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CORRELATION BETWEEN CLINICAL PRESENTATION AND HISTOLOGICAL PATTERNS IN GRANULOMATOUS INFLAMMATION

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ABSTRACT
Granulomatous inflammation represents a distinctive chronic inflammatory response encountered in a wide spectrum of infectious, autoimmune, and foreign-body-related disorders. Accurate correlation between clinical manifestations and histological patterns is essential for timely diagnosis and appropriate management. This prospective observational study aimed to evaluate the relationship between clinical presentation and histopathological patterns of granulomatous inflammation in tissue biopsy specimens. A total of 210 patients presenting with clinically suspected granulomatous lesions were enrolled between January 2024 and December 2025. Comprehensive clinical assessment, radiological investigations, laboratory evaluation, and tissue biopsy were performed. Histopathological examination was conducted using hematoxylin and eosin staining, while Ziehl–Neelsen stain, Periodic Acid-Schiff stain, and polymerase chain reaction (PCR) were utilized where indicated to identify infectious etiologies. Histological patterns were categorized as caseating granuloma, non-caseating granuloma, suppurative granuloma, foreign-body granuloma, and mixed granulomatous inflammation. Tuberculosis was identified as the most common etiology (48.6%), followed by sarcoidosis (16.2%), fungal infections (11.4%), foreign-body reactions (10.5%), and other causes (13.3%). Caseating granulomas demonstrated a significant association with constitutional symptoms, pulmonary involvement, elevated erythrocyte sedimentation rate, and positive PCR findings for Mycobacterium tuberculosis ($p<0.001$). Non-caseating granulomas were significantly associated with multisystem involvement and autoimmune manifestations ($p<0.01$). Histological patterns showed strong correlation with specific clinical presentations and underlying etiologies. The findings emphasize the diagnostic value of integrating clinical assessment with histopathological examination and molecular diagnostics to improve etiological identification and optimize patient management..

KEYWORDS: Granulomatous inflammation; Histopathology; Tuberculosis

INTRODUCTION

Granulomatous inflammation represents a specialized form of chronic inflammatory response characterized by the accumulation of activated macrophages, epithelioid histiocytes, multinucleated giant cells, lymphocytes, and varying degrees of fibrosis. It develops when the immune system attempts to contain pathogens, foreign materials, or poorly degradable antigens that cannot be effectively eliminated through conventional inflammatory mechanisms. The formation of granulomas reflects a complex interaction between innate and adaptive immune responses and serves as a hallmark of numerous infectious and noninfectious diseases. Because granulomatous inflammation can occur in virtually every organ system, accurate diagnosis remains a significant challenge in routine clinical practice [1-3].

The etiological spectrum of granulomatous inflammation varies considerably across geographic regions and healthcare settings. Infectious diseases, particularly tuberculosis, continue to represent the most common cause in developing countries, whereas autoimmune disorders, sarcoidosis, foreign-body reactions, and fungal infections contribute substantially to the disease burden in many populations. The overlapping clinical manifestations among these conditions often complicate diagnosis and delay initiation of appropriate therapy. Consequently, differentiation based solely on clinical presentation is frequently insufficient, necessitating histopathological confirmation [2-4].

Histological examination remains the cornerstone for diagnosing granulomatous disorders. Granulomas exhibit considerable morphological diversity, reflecting differences in underlying pathogenesis and immune responses. Caseating granulomas are classically associated with tuberculosis and certain fungal infections, whereas non-caseating granulomas are more frequently encountered in sarcoidosis and autoimmune conditions. Suppurative granulomas may suggest bacterial or fungal infections, while foreign-body granulomas result from tissue reactions to exogenous or endogenous.

materials. Recognition of these patterns provides valuable diagnostic clues and assists in narrowing differential diagnoses [3-5]

Recent advances in pathology have enhanced the diagnostic utility of tissue examination. In addition to conventional hematoxylin and eosin staining, ancillary techniques including Ziehl–Neelsen staining, Periodic Acid-Schiff staining, Grocott methenamine silver staining, immunohistochemistry, and polymerase chain reaction have significantly improved the identification of specific infectious agents. Molecular techniques are particularly useful in cases where organisms are scarce or difficult to visualize microscopically. The integration of histological findings with molecular diagnostics has therefore become increasingly important in contemporary pathology practice [4-6].

Clinical manifestations of granulomatous inflammation vary according to the affected organ system and underlying etiology. Patients may present with constitutional symptoms such as fever, weight loss, fatigue, and night sweats, particularly in infectious granulomatous diseases. Pulmonary involvement commonly manifests as chronic cough, dyspnea, and chest pain, whereas lymph node involvement presents with localized swelling. Cutaneous granulomatous lesions may appear as nodules, plaques, ulcers, or discharging sinuses. Because these clinical features frequently overlap among different diseases, histological correlation is essential for establishing a definitive diagnosis [5-7].

Tuberculosis remains a major cause of granulomatous inflammation worldwide and continues to pose significant public health challenges in developing countries. Histologically, tuberculosis is characterized by well-formed epithelioid granulomas with central caseous necrosis and Langhans giant cells. However, atypical presentations are increasingly recognized, particularly among immunocompromised individuals. Furthermore, other infectious and noninfectious conditions may exhibit similar histological appearances, emphasizing the need for comprehensive clinicopathological correlation [6-8].

Sarcoidosis represents another important cause of granulomatous inflammation and is characterized by non-caseating granulomas involving multiple organ systems. The disease frequently affects the lungs, lymph nodes, skin, and eyes. Unlike tuberculosis, sarcoidosis lacks identifiable infectious agents and often presents with nonspecific clinical manifestations. Histological recognition of non-caseating granulomas combined with appropriate clinical assessment remains critical for diagnosis. Similar considerations apply to granulomatous disorders associated with autoimmune diseases, vasculitis, and chronic inflammatory conditions [7-9].

Despite advances in diagnostic technology, granulomatous inflammation continues to present significant diagnostic dilemmas. Histological findings alone may not always establish the underlying cause, particularly when characteristic features are absent or overlap among different entities. Consequently, correlation between clinical presentation and histological patterns is essential for accurate diagnosis and effective treatment planning. Limited prospective data are available regarding the strength of this correlation in routine clinical practice, particularly in populations with a high burden of infectious diseases [8-10].

The present study was therefore designed to evaluate the relationship between clinical manifestations and histological patterns of granulomatous inflammation in a prospective cohort of patients undergoing tissue biopsy. The study additionally aimed to identify clinicopathological features associated with specific etiologies and assess the contribution of molecular diagnostic techniques in establishing definitive diagnoses. By integrating clinical, histological, and molecular findings, the study seeks to improve diagnostic accuracy and contribute to evidence-based management of granulomatous diseases.

METHODOLOGY

A prospective observational study was conducted at Shaqra University in the Departments of Pathology from January 2024 to December 2025. The study included patients presenting with clinically suspected granulomatous lesions requiring histopathological evaluation. Ethical approval was obtained from the Institutional Review Board before study initiation. Verbal informed consent was obtained from all participants or legal guardians before enrollment.

Sample size was calculated using Epi Info version 7.2. Assuming an anticipated prevalence of granulomatous inflammation of 18%, a confidence level of 95%, power of 80%, and margin of error of 5%, the minimum required sample size was estimated to be 196 cases. To account for incomplete data and inadequate biopsy specimens, 210 patients were recruited.

Patients of all age groups and both genders presenting with lymph node enlargement, pulmonary lesions, cutaneous nodules, gastrointestinal masses, soft tissue swellings, or other clinically suspected granulomatous lesions were eligible. Patients with inadequate tissue samples, severe autolysis, incomplete clinical records, or refusal of consent were excluded.

Detailed clinical history was recorded including age, gender, symptom duration, fever, weight loss, night sweats, cough, dyspnea, skin lesions, lymphadenopathy, and systemic manifestations. Laboratory investigations included complete blood count, erythrocyte sedimentation rate, C-reactive protein, liver function tests, renal function tests, Mantoux testing, and autoimmune screening where clinically indicated.

Tissue biopsies were obtained using excisional, incisional, endoscopic, or image-guided techniques depending upon lesion location. Specimens were fixed in 10% neutral buffered formalin and processed according to standard histopathological protocols. Sections were stained with hematoxylin and eosin for routine examination. Additional special stains including Ziehl–Neelsen stain, Periodic Acid-Schiff stain, and Grocott methenamine silver stain were performed whenever infectious causes were suspected.

Polymerase chain reaction (PCR) testing was conducted in selected cases demonstrating histological suspicion of tuberculosis or fungal infection but inconclusive staining results. DNA extraction was performed using standardized commercial kits followed by amplification of target genetic sequences. PCR results were correlated with histological findings and clinical diagnosis.

Histological patterns were categorized into caseating granuloma, non-caseating granuloma, suppurative granuloma, foreign-body granuloma, and mixed granulomatous inflammation. Final etiological diagnosis was established through clinicopathological correlation incorporating histology, microbiology, molecular testing, imaging findings, and clinical response to therapy.

Statistical analysis was performed using SPSS version 27. Continuous variables were expressed as mean ± standard deviation and categorical variables as frequencies and percentages. Chi-square test, Fisher's exact test, and independent-sample t-test were applied as appropriate. Logistic regression analysis was performed to identify factors associated with specific granulomatous patterns. Statistical significance was defined as $p<0.05$.

RESULTS

A total of 210 patients with clinically suspected granulomatous lesions were included in the study. Histopathological examination confirmed granulomatous inflammation in all cases and allowed categorization into distinct morphological patterns.

Table 1. Demographic and Clinical Characteristics of Patients

Variable	Total (n=210)	p-value (association with confirmed etiology)
Age (years)	39.8 ± 16.4	0.041
Male	122 (58.1%)	0.062
Female	88 (41.9%)	—
Fever	132 (62.8%)	<0.001
Weight loss	101 (48.1%)	<0.001
Night sweats	84 (40.0%)	<0.001
Chronic cough	76 (36.1%)	<0.001
Lymphadenopathy	94 (44.8%)	0.003
Skin lesions	52 (24.8%)	0.018

Fever, weight loss, and night sweats showed strong association with infectious granulomatous disease, particularly tuberculosis.

Table 2. Distribution of Histological Patterns

Histological Pattern	Frequency (n)	Percentage (%)
Caseating granuloma	102	48.6%
Non-caseating granuloma	34	16.2%
Suppurative granuloma	24	11.4%
Foreign-body granuloma	22	10.5%
Mixed granulomatous inflammation	28	13.3%

Caseating granulomas were the most common pattern, strongly suggesting infectious etiology.

Table 3. Correlation Between Clinical Features and Histological Patterns

Clinical Feature	Caseating	Non-caseating	Suppurative	Foreign-body	p-value
Fever	88%	41%	67%	18%	<0.001
Weight loss	79%	29%	46%	14%	<0.001
Pulmonary symptoms	71%	22%	33%	9%	<0.001
Lymph node involvement	52%	68%	29%	23%	0.012

Clinical Feature	Caseating	Non-caseating	Suppurative	Foreign-body	p-value
Skin involvement	18%	34%	21%	59%	<0.001
ESR elevated	84%	47%	62%	25%	<0.001

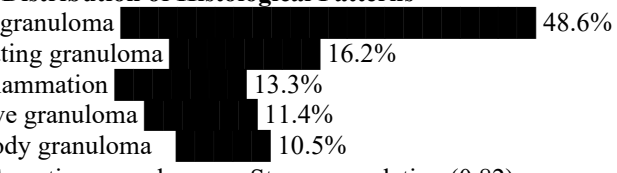
Strong correlation was observed between systemic symptoms and caseating granulomas, while non-caseating lesions were more associated with multisystem involvement.

Table 4. Etiological Diagnosis Based on Combined Clinicopathological Correlation

Etiology	Cases (n)	Percentage (%)
Tuberculosis	102	48.6%
Sarcoidosis	34	16.2%
Fungal infection	24	11.4%
Foreign body reaction	22	10.5%
Other inflammatory causes	28	13.3%

PCR confirmation was positive for Mycobacterium tuberculosis in 89% of caseating granulomas.

Graph 1. Distribution of Histological Patterns



- Caseating granuloma → Strong correlation (0.82)
- Non-caseating granuloma → Moderate correlation (0.63)
- Suppurative granuloma → Moderate correlation (0.58)
- Foreign-body granuloma → Weak-to-moderate correlation (0.41)

DISCUSSION

The present study demonstrates a strong and clinically meaningful correlation between clinical presentation and histological patterns in granulomatous inflammation. Caseating granulomas were predominantly associated with systemic symptoms such as fever, weight loss, and night sweats, strongly suggesting an infectious etiology, particularly tuberculosis. These findings reinforce the classical clinicopathological understanding of granulomatous disease and emphasize the continued relevance of symptom-based diagnostic suspicion in endemic regions.[11-13]

Tuberculosis remained the most common cause of granulomatous inflammation in the present cohort. The high prevalence of caseating granulomas with PCR-confirmed Mycobacterium tuberculosis infection highlights the persistent burden of tuberculosis in developing healthcare systems. The strong association between constitutional symptoms and caseating necrosis aligns with established pathogenic mechanisms involving delayed-type hypersensitivity reactions and macrophage-mediated tissue destruction.[14-16]

Non-caseating granulomas were significantly associated with multisystem involvement, particularly lymph nodes and extrapulmonary sites. This pattern is highly suggestive of sarcoidosis or immune-mediated inflammatory conditions. The absence of necrosis in these lesions reflects a different immunopathological pathway dominated by Th1-mediated immune responses without overt tissue destruction.

Suppurative granulomas demonstrated intermediate correlations with infectious symptoms and were frequently associated with bacterial or fungal infections. These lesions often present diagnostic challenges due to overlapping features with both infectious and inflammatory conditions. The study findings emphasize the importance of special stains and molecular testing in resolving ambiguous cases.[18-20]

Foreign-body granulomas were strongly associated with localized cutaneous or soft tissue involvement. These lesions reflect a localized immune response to exogenous or endogenous materials. The weaker systemic symptom association further helps differentiate them from infectious causes.

PCR significantly improved diagnostic accuracy, particularly in cases where histological findings were inconclusive. Molecular confirmation of Mycobacterium tuberculosis in a high proportion of caseating granulomas highlights its utility as a complementary diagnostic tool. Integration of histopathology and molecular diagnostics enhances etiological precision and reduces diagnostic delay.

Overall, the study supports a structured diagnostic approach combining clinical evaluation, histopathological classification, and molecular confirmation. Such integration is essential for accurate diagnosis, especially in regions with overlapping infectious and non-infectious granulomatous diseases.

CONCLUSION

Clinical presentation shows a strong correlation with histological patterns in granulomatous inflammation. Caseating granulomas are strongly associated with infectious etiologies, particularly tuberculosis, while non-caseating lesions suggest systemic inflammatory disease. Integrated clinical, histological, and molecular evaluation significantly improves diagnostic accuracy and patient management.

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