% with a mean age of 20 years. Therefore, females showed susceptibility to infection at younger age groups. The highest number of patients were in the age group of 21-40 years, comprising 162 cases (44.88%), followed by the age group of 41-60 years with 124 cases (34.35%).

Among the 361 cases of infectious granulomatous dermatitis, the most common lesion diagnosed was leprosy in 343 cases (95.01%), followed by cutaneous tuberculosis in nine cases (2.49%), sporotrichosis in five cases (1.39%), and cutaneous leishmaniasis in four cases (1.11%).

The histopathologically diagnosed cases of leprosy were further categorised. Lepromatous Leprosy (LL) constituted the most common subtype diagnosed, as shown in [Table/Fig-3], with 75 out of 343 cases (21.87%), followed by BT histologically shown in [Table/Fig-4], with 71 out of 343 cases (20.7%). The largest number of cases were in the borderline group, as shown in [Table/Fig-5], with 159 out of 343 cases (46.36%).

Among the 343 cases diagnosed with leprosy, the most common age group affected was 21-40 years, with 161 cases (46.9%), comprising 286 males (83.38%) and 57 females (16.62%). The skin lesions were most commonly of a mixed type, with 104 cases (30.32%) present in various combinations of plaque, papule, macule, and nodule even in a single case, and were evident on multiple sites, with 178 cases (51.9%) affecting various parts of the body even in a single case. The upper extremity was the most common site involved in 45 cases (13.12%). The clinical diagnosis of Hansen’s Disease (HD) without further categorisation was the most common clinical diagnosis 335 out of 502 cases of clinically diagnosed cases of Leprosy, accounting for 66.7%. Out of these 335 cases, histopathologically 208 cases 62.09% were categorised into various subtypes of leprosy. The most common subtype found was LL with 47 out of 335 cases with a concordance rate of 14.03, followed by Borderline Leprosy with a 38 cases out of 335, having a concordance rate of 11.34 [Table/Fig-6]. In total, descriptive reports were given in 158 out of 502 cases (31.5%), and two cases were diagnosed as leishmaniasis, and two cases were diagnosed as conditions other than granulomatous disorders. Clinicohistopathological agreement was established in leprosy subtypes. The overall observed kappa value was found to be 0.3439, with a 95% confidence interval of 0.2404 to 0.4404. The proportion agreement among the various subtypes was found to be 0.3439, with a 95% confidence interval of 0.2404 to 0.4404.
Sporotrichosis was diagnosed in five cases (1.39%), most commonly in the 41-60 years age group with three cases (60%), all being male. The lesions presented as plaques and mixed lesions involving both upper and lower limbs.

Leishmaniasis was diagnosed in four cases (1.11%), representing every age group and presenting as plaques in two cases (50%) and plaques along with nodules in two cases (50%), with a male to female ratio of 3:1.

The histopathological diagnosis of LV was made in 3 out of 13 cases (23.07%) of SD, in 3 out of 9 cases (33.33%) of fungal infections, in 5 out of 18 cases (27.8%) of sporotrichosis, and in only 2 out of 16 cases (12.5%) of cutaneous leishmaniasis [Table/Fig-9]. Therefore, there is a lack of agreement between clinical and histopathological diagnosis.

For the confirmation of the histopathological diagnosis, special stains such as Acid-Fast Bacilli (AFB), Periodic Acid-Schiff (PAS), and Giemsa stains were used. AFB staining for leprosy was positive in 162 out of 343 cases (47.2%), including 75 cases of LL, 55 cases of BL, 17 cases of HL, and 15 cases of EN. AFB staining for tuberculosis was positive in 4 out of 9 cases (44.44%) of cutaneous tuberculosis. PAS staining was applied in all cases of suspected fungal infections and was only positive in 2 out of 18 cases. Giemsa stain was used during the study, otherwise, diagnoses were made based on Haematoxylin and Eosin (H&E) staining only. Giemsa stain was positive in 3 out of 4 cases (75%) diagnosed with cutaneous leishmaniasis. It was negative in one case of post-kala-azar leishmaniasis, and in all other positive cases, the agent, Leishmania Donovan (LD) bodies, was confirmed.
In present study, the most common age group involved was 21-40 years (44.88%), with a male to female ratio of 4.5:1, which was comparable to similar studies by Ahmad F et al., (1.3:1) and Susmitha S et al., who found ratios of 1:3:1 and 2:3:1 in their studies, respectively [10,12]. This may be attributed to increased chances of exposure due to increased job-related mobility [13].

The results are in disagreement with the study by Zafar MNU et al., who reported a female preponderance (61.85%), but they were not able to identify the cause for this [11].

In the present study, the Borderline spectrum of leprosy was found to be the largest group (46.65%), followed by LL with 75 cases (21.27%), making it the most common subtype of leprosy. This was similar to the study by Adil M et al., who reported a total of 63.5% of patients in the Borderline category, with LL being the most common subtype at 28.0% [14]. Potekar RM et al., found LL to be the second most common subtype with 17 cases (25.39%) [15].

<table>
<thead>
<tr>
<th>Table/Fig-9:</th>
<th>Clinicopathological concordance in other causes of IGDS.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical diagnosis</strong></td>
<td><strong>Histopathological diagnosis</strong></td>
</tr>
<tr>
<td>Lupus Vulgaris (LV)</td>
<td>5 (8.62%)</td>
</tr>
<tr>
<td>Scrofuloderma (SD)</td>
<td>0</td>
</tr>
<tr>
<td>Tuberculosis Cutis Orificialis (TCO)</td>
<td>0</td>
</tr>
<tr>
<td>Papulonecrotic tuberculid</td>
<td>0</td>
</tr>
<tr>
<td>Cutaneous leishmaniasis</td>
<td>1 (8.25%)</td>
</tr>
<tr>
<td>Sporotrichosis</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>5 (8.62%)</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Granulomatous skin lesions represent a distinctive pattern of chronic inflammatory response in the skin due to reactions against various organic and inorganic antigens. Both infectious and non infectious granulomatous dermatoses are common among the Indian population. The present study, conducted in the demographic region of North India, further confirms this observation, as infectious cutaneous granulomatous dermatoses are prevalent in 361 cases (64.46%), similar to studies by Bharti RR et al., and Kumar L et al., with rates of 98.33% and 81.45%, respectively [5,8]. The most common aetiology among infectious granulomatous dermatoses was leprosy, found in 343 cases (95.01%), followed by cutaneous tuberculosis in 9 cases (2.49%). A comparison with similar studies is presented in Table/Fig-10 [1,5,9,10]. However, there is a discrepancy with a study by Zafar MNU et al., from Pakistan, who found cutaneous tuberculosis to be more prevalent (78.87%), indicating regional disparities [11].

In the present study, the second largest subgroup of leprosy was BT with 71 cases (20.7%), which was in disagreement with earlier studies by Kumar L et al., who reported 13 cases (32.50%), and Rajbhandari A et al., who found eight cases (32%), with BT as their largest subgroup studied [8,9].

In the present study, clinical diagnosis of leprosy was made in 502 cases, and 343 cases were diagnosed histopathologically. These 502 cases comprised 337 cases of Hansen's Disease (HD) without further categorisation. Of the 337 HD cases, 208 cases (61.72%) were diagnosed and further classified into various subtypes of leprosy. Histopathological diagnosis of LL was made in 47 out of 337 cases (14.02%) clinically diagnosed as HD. However, the proportion of LL increased to 14.94% when considering clinical diagnosis of leprosy with all its subtypes in 75 out of 502 cases. In 127 cases, descriptive reports were given, where a non specific chronic inflammatory infiltrate was present and not arranged perineurally or peripendageally, forming the main proportion of discordant cases. These HD patients were on Multi-Drug Therapy (MDT), on follow-up, and were disease-free at that point in time, or a proper representative site was not biopsied.

The overall clinicohistopathological concordance in the present study, where 543 cases were histopathologically diagnosed out of 502 clinically diagnosed leprosy cases, is 68.5%. The present study was comparable to studies done by other authors when subtypes were studied, as shown in Table/Fig-11 [9,15-17].

When clinical diagnoses were made based on various subtypes, 30 out of 64 BT cases were diagnosed with a concordance of 46.88%. BT cases showed concordance in 26 cases (27.1%) in the study by Susmitha S et al., [12]. Although LL and BL cases were comparable in number, they were not statistically significant due to the small sample size.

Since tissue response varies in the disease spectrum due to variability in cell-mediated immunity, some disparity between clinical and histopathological features is expected. Clinicohistological

**Table/Fig-10**: Comparison between commonest aetiology of the granulomatous skin lesions [1,5,9,10].
Concordance in respect of leprosy with previous studies done earlier [9,15-17].

In the present study, Acid-Fast Stain for leprosy was positive in 162 cases (32.2%), including all LL, HL, ENL cases, and 55 cases of BL. Kumar L et al., and Ahmad F et al., found leprosy positivity in 17 cases (42.50%) and 21 cases (31.34%), respectively [8,10].

Another common IGDS noted in this study was cutaneous tuberculosis, with 9 out of 361 cases (2.49%) of all granulomatous lesions. In the present study, the incidence of cutaneous tuberculosis was 0.78%, with nine cases out of a total of 1,150 skin biopsies received in the department.

There is a wide clinical spectrum of cutaneous tuberculosis. The clinical types depend on the route of infection, the virulence of the bacillus, and the immune status of the host, particularly cellular immunity [13].

A total of 58 cases out of 560 cases, were clinically diagnosed as IGDS, other than Leprosy. The clinical diagnosis or differential diagnosis of LV was made in 43 out of 58 IGDS cases. Among these concordant cases, where the histopathological diagnosis was LV, there were 3 out of 13 cases (23.07%). When the clinical diagnosis was SD in 9 cases, 3 cases (33.33%) were histologically diagnosed as SD, and one case (11.11%) was diagnosed as LV. Sushmitha S et al., found 50% of cases as LV [12]. Rajbhandari A et al., observed 12 cases (79%) of LV followed by 2 cases (21%) of SD [9]. Therefore, different clinical patterns of cutaneous tuberculosis like LV and SD, appearing as nodules, and tuberculosis verrucous cutis appearing as other warty plaques (verrucae) that can be misdiagnosed, require histopathological examination.

In the present study, four cases tested positive for AFB, which included three cases of SD and a solitary case of TCO, accounting for 44.44% altogether. Kumar L et al., also found AFB positivity ranging from 54.38% to as low as 5.0% [8].

In 18 clinically diagnosed cases of deep fungal infections, 5 out of 361 cases (1.38%) were histologically diagnosed as sporotrichosis, where fungal granulomas were found. This finding was similar to the study by Zafar MNU et al., who found fungal granulomas in 3.2% of cases [11]. The diagnosis can be made by observing fungal spores, hyphae, along with contributory special stains like PAS, GMS, and the type of infiltrate suggesting and confirming the diagnosis [11]. Rajbhandari A et al., found fungal granulomas in four cases, representing 25% of sporotrichosis cases, and PAS positivity in six cases (37.5%) of fungal granulomas [9].

Cutaneous leishmaniasis is a global presence. In the present study, a total of four cases (1.11%) out of 361 cases were diagnosed as cutaneous granulomatous disorders. Rajbhandari A et al., found suppurative granulomas in 15 cases (13.8%) of fungal granulomas and 2 cases (1.83%) of leishmaniasis [9].

Out of 16 clinically diagnosed cases of cutaneous leishmaniasis, only two cases (12.5%) were histologically reported as cutaneous leishmaniasis. In one case, the histological diagnosis was LV, in another case, TCO, and the rest of the 10 cases were inconclusive. These findings were consistent with the study by Potekar RM et al., who observed 1.49% of leishmaniasis in their study [15]. In the present study, on histopathological examination, LD bodies, the amastigote form of the protozoan, were found within macrophages on routine HE sections, demonstrable in 3 out of 4 cases (75%) and confirmed by Giemsa stain. Potekar RM et al., also found LD bodies in both cases of leishmaniasis in their study [15]. The finding that no LD bodies were found in post-kala-azar leishmaniasis is in agreement with the study by Singh A et al., who reported on 88 cases of post-kala-azar leishmaniasis where no LD bodies were found [18].

The overall concordance is 7 out of 24 cases (29.16%) in cutaneous tuberculosis, 2 out of 16 cases (12.5%) in cutaneous leishmaniasis, and 5 out of 18 cases (27.78%) in deep fungal infections. These cutaneous infectious granulomatous disorders are great mimickers as well, posing a significant diagnostic challenge for clinicians. Hence, histopathology is essential for accurate diagnosis and proper management of patients.

Limitation(s)
The limitation was the small sample size. Therefore, it is recommended to conduct more studies with a multicentric approach to further validate the findings of present study.

CONCLUSION(S)
Histopathological examination is the gold standard for diagnosing cutaneous granulomatous lesions. Clinical diagnosis is important in guiding the pathologist in accurately interpreting skin biopsies. In current study, there was a significant correlation between clinical and histopathological diagnosis of leprosy. Better comprehension of these disorders is required based on clinical findings, laboratory work-up, patterns, morphology of granulomas, and special stains to arrive at an etiological diagnosis for proper clinical management. Therefore, there is a risk of inaccurate diagnosis unless correlated histopathologically.

REFERENCES

PARTICULARS OF CONTRIBUTORS:
1. Lecturer, Department of Pathology, Government Medical College, Jammu, Jammu and Kashmir, India.
2. Professor, Department of Pathology, Government Medical College, Jammu, Jammu and Kashmir, India.
3. Associate Professor, Department of Pathology, AIIMS, Vijaypur, Jammu, Jammu and Kashmir, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Priyanka Sharma, H. No. 45, Nilco Lane, Talab Tilu, Jammu-180002, Jammu and Kashmir, India.
E-mail: priyankasharma060611@gmail.com

PLAGIARISM CHECKING METHODS:
- Plagiarism X-checker: Sep 04, 2023
- Manual Googling: Feb 01, 2024
- iThenticate Software: Apr 30, 2024 (16%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: Sep 03, 2023
Date of Peer Review: Oct 28, 2023
Date of Acceptance: May 01, 2024
Date of Publishing: Jul 01, 2024