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Original Research Article

Histopathological Spectrum of Granulomatous Lesions in Biopsy Samples: Prevalence, Morphology, and Anatomical Distribution

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Abstract:

Background: Granulomatous inflammation is a distinctive chronic inflammatory response encountered frequently in histopathological practice, with diverse infectious and non-infectious etiologies and varied morphological patterns, often posing diagnostic challenges.

Aim: To evaluate the histopathological spectrum of granulomatous lesions in biopsy samples with respect to their prevalence, morphology, and anatomical distribution.

Methodology: This hospital-based descriptive observational study included 80 biopsy specimens showing granulomatous inflammation. Routine hematoxylin and eosin staining was performed, supplemented with special stains such as Ziehl–Neelsen and PAS where indicated. Data were analyzed using descriptive statistics and expressed as frequencies and percentages.

Results: Granulomatous lesions were more common in adults, with a female predominance (60%). Lymph nodes (32.5%) and skin (22.5%) were the most frequently involved sites. Caseating granulomas were the predominant morphological pattern (52.5%). Tuberculosis was the most common etiology (35%), followed by sarcoidosis and granulomatous lesions not otherwise specified (17.5% each). Ziehl–Neelsen stain was positive in 30% of cases.

Conclusion: Granulomatous lesions show wide morphological and etiological diversity. Histopathological examination, supported by special stains and clinicopathological correlation, remains crucial for accurate diagnosis and effective patient management.

Keywords: Granulomatous inflammation, biopsy, caseating granuloma, tuberculosis, histopathology.

Introduction

Granulomatous inflammation is a distinctive form of chronic inflammatory response that exhibits a unique and organized pattern of tissue reactivity. It is an important pathological entity in routine histopathological practice and is associated with a wide spectrum of infectious and non-infectious diseases.[1] This kind of inflammation is a reflection of a complex host immune response and usually occurs when the immune system attempts to confine and isolate agents from the body that are resistant to eradication. Because of its varied etiology and histological presentations, granulomatous inflammation still remains one of the formidable challenges that face pathologists and clinicians nowadays.

Histologically, granulomatous inflammation is characterized by the aggregation of activated macrophages, usually referred to as histiocytes, which often undergo transformation into epithelioid cells. These cells are very often associated with multinucleated giant cells and are usually embedded in a variable number of lymphocytes. In some instances, central necrosis may be seen in the center of the granulomas, further complicating the morphological nature of their appearance.[2] The presence of these histological features is crucial since they constitute the hallmark for the identification of granulomatous lesions on biopsy specimens. Depending on the nature of the underlying etiology and host response, granulomas can exhibit marked variation in terms of size, cellular composition, and distribution within affected tissues.

According to the literature, several histopathological patterns of granulomatous inflammation are identified. These include necrotizing granulomas, non-necrotizing granulomas, suppurative granulomas, diffuse or widespread granulomatous inflammation, and foreign body giant cell reactions.[3] Necrotizing granulomas generally occur in the setting of infectious etiologies such as tuberculosis and demonstrate central areas of caseous necrosis. In contrast, conditions such as sarcoidosis and some autoimmune disorders usually exhibit non-necrotizing granulomas. Suppurative granulomas, characterized by a significant neutrophilic component, often result

from fungal or bacterial infections. Foreign body granulomas have resulted from materials such as sutures and talc and point to the wide range of etiologies in granulomatous reactions.

From an immunopathological standpoint, granulomatous inflammation is considered a type IV delayed hypersensitivity reaction. This response is mediated essentially through T lymphocytes and macrophages, developing over a period of time in response to constant antigenic stimulation.[4] Such a reaction is induced by a myriad of elements that include infectious agents, autoimmune processes, toxic exposure, allergens, certain drugs, and even neoplastic disorders. The chronic nature of antigen exposure leads to the persistence of immune activation, eventuating in granuloma formation as its protective response, with the aim of confining tissue damage and preventing the spread of the offending agent.

Accurate histopathological diagnosis of granulomatous inflammation and determination of its etiology in biopsy samples are of prime importance in clinical practice.[5] Correct diagnosis not only helps in appropriate therapeutic interventions but also has a very important role in prognosis and management of patients. Misinterpretation or nonrecognition of specific granulomatous patterns may result in delays in diagnosis, inappropriate treatment, and poor clinical outcome. A good understanding of the histological spectrum and the associated etiologies of granulomatous lesions is, therefore, critical for pathologists.

The causes of granulomatous inflammation are legion and include environmental exposures, genetic predisposition, infectious agents, and idiopathic conditions where no definitive cause can be found.[6] Infectious etiologies remain some of the most common causes globally, especially in developing countries where diseases such as tuberculosis and leprosy are considered endemic. The contribution of non-infectious causes to the burden of granulomatous diseases is also high and includes autoimmune disorders and foreign body reactions. The prevalence of these relative causes will vary according to geographic location, population, and health care setting, emphasizing the need for region-specific studies.

The persistence of poorly digested or indigestible antigens is an event especially linked to the pathogenesis of granuloma formation. Mycobacterium tuberculosis, Mycobacterium leprae, suture materials, and talc particles represent agents that are resistant to degradation by macrophages and thereby elicit a chronic inflammatory response.[7] Although granuloma formation is believed to be a mechanism that confines such agents, sustained inflammation can lead to tissue destruction and necrosis. The dual nature of granulomatous inflammation, being both a protective and a detrimental process, underlines its clinical importance.

Examination by biopsy remains the gold standard for the diagnosis of granulomatous lesions. Histopathological evaluation allows for an assessment of granuloma morphology, identification of necrosis, detection of foreign material, and evaluation of the surrounding tissue response. When combined with special stains, immunohistochemistry, and relevant clinical information, histopathology is crucial in narrowing the differential diagnosis, thereby reaching an etiology for granulomatous inflammation. Given the wide anatomical distribution, biopsy specimens from granulomatous lesions could emanate from a wide variety of organs, including lymph nodes, skin, lungs, gastrointestinal tract, among others.

Accurate diagnosis and care for the patients can only be enhanced by understanding the prevalence, morphological patterns, and anatomical distribution of granulomatous lesions. The information obtained from such a study is also useful in bringing out the disease patterns in a given population and helps in understanding the various common and uncommon etiologies for granulomatous inflammation. In spite of the clinical significance of granulomatous lesions, comprehensive studies that systematically review the histopathological spectrum in biopsy samples are few and scarce.

The main objective of the present study was the evaluation of the spectrum of granulomatous lesions observed in biopsy specimens and their prevalence, morphological characteristics, and anatomical distribution. Thus, based on the investigation of the aforementioned parameters, the work will try to contribute to a better understanding of granulomatous inflammation and support pathologists and clinicians for early and definitive diagnosis in order to ensure appropriate patient management.

Methodology

Study Design: This was a hospital-based descriptive observational study conducted to evaluate the histopathological spectrum, prevalence, morphological patterns, and anatomical distribution of granulomatous lesions in biopsy specimens.

Study Area: The study was carried out in the Department of Pathology, Madhubani Medical College & Hospital, Madhubani, Bihar, India.

Study Duration: The study was carried out over a period from January 2024 to July 2025

Sample Size: A total of 80 biopsy samples diagnosed histopathologically as granulomatous lesions were included in the study.

Study Population: The study population consisted of patients of all age groups and both sexes who underwent biopsy procedures at Madhubani Medical College & Hospital and whose biopsy specimens showed granulomatous inflammation on histopathological examination.

Inclusion Criteria

- All biopsy samples showing histopathological evidence of granulomatous inflammation
- Adequately preserved biopsy specimens
- Patients of all age groups and both sexes

Exclusion Criteria

- Poorly preserved or inadequately fixed tissue samples
- Biopsy specimens with inconclusive histopathological findings
- Recurrent biopsies from the same lesion

Data Collection: Relevant clinical and demographic information was collected from the pathology requisition forms and hospital medical records accompanying each biopsy specimen. The data included patient age, sex, anatomical site of the lesion, clinical presentation, and provisional diagnosis. Biopsy specimens were obtained through excisional biopsy, endoscopic surgical biopsy, or skin punch biopsy procedures. All samples were received in the Department of Pathology in 10% neutral buffered formalin and were assigned unique laboratory identification numbers to ensure proper tracking and confidentiality throughout processing and analysis.

Histopathological Examination: Following fixation, the biopsy specimens were subjected to routine tissue processing, paraffin embedding, and sectioning at a thickness of 3–5 µm. The tissue sections were routinely stained with hematoxylin and eosin (H&E) for detailed morphological evaluation of granulomatous inflammation. Special staining techniques were employed wherever indicated to identify specific etiological agents. Ziehl–Neelsen staining was performed to demonstrate acid-fast bacilli, particularly Mycobacterium tuberculosis, while Periodic acid–Schiff (PAS) staining was used to detect fungal elements. All stained slides were examined under light microscopy to assess the type and morphology of granulomas, presence of necrosis, multinucleated giant cells, and associated inflammatory features, thereby aiding in determining the underlying etiology of the granulomatous lesions.

Procedure: All biopsy specimens were grossly examined, processed using standard histopathological techniques, and stained appropriately. Microscopic evaluation was performed independently by pathologists to classify granulomatous lesions based on morphology and etiology. Clinical correlation was done wherever relevant.

Statistical Analysis: The collected data were entered into Microsoft Excel and analyzed using appropriate statistical software. Results were expressed in terms of frequencies and percentages. Descriptive statistics were used to assess the prevalence, morphological patterns, and anatomical distribution of granulomatous lesions. The findings were presented in tables and charts for clarity."

Result

Table 1 depicts the age and gender distribution of 80 patients diagnosed with granulomatous lesions. Females constituted a higher proportion of cases (60.0%) compared to males (40.0%), indicating a female predominance. The majority of patients were in the 21–40 years and 41–60 years age groups, each accounting for 35.0% of cases, suggesting that granulomatous lesions were most commonly observed in middle-aged adults. Patients younger than 20 years comprised 12.5% of the cohort, while those older than 60 years represented 17.5%. Across all age groups, females outnumbered males, particularly in the 21–40 and 41–60 year categories. Overall, the table highlights a higher prevalence of granulomatous lesions among females and a peak incidence in the middle-age decades.

Table 1: Age and Gender Distribution of Patients with Granulomatous Lesions (N = 80)

Age group (years)	Male n (%)	Female n (%)	Total n (%)
< 20	4 (5.0)	6 (7.5)	10 (12.5)
21–40	10 (12.5)	18 (22.5)	28 (35.0)
41–60	12 (15.0)	16 (20.0)	28 (35.0)
> 60	6 (7.5)	8 (10.0)	14 (17.5)
Total	**32 (40.0)**	**48 (60.0)**	**80 (100.0)**

Table 2 shows the anatomical distribution of granulomatous lesions among the 80 patients studied. Lymph nodes were the most commonly affected site, accounting for 32.5% of cases, highlighting their primary involvement in granulomatous pathology. Cutaneous lesions were the second most frequent (22.5%), followed by involvement of the gastrointestinal tract (15.0%). Pulmonary granulomatous lesions constituted 10.0% of cases, while the liver (7.5%) and bone (6.3%) were less commonly affected. A small proportion of lesions were categorized under other sites (6.2%). Overall, the findings indicate that granulomatous lesions most frequently involve lymph nodes and skin, with variable involvement of visceral organs.

Table 2: Anatomical Distribution of Granulomatous Lesions (N = 80)		
Site of lesion	**Frequency (n)**	**Percentage (%)**
Lymph node	26	32.5
Skin	18	22.5
Gastrointestinal tract	12	15
Lung	8	10
Liver	6	7.5
Bone	5	6.3
Others	5	6.2
Total	**80**	**100**

Table 3 illustrates the histomorphological patterns of granulomas observed in the study population. Caseating granulomas were the most prevalent, comprising 52.5% of cases, suggesting a strong association with infectious etiologies such as tuberculosis. Non-caseating granulomas accounted for 27.5% of cases and are typically seen in conditions like sarcoidosis and certain immune-mediated disorders. Foreign body granulomas represented 12.5% of cases, reflecting tissue reactions to exogenous or endogenous materials. Suppurative granulomas were the least common pattern (7.5%), often associated with bacterial or fungal infections. Overall, the predominance of caseating granulomas underscores the significant role of infectious causes in granulomatous lesions in this cohort.

Table 3: Histomorphological Pattern of Granulomas (N = 80)		
Type of granuloma	**Frequency (n)**	**Percentage (%)**
Caseating granuloma	42	52.5
Non-caseating granuloma	22	27.5
Foreign body granuloma	10	12.5
Suppurative granuloma	6	7.5
Total	**80**	**100**

Table 4 summarizes the etiological diagnoses of granulomatous lesions in the study population. Tuberculosis was the most common cause, accounting for 35% of cases, highlighting its continued predominance as an important infectious etiology of granulomatous inflammation. Sarcoidosis and granulomatous lesions not otherwise specified (NOS) each constituted 17.5% of cases, reflecting a substantial proportion of non-infectious or diagnostically indeterminate granulomas. Leprosy was identified in 12.5% of patients, indicating its ongoing clinical relevance in endemic regions. Fungal infections accounted for 10% of cases, while foreign body reactions comprised 7.5%. Overall, infectious causes—particularly tuberculosis—formed the majority of granulomatous lesions, emphasizing the need for thorough clinicopathological correlation and microbiological confirmation to establish definitive diagnoses.

Table 4: Etiological Diagnosis of Granulomatous Lesions (N = 80)		
Final diagnosis	**Frequency (n)**	**Percentage (%)**
Tuberculosis	28	35
Sarcoidosis	14	17.5
Leprosy	10	12.5
Fungal infection	8	10
Foreign body reaction	6	7.5
Granulomatous NOS	14	17.5
Total	**80**	**100**

Table 5 depicts the results of special staining in granulomatous lesions. Ziehl–Neelsen (ZN) stain positivity was observed in 30% of cases, supporting the diagnosis of mycobacterial infection, particularly tuberculosis, as a major etiological factor. Periodic acid–Schiff (PAS) stain was positive in 10% of cases, indicating the presence of fungal organisms in a subset of lesions. Notably, 60% of cases were negative for special stains, suggesting either non-infectious causes of granulomatous inflammation or infectious etiologies with low organism load not detectable by routine special stains. These findings underscore the importance of correlating histopathological features with clinical, radiological, and microbiological data to achieve an accurate etiological diagnosis.

Table 5: Special Stain Positivity in Granulomatous Lesions (N = 80)		
Special stain	**Positive cases (n)**	**Percentage (%)**
Ziehl–Neelsen stain	24	30
PAS stain	8	10
Negative for special stains	48	60
Total	**80**	**100**

Discussion

The present study highlights the varied histopathological spectrum of granulomatous lesions and forms important similarities and contrasts with the published literature. In our series of 80 biopsy-proven granulomatous lesions, most cases were found in adults, with the highest frequency in the age groups 21–40 years and 41–60 years (35% each). The predominance of adult involvement is in concern with previous studies that have recorded granulomatous diseases as more common in young and middle-aged individuals, probably because of a higher incidence of infections and immune responsiveness during these two decades of life (Manandhar et al., 2013; Moorthy et al., 2005) [8,9]. Unlike certain reports highlighting the peak incidence as being in the third decade alone, we report the burden to be continued well into the later adult years, arguing for chronic infections like tuberculosis and long-standing inflammatory conditions to continue to contribute significantly beyond early adulthood."

A notable observation in our study was the female predominance, with females accounting for 60% of cases and a male-to-female ratio of 1:1.5. This contrasts with many earlier studies reporting male predominance in granulomatous lesions, especially tubercular ones (Permi et al., 2017; Adams, 1976) [4,6]. The increased frequency in females in our cohort may point to changing epidemiology, improved access to healthcare for females, or greater contribution from immune-mediated diseases like sarcoidosis and idiopathic granulomatous disorders, which are known to have female preponderance in several populations (Rubin et al., 2012) [5]. These gender differences point toward socio-cultural, biological, and regional influences that act upon disease patterns.

Anatomically, lymph nodes were the most common site involved in our study, 32.5%, followed by skin, 22.5%, and the gastrointestinal tract, 15%. This is in agreement with several series that have reported lymph nodes as the commonest site of granulomatous inflammation, especially from regions where tuberculosis is still endemic (Permi et al., 2017; Adams, 1976) [4,6]. There are, however, other authors who have found the skin or gastrointestinal tract to be the predominant site, reflecting regional differences in disease prevalence and biopsy practices. For example, Permi et al. reported that the cutaneous site was the commonest presentation, while other studies have emphasized gastrointestinal involvement due to diseases like Crohn's disease and intestinal tuberculosis [4]. The relatively high cutaneous lesion rate in our study further highlights the role of skin biopsies in the diagnosis of granulomatous disorders, particularly leprosy and foreign body reactions.

Caseating granulomas represented the most common histomorphologic pattern in our series at 52.5%. This observation is in keeping with the classic association between caseation necrosis and infectious etiologies, mainly tuberculosis, reported in standard pathology texts and earlier reviews (Rubin et al., 2012; Goodnight & Danese, 1969) [5,7]. Similar proportions have been reported in studies from regions where tuberculosis is endemic, illustrating the continued relevance of the disease in granulomatous pathology (Permi et al., 2017) [4]. Non-caseating granulomas made up 27.5% in our series, a figure comparable to that in series where sarcoidosis and idiopathic granulomatous inflammation contributed significantly. This underscores the challenge posed by non-caseating granulomas, whose diagnosis is critically dependent on careful clinicopathological correlation aimed at excluding infectious etiologies.

Foreign body granulomas accounted for 12.5% of our series, which is slightly higher than what was reported in some series but comparable to others from tertiary care settings where surgical and cosmetic procedures are common (Permi et al., 2017) [4]. Suppurative granulomas were relatively few, 7.5%, in concurrence with previous observations that this pattern is usually associated with specific infections such as fungal or atypical bacterial etiologies rather than the more prevalent mycobacterial infections (Adams, 1976) [6].

Etiologically, tuberculosis emerged as the leading cause of granulomatous lesions in our study with 35% cases. This finding closely parallels figures from several Indian and South Asian studies and reinforces tuberculosis as the most important cause of granulomatous inflammation in endemic regions (Permi et al., 2017; Rubin et al., 2012) [4,5]. Sarcoidosis and granulomatous lesions not otherwise specified each formed 17.5% of cases, a figure that represents both the increasing awareness of immune-mediated granulomatous diseases as well as the intrinsic limitations in arriving at an exact etiology in a subset of biopsies. Leprosy made up 12.5% of cases, similar to previous dermatopathological

studies that cited a continued burden of this disease despite national elimination programs (Manandhar et al., 2013) [8]. Fungal infections (10%) and foreign body reactions (7.5%) further accentuate the heterogeneous nature of granulomatous pathology.

Special stains supported the histological diagnosis in a subset of cases, with Ziehl-Neelsen positivity in 30% and PAS positivity in 10%. These figures are comparable to previous reports that have noted variable detection rates depending on organism load and tissue sampling (Permi et al., 2017; Adams, 1976) [4,6]. The high proportion of stain-negative cases serves to reinforce the mainstay of diagnosis as integration of histomorphology with clinical, radiological, and microbiological data. Overall, our findings both corroborate and extend existing literature, highlighting regional variations while reaffirming the central role of tuberculosis and lymph node involvement in the histopathological spectrum of granulomatous lesions.

Conclusion

This study emphasizes a wide histopathological spectrum of granulomatous lesions in biopsy material, highlighting their diverse demographic involvement, anatomical distribution, and morphological patterns. Granulomatous lesions were observed more frequently in adults with female predominance. Lymph nodes and skin were commonly involved, followed by visceral and skeletal sites. Caseating granulomas were the most frequent histomorphological pattern, reflecting the predominance of the infectious etiology, especially tuberculosis, while non-caseating and foreign body granulomas reflected immune-mediated and reactive processes. The etiological profile showed that about one-third of the cases could be assigned to specific diseases like tuberculosis, sarcoidosis, leprosy, and fungal infections, although a subset remained nonspecific despite detailed evaluation. Special stains helped confirm infectious etiology in selected cases but were negative in many, thus reiterating that histomorphology must be interpreted in the light of clinical and ancillary findings. The study therefore supports the critical role played by histopathological examination assisted with special stains and clinicopathological correlation for the correct diagnosis and classification of granulomatous lesions.

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