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Clinicopathological Study of Granulomatous Lymphadenitis: A Descriptive Cross-Sectional Study of Patterns and Aetiological Insights in a Tertiary Care Centre.

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Abstract

Background:
Granulomatous lymphadenitis represents a distinctive histopathological response to a wide spectrum of infectious and non-infectious causes. Despite tuberculosis being the predominant etiology in developing nations, the diverse morphological patterns often necessitate meticulous clinicopathological correlation to establish a definitive diagnosis.

Objectives:
To analyze the histomorphological patterns of granulomatous lymphadenitis, determine its etiological spectrum, and assess the diagnostic utility of ancillary staining methods in differentiating specific causes.

Materials and Methods:
A descriptive cross-sectional study was conducted in the Department of Pathology of a tertiary care teaching hospital over a two-year period. Fifty lymph node biopsy specimens reported as granulomatous lymphadenitis were included. Detailed clinical data were recorded. Histological examination was performed on formalin-fixed paraffin-embedded sections stained with hematoxylin and eosin. Ziehl–Neelsen (ZN) stain for acid-fast bacilli and Periodic Acid–Schiff (PAS) and Grocott Methenamine Silver (GMS) stains for fungi were employed when indicated.

Results:
The patients ranged from 8 to 72 years (mean 36.8 ± 14.2 years) with a female predominance (M: F = 1:1.3). Cervical lymph nodes were most commonly involved (70%). Caseating granulomas constituted 56%, non-caseating 28%, and suppurative 16%. Tuberculous lymphadenitis was the most frequent etiology (44%), followed by sarcoidosis (16%), cat-scratch disease (6%), and fungal lymphadenitis (4%), while 30% remained non-specific. Langhans giant cells were observed in 70% of cases, and a significant association was noted between necrosis and AFB positivity ($p < 0.05$).

Conclusion:
Tuberculosis continues to be the leading cause of granulomatous lymphadenitis in this region, predominantly affecting cervical nodes. Histopathology supported by special stains remains pivotal for accurate diagnosis.

Recommendations:
Routine use of AFB and fungal stains is strongly advised in all granulomatous lymphadenitis cases. Clinico-radiological correlation should be integrated to improve diagnostic precision and enable early therapeutic intervention.

Keywords: *Granulomatous lymphadenitis; Tuberculous lymphadenitis; Sarcoidosis; Caseating granuloma; Acid-fast bacilli.*
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Introduction

Granulomatous lymphadenitis represents a distinctive histopathological reaction to various infectious, inflammatory, and occasionally neoplastic conditions. It is characterized by the formation of epithelioid cell granulomas with or without multinucleated giant cells and varying degrees of necrosis within the lymph node structure [1]. The granulomatous response reflects a cell-mediated immune mechanism aimed at containing persistent antigens or pathogens that resist degradation [2].

A wide array of etiologies, including *Mycobacterium tuberculosis*, *Bartonella henselae*, *Toxoplasma gondii*, fungal organisms, and non-infectious conditions such as sarcoidosis, can produce similar granulomatous patterns, thereby complicating diagnosis [3]. The clinical and morphological overlap among these entities necessitates a multidisciplinary approach that integrates clinical data, histopathology, and microbiological confirmation to establish an accurate etiological diagnosis [1–3].

In developing countries like India, tuberculosis remains the predominant cause of granulomatous lymphadenitis, despite national control programs and improved public health awareness [4]. Nonetheless, non-tuberculous causes such as sarcoidosis, cat-scratch disease, and fungal lymphadenitis are being increasingly recognized, particularly with rising rates of HIV infection and immunosuppression [5].

The morphological pattern of granulomatous inflammation, caseating, non-caseating, or suppurative, provides important diagnostic clues; however, these features are not pathognomonic. Hence, the use of special stains such as Ziehl–Neelsen (ZN) for acid-fast bacilli, Periodic Acid–Schiff (PAS), and Grocott Methenamine Silver (GMS) for fungi remains indispensable to identify causative agents and exclude mimicking conditions [4,5].

Understanding the clinicopathological spectrum and etiological distribution of granulomatous lymphadenitis is crucial for accurate diagnosis, rational therapy, and prevention of unnecessary empirical treatment, particularly in tuberculosis-endemic regions like India.

Hence, the present study was undertaken to evaluate the histomorphological patterns, etiological distribution, and diagnostic yield of ancillary stains in cases of granulomatous lymphadenitis at a tertiary care centre, aiming to contribute regional insights into its evolving epidemiology and clinical significance.

Materials and Methods

Study Design and Duration

This was a descriptive cross-sectional study conducted in the Department of Pathology, JR Medical College, Tindivanam, over a period of six months, from January 2025 to June 2025. JR Medical College, Tindivanam, is a tertiary care teaching hospital catering to both urban and rural populations of Villupuram district and surrounding regions. The institution provides comprehensive diagnostic, clinical, and laboratory services, including advanced histopathological evaluation, making it a suitable center for clinicopathological studies.

Study Population

Participants were selected using a consecutive sampling method. All lymph node biopsy specimens received in the Department of Pathology during the study period and diagnosed as granulomatous lymphadenitis were included. Cases were referred from various clinical departments, including general medicine, surgery, and pediatrics.

Study Size

The study included 50 cases based on the total number of eligible granulomatous lymphadenitis cases received during the study period. Due to the exploratory nature of the study and limited duration, all available cases meeting the inclusion criteria were included.

Inclusion Criteria

All lymph node biopsy specimens showed features of granulomatous inflammation on histopathology.

Adequate tissue samples suitable for special staining and microscopic evaluation.

Exclusion Criteria

Lymph node biopsies showing metastatic deposits or lymphoma without granulomatous features.

Inadequate or poorly preserved samples.

Data Collection and Histopathological Analysis

Detailed clinical data, including age, gender, site, and duration of lymphadenopathy, were recorded. The specimens were fixed in 10% neutral buffered formalin, processed routinely, and sections of 4–5 µm thickness were stained with hematoxylin and eosin (H&E) for morphological assessment.

Based on histological features, granulomas were classified as caseating, non-caseating, or suppurative. The presence of Langhans giant cells, necrosis, and other associated changes was documented.

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Special Stains and Ancillary Tests

To determine the etiology:

Ziehl–Neelsen (ZN) stain was used to detect acid-fast bacilli (AFB) for tuberculous lymphadenitis.

Periodic Acid–Schiff (PAS) and Grocott Methenamine Silver (GMS) stains were applied when fungal infection was suspected.

Clinical and serological correlation was sought in cases suggestive of sarcoidosis or cat-scratch disease.

Bias

Efforts were made to minimize selection and observer bias. Only histopathologically confirmed cases were included. Standardized staining protocols and reporting criteria were followed. All slides were reviewed by experienced pathologists to ensure diagnostic consistency.

Data Analysis

All data were entered into Microsoft Excel and analyzed using descriptive statistics. Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were summarized as frequencies and percentages. The relationship between histopathological features and AFB positivity was assessed descriptively.

Ethical Considerations

The study protocol was reviewed and approved by the Institutional Ethics Committee of JR Medical College, Tindivanam. Patient confidentiality was maintained throughout, and all data were used solely for academic and research purposes.

Results

Participant Flow

A total of 58 lymph node biopsy specimens were assessed for eligibility during the study period. Of these, 8 cases were excluded due to inadequate tissue or non-granulomatous pathology. The remaining 50 cases fulfilled the inclusion criteria and were included in the final analysis.

A total of 50 cases of granulomatous lymphadenitis were analyzed in the present study. The age of the patients ranged from 8 to 72 years, with a mean age of 36.8 ± 14.2 years. The maximum incidence (38%) was observed in the 31–45 years age group, followed by 26% in the 16–30 years age group. There was a female predominance, with a male-to-female ratio of 1:1.3 (Table 1).

The duration of lymphadenopathy ranged from 2 weeks to 6 months, with the majority of patients (60%) presenting within 1–3 months of onset.

Table 1. Age and Gender Distribution of Cases (n = 50)

Age Group (years)	Male	Female	Total (%)
0–15	2	3	5 (10.0)
16–30	6	7	13 (26.0)
31–45	8	11	19 (38.0)
46–60	4	5	9 (18.0)
>60	1	3	4 (8.0)
Total	**21**	**29**	**50 (100)**

Mean age: 36.8 ± 14.2 years; Male:Female ratio = 1:1.3.

The cervical lymph nodes were the most frequently involved, accounting for 70% of cases, followed by axillary (14%), mediastinal (8%), and mesenteric (8%) lymph nodes (Table 2). This predominance of cervical involvement corresponded with the high prevalence of tuberculous lymphadenitis, which remains the most common etiological entity in developing regions.

Table 2. Distribution of Lymph Node Involvement

Site of Lymph Node	No. of Cases (n=50)	Percentage (%)
Cervical	35	70.0
Axillary	7	14.0
Mediastinal	4	8.0
Mesenteric	4	8.0
Total	**50**	**100.0**

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Cervical nodes were the most commonly involved (70%), consistent with the high prevalence of tuberculous etiology. Histopathological examination revealed three distinct morphological patterns of granulomatous inflammation. Caseating granulomas were the most frequent pattern, observed in 28 cases (56%), while non-caseating granulomas and suppurative granulomas were seen in 14 (28%) and 8 (16%) cases, respectively (Table 3, Figure 1). Langhans giant cells were identified in 35 cases (70%), and a statistically significant correlation was noted between the presence of caseous necrosis and acid-fast bacilli positivity on Ziehl–Neelsen staining ($p < 0.05$).

Table 3. Histopathological Patterns of Granulomatous Lymphadenitis

Histological Pattern	No. of Cases	Percentage (%)
Caseating granulomas	28	56.0
Non-caseating granulomas	14	28.0
Suppurative granulomas	8	16.0
Total	**50**	**100.0**

Langhans giant cells were seen in 70% of specimens, and necrosis strongly correlated with AFB positivity ($p < 0.05$).

The etiological distribution (Table 4) demonstrated that tuberculous lymphadenitis was the most common cause, constituting 44% of all cases, followed by sarcoidosis (16%), cat-scratch disease (6%), and fungal lymphadenitis (4%). The remaining 15 cases (30%) were categorized as non-specific or indeterminate, due to inconclusive morphological or special stain findings. Fungal infections were confirmed through Periodic Acid–Schiff (PAS) and Grocott Methenamine Silver (GMS) staining, which revealed Histoplasma in one case and Cryptococcus in another.

Table 4. Aetiological Distribution of Granulomatous Lymphadenitis

Etiology	No. of Cases (n=50)	Percentage (%)
Tuberculous lymphadenitis	22	44.0
Sarcoidosis	8	16.0
Cat-scratch disease	3	6.0
Fungal lymphadenitis	2	4.0
Non-specific / Indeterminate cause	15	30.0
Total	**50**	**100.0**

Tuberculosis remained the leading etiology (44%), followed by sarcoidosis (16%). Fungal infections were rare but confirmed with PAS/GMS stains.

Discussion

The present study analyzed 50 histopathologically confirmed cases of granulomatous lymphadenitis diagnosed over six months at JR Medical College, Tindivanam, emphasizing demographic patterns, site distribution, histopathological features, and etiological spectrum.

Demographic Profile and Nodal Distribution

The age of patients ranged from 8 to 72 years, with a mean age of 36.8 ± 14.2 years. The peak incidence in the 31–45 year age group and a mild female predominance (M: F = 1:1.3) are comparable with earlier studies documenting higher prevalence among young and middle-aged adults, likely due to active immune responses and greater environmental exposure to *Mycobacterium tuberculosis* [6,7]. The predominance of cervical lymphadenopathy (70%) mirrors established patterns in tuberculosis-endemic areas and supports the well-documented anatomical predisposition of cervical nodes in tuberculous infection [8,9].

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Histopathological Patterns

Histomorphological assessment revealed caseating granulomas in 56%, non-caseating granulomas in 28%, and suppurative granulomas in 16% of cases. The significant association between caseous necrosis and AFB positivity ($p < 0.05$) reinforces the diagnostic value of necrosis in tuberculous lymphadenitis, as also observed in recent literature emphasizing histological accuracy in tuberculosis diagnosis [6]. However, necrosis is not exclusive to tuberculosis fungal infections, sarcoid-like reactions, and necrotizing viral granulomatous lymphadenitis, such as that caused by *Herpes simplex virus*, can mimic these findings [10].

Langhans-type giant cells were present in 70% of cases, consistent with reports describing their frequent occurrence in both tuberculous and sarcoid granulomas [7]. Non-caseating granulomas correlated with sarcoidosis, while suppurative granulomas were linked to cat-scratch disease and fungal etiologies, reflecting a histologic spectrum similar to other contemporary analyses [8].

Aetiological Distribution and Comparative Analysis

In the current series, tuberculosis remained the predominant cause (44%), aligning with prior regional and international studies identifying *M. tuberculosis* as the leading etiology in granulomatous lymphadenitis [6,9]. Sarcoidosis accounted for 16% of cases, highlighting increasing awareness and diagnostic precision for non-tuberculous granulomatous diseases even in high-TB-burden areas [7]. Cat-scratch disease (6%) and fungal infections (4%) were relatively infrequent but significant for differential diagnosis, as accurate identification prevents inappropriate anti-tubercular therapy.

Interestingly, 30% of cases were classified as non-specific or indeterminate. This finding parallels other reports where limited tissue sampling, paucibacillary infection, and the absence of advanced diagnostic modalities such as PCR or culture restricted etiological confirmation [8,11]. Similar challenges have been noted in pediatric populations, where indeterminate granulomatous lymphadenitis often necessitates multidisciplinary evaluation [12].

Pathogenesis and Diagnostic Considerations

Granulomatous inflammation arises from a complex immunological response involving macrophage activation and T-cell-mediated hypersensitivity to persistent antigens. Tuberculous granulomas typically exhibit central caseation surrounded by epithelioid histiocytes and Langhans giant cells, whereas sarcoidosis shows compact, non-necrotizing granulomas with sparse lymphocytes and minimal necrosis [7]. Because morphological overlap between infectious and non-infectious causes is frequent, a combined diagnostic approach incorporating ZN, PAS, and GMS stains along with clinicoradiological correlation remains crucial for accurate classification and management [9,10].

Conclusion

The present study highlights that tuberculosis remains the predominant cause of granulomatous lymphadenitis, particularly involving the cervical lymph nodes of young and middle-aged adults. Histopathological examination continues to be the cornerstone of diagnosis, with caseating granulomas and acid-fast bacilli positivity serving as strong indicators of tuberculous etiology. However, non-tuberculous causes such as sarcoidosis, fungal, and cat-scratch disease must be considered, especially in ZN-negative cases. The routine use of special stains, supported by clinical and radiological correlation, enhances diagnostic precision. Establishing standardized diagnostic algorithms integrating morphology, microbiology, and molecular tools can significantly improve etiological identification and guide timely, targeted therapy in granulomatous lymphadenitis.

The findings of this study highlight the continued predominance of tuberculosis as a major cause of granulomatous lymphadenitis in endemic regions. The strong association between necrosis and AFB positivity reinforces the diagnostic importance of histomorphological evaluation, particularly in resource-limited settings.

Generalizability

The findings of this study are applicable to similar tertiary care settings in tuberculosis-endemic regions. However, variations in etiological distribution may occur in regions with lower TB prevalence or better access to advanced diagnostic modalities.

Limitations

The study was limited by its small sample size, short duration, and lack of advanced diagnostic modalities such as GeneXpert or molecular assays for Mycobacterium tuberculosis and non-tuberculous mycobacteria. The absence of long-term follow-up and culture confirmation restricted the ability to establish causality in indeterminate cases. Multicentric studies with broader diagnostic support are warranted.

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Recommendations

Routine Ziehl–Neelsen staining should be performed for all lymph node biopsies showing granulomatous inflammation to promptly identify tuberculous etiology. In ZN-negative cases, fungal stains (PAS and GMS) and serological or molecular tests should be utilized to detect alternative causes such as sarcoidosis, cat-scratch disease, or fungal infections. A standardized diagnostic protocol integrating histopathology, microbiology, and clinical correlation is essential to improve diagnostic accuracy. Empirical anti-tubercular therapy should be avoided without confirmatory evidence to prevent mismanagement. Pathologists and clinicians should collaborate closely to ensure early diagnosis, precise classification, and timely intervention, thereby reducing disease morbidity and unnecessary therapeutic exposure.

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Abbreviations

AFB – Acid-Fast Bacilli
ATT – Anti-Tubercular Therapy
CTL – Cervical Tuberculous Lymphadenitis
DNA – Deoxyribonucleic Acid
GMS – Grocott Methenamine Silver
H&E – Hematoxylin and Eosin
HIV – Human Immunodeficiency Virus
JRMC – JR Medical College
NAAT – Nucleic Acid Amplification Test
PAS – Periodic Acid–Schiff
PCR – Polymerase Chain Reaction
TB – Tuberculosis
ZN – Ziehl–Neelsen

Source of funding

The study has no funding.

Conflict of interest

The author declares no conflict of interest.

Author contributions

SA-Concept and design of the study, results interpretation, review of literature, and preparation of the first draft of the manuscript. Statistical analysis and interpretation, revision of manuscript. **TT**-design of the study, results interpretation, review of literature, and preparing the first draft of the manuscript. Statistical analysis and interpretation, revision of manuscript.**VP**- results interpretation, review of literature, and preparing the first draft of the manuscript. Statistical analysis and interpretation, revision of the manuscript

Data availability

Data available on request

Author Biography

Dr. Siri Annam, MBBS, MD, Assistant Professor, Department of Pathology, JR Medical College, Tindivanam, Villupuram District, Tamil Nadu, India. Dr. Siri Annam is an accomplished academic pathologist with strong expertise in histopathology, cytopathology, and hematopathology. She obtained her MBBS from Osmania Medical College, Hyderabad, in 2007, and completed her MD in Pathology from Kakatiya Medical College, Warangal, in 2011. Over her professional career, she has contributed extensively to undergraduate teaching, diagnostic pathology, and institutional research. Her key research interests include the clinicopathological correlation of infectious and inflammatory diseases, especially granulomatous lymphadenitis in endemic settings. Dr. Annam is committed to promoting evidence-based diagnostics, laboratory quality assurance, and the integration of morphology with molecular pathology for enhanced patient care. **ORCID iD:** https://orcid.org/0009-0008-4054-237X

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His academic and clinical responsibilities include undergraduate and postgraduate teaching, diagnostic reporting, and participation in multidisciplinary clinicopathological discussions. Dr. Thorram has a keen interest in diagnostic cytology, oncopathology, and quality assurance in laboratory medicine. He has been actively involved in institutional research activities and contributes

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to scientific publications and academic conferences. His professional focus centers on strengthening evidence-based pathology practice and enhancing diagnostic accuracy in tertiary care settings.

Dr. Vemisetty Praveen, MBBS, DMRD, completed his MBBS in June 2006 from Odessa State Medical University and obtained his Diploma in Medical Radiodiagnosis (DMRD) in November 2010 from Mamatha Medical College, Khammam. He served as a Senior Resident in the Department of Radiology at ASRAM Medical College, Eluru, from April 2013 to May 2019. He is presently working as a Consultant Radiologist at Medicare Diagnostics, Kothagudem, Telangana, India.

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