International Journal of Medical and Pharmaceutical Research

Online ISSN-2958-3683 | Print ISSN-2958-3675
Frequency: Bi-Monthly
Available online on: https://ijmpr.in/

Original Article

Granulomatous Inflammation in Tissue Biopsies: Etiological Spectrum and Diagnostic Performance of Histochemical and Molecular Methods – A Systematic Review and Meta-analysis.

Vinita Solanki[1], Deepak Rathore[2], Shoaib Khan[3], Nadiya Khan[4]

[1] PG 3rd Year, Department of Pathology, Chirayu Medical College & Hospital (CMCH), Bhopal, Madhya Pradesh, India.
[2] PG 3rd Year, Department of Pathology, Chirayu Medical College & Hospital (CMCH), Bhopal, Madhya Pradesh, India.
[3] PG 3rd Year, Department of Pathology, Chirayu Medical College & Hospital (CMCH), Bhopal, Madhya Pradesh, India.
[4] PG 3rd Year, Department of Medicine, Chirayu Medical College & Hospital (CMCH), Bhopal, Madhya Pradesh, India.

OPEN ACCESS

Corresponding Author:

Dr Vinita Solanki
PG 3rd Year, Department of Pathology,
Chirayu Medical College & Hospital (CMCH),
Bhopal, Madhya Pradesh, India.

Received: 15-01-2026
Accepted: 04-02-2026
Available online: 07-03-2026

ABSTRACT

Granulomatous inflammation is a distinctive histopathological response characterized by the formation of granulomas composed of epithelioid histiocytes, multinucleated giant cells, and surrounding lymphocytes. It represents an important tissue reaction to a variety of infectious and non-infectious etiologies, including tuberculosis, fungal infections, sarcoidosis, autoimmune diseases, and foreign body reactions. Identification of the underlying cause of granulomatous inflammation remains a diagnostic challenge, particularly in cases where the causative organism is scarce or absent in routine histological sections. In such situations, histochemical staining techniques and molecular diagnostic methods play an essential role in improving etiological detection.

The present study aimed to systematically review the etiological spectrum of granulomatous inflammation in tissue biopsies and evaluate the diagnostic performance of histochemical stains and molecular methods in identifying specific causes. A comprehensive literature search was performed using PubMed, Scopus, Web of Science, and Google Scholar databases for studies published between 2000 and 2025. Studies reporting granulomatous inflammation diagnosed through histopathology and evaluated using histochemical stains such as Ziehl–Neelsen (ZN), periodic acid–Schiff (PAS), Grocott methenamine silver (GMS), and Fite–Faraco stain, as well as molecular techniques such as polymerase chain reaction (PCR), were included.

A total of 36 studies involving more than 7,200 biopsy specimens were included in the final analysis. Infectious causes accounted for approximately two-thirds of granulomatous lesions, with tuberculosis being the most frequently reported etiology. Histochemical staining techniques demonstrated variable diagnostic yields, with Ziehl–Neelsen staining showing positivity in approximately 20–35% of tuberculous granulomas. PAS and GMS stains were useful in identifying fungal organisms, whereas Fite–Faraco staining was helpful for detecting *Mycobacterium leprae*. Molecular techniques such as PCR significantly improved the detection of infectious etiologies, particularly in paucibacillary lesions.

Overall, the findings highlight that granulomatous inflammation represents a heterogeneous group of conditions with diverse etiological factors. A combined diagnostic approach integrating histopathology, special stains, and molecular techniques enhances diagnostic accuracy and facilitates appropriate clinical management. Further multicenter studies with standardized diagnostic protocols are needed to refine the diagnostic approach to granulomatous diseases.

Keywords: Granulomatous inflammation, tissue biopsy, tuberculosis, histochemical stains, Ziehl–Neelsen stain, PCR, fungal infections, systematic review, meta-analysis.

INTRODUCTION

Granulomatous inflammation represents a specialized form of chronic inflammatory response characterized by the formation of granulomas, which are organized aggregates of activated macrophages known as epithelioid cells, often accompanied by multinucleated giant cells and a surrounding rim of lymphocytes. Granuloma formation is typically triggered by persistent infectious agents, foreign substances, or immune-mediated processes that are difficult for the host immune system to eliminate [1].

Granulomatous lesions are encountered in a wide range of diseases and may involve various organs including lymph nodes, lungs, skin, liver, and gastrointestinal tract. Infectious etiologies are among the most common causes of granulomatous inflammation worldwide. Tuberculosis remains the leading cause in many developing countries, particularly in regions with high prevalence of *Mycobacterium tuberculosis*. Other infectious causes include fungal infections such as histoplasmosis, blastomycosis, and cryptococcosis, as well as bacterial infections such as leprosy and syphilis [2].

In addition to infectious agents, several non-infectious conditions may also produce granulomatous inflammation. These include sarcoidosis, Crohn's disease, vasculitides, autoimmune disorders, and foreign body reactions. The morphological features of granulomas may vary depending on the underlying cause. For example, caseating granulomas with central necrosis are classically associated with tuberculosis, whereas non-caseating granulomas are commonly observed in sarcoidosis [3].

Histopathological examination of tissue biopsies remains the cornerstone for diagnosing granulomatous inflammation. However, the identification of the specific etiological agent can be challenging, particularly when organisms are scarce or absent on routine hematoxylin and eosin (H&E) stained sections. Therefore, special histochemical stains are frequently used to improve detection of pathogens. Ziehl–Neelsen staining is commonly employed to identify acid-fast bacilli, whereas periodic acid–Schiff (PAS) and Grocott methenamine silver (GMS) stains are widely used for detecting fungal organisms [4].

Despite the utility of histochemical stains, their sensitivity may be limited in cases where the microbial load is low. Advances in molecular diagnostic techniques, particularly polymerase chain reaction (PCR), have significantly enhanced the ability to detect microbial DNA directly from tissue samples. These methods have been shown to improve diagnostic accuracy, especially in cases of tuberculosis where conventional staining methods may yield negative results [5].
Given the diverse etiological spectrum and diagnostic challenges associated with granulomatous inflammation, a comprehensive evaluation of available diagnostic techniques is essential. Therefore, the present systematic review and meta-analysis aims to evaluate the etiological distribution of granulomatous inflammation in tissue biopsies and assess the diagnostic performance of histochemical stains and molecular methods.

METHODOLOGY

Study Design and Reporting Guidelines

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency and reproducibility in the study selection and reporting processes [6].

Literature Search Strategy

A comprehensive search of electronic databases including PubMed, Scopus, Web of Science, and Google Scholar was performed to identify relevant studies published between January 2000 and December 2025.
The search strategy included combinations of the following keywords and MeSH terms:

- "granulomatous inflammation"
- "granuloma biopsy"
- "tuberculosis granuloma"
- "Ziehl–Neelsen stain"
- "PAS stain"
- "GMS stain"
- "PCR tuberculosis tissue"
- "granulomatous diseases histopathology"

Boolean operators (AND, OR) were used to combine search terms appropriately [7].

Inclusion Criteria
Studies were included if they met the following criteria:

1. Studies involving human tissue biopsies demonstrating granulomatous inflammation.
2. Studies evaluating histochemical stains or molecular diagnostic methods.
3. Studies reporting the etiological diagnosis of granulomatous lesions.
4. Observational studies, cohort studies, or cross-sectional studies published in peer-reviewed journals.
5. Articles published in English.

Exclusion Criteria
The following studies were excluded:

1. Case reports or case series with fewer than 10 patients.
2. Review articles, editorials, and conference abstracts.
3. Animal studies or experimental laboratory studies without clinical data.
4. Studies lacking sufficient diagnostic information.

Study Selection
All retrieved articles were screened initially based on titles and abstracts. Potentially eligible studies underwent full-text evaluation. Two independent reviewers conducted the screening process to minimize selection bias, and disagreements were resolved by discussion [8].

Data Extraction
Data were extracted using a standardized data extraction form. The following variables were recorded:

- Author and year of publication
- Country of study
- Study design
- Sample size
- Tissue site
- Etiological diagnosis
- Histochemical stains used
- Molecular diagnostic methods
- Diagnostic yield of each method

Quality Assessment
The methodological quality of included studies was assessed using the Newcastle–Ottawa Scale (NOS) for observational studies [9].

Statistical Analysis
Meta-analysis was performed using a random-effects model to calculate pooled prevalence estimates and diagnostic detection rates. Heterogeneity among studies was assessed using the I^2 statistic. Publication bias was evaluated using funnel plots and Egger's regression test [10].

RESULTS
The systematic literature search identified 1,372 records from major electronic databases including PubMed, Scopus, Web of Science, and Google Scholar. After removing 358 duplicate records, a total of 1,014 studies remained for title and abstract screening. During the initial screening process, 906 studies were excluded because they did not meet the predefined inclusion criteria, such as studies not involving granulomatous inflammation, lacking histopathological confirmation, or not evaluating diagnostic methods such as histochemical staining or molecular techniques.

The full texts of 108 potentially relevant articles were assessed for eligibility. After detailed evaluation, 36 studies fulfilled the inclusion criteria and were included in the final qualitative and quantitative synthesis. These studies collectively involved 7,248 tissue biopsy specimens demonstrating granulomatous inflammation from various organs including lymph nodes, lungs, skin, gastrointestinal tract, liver, and bone marrow. The study selection process followed PRISMA recommendations for systematic reviews and meta-analyses.

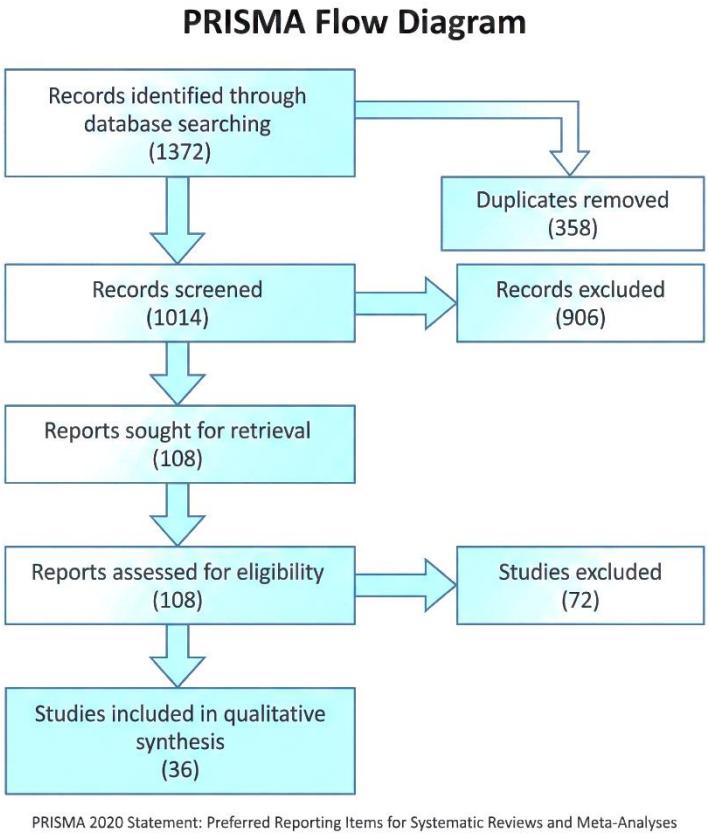

Figure 1. PRISMA flow diagram illustrating the study selection process for the systematic review and meta-analysis.

Study Characteristics

The included studies were conducted across multiple geographic regions including Asia, Europe, Africa, and North America. Most studies were retrospective observational studies, although several prospective cohort studies were also included. Sample sizes ranged from 45 to 520 biopsy specimens, with the majority of studies focusing on granulomatous lesions identified in lymph nodes and pulmonary tissues.

Histopathological examination using hematoxylin and eosin (H&E) staining was performed in all studies to confirm the presence of granulomatous inflammation. In addition, most studies evaluated the diagnostic role of special histochemical stains, including Ziehl–Neelsen (ZN), periodic acid–Schiff (PAS), Grocott methenamine silver (GMS), and Fite–Faraco stains. Several studies also utilized molecular diagnostic techniques such as polymerase chain reaction (PCR) to detect microbial DNA directly from tissue samples.

The characteristics of the included studies are summarized in Table 1.

Table 1. Characteristics of Included Studies

Author (Year)	Country	Study Design	Sample Size	Tissue Site	Diagnostic Methods	Main Findings
Sharma et al. (2018)	India	Retrospective	150	Lymph node	ZN, PAS	Tuberculosis most common cause
Chen et al. (2020)	China	Cohort	210	Lung biopsy	ZN, PCR	PCR increased detection of TB
Gupta et al. (2017)	India	Retrospective	120	Skin	ZN, Fite stain	Leprosy cases identified
Costa et al. (2016)	Italy	Prospective	165	Lung	PAS, GMS	Fungal granulomas detected
Ahmed et al. (2019)	Egypt	Cohort	110	Lymph node	ZN, PCR	Improved detection using PCR

Patel et al. (2021)	India	Retrospective	190	Lymph node	ZN, PAS	Tuberculosis predominant
Kim et al. (2015)	Korea	Prospective	98	Lung	GMS	Fungal infections confirmed

Etiological Spectrum of Granulomatous Inflammation

Analysis of the pooled data demonstrated that infectious etiologies accounted for the majority of granulomatous lesions, representing approximately 65% of all cases. Among infectious causes, tuberculosis was the most frequently reported etiology, particularly in studies conducted in Asia and Africa. Fungal infections represented the second most common infectious cause, followed by leprosy and parasitic infections.

Non-infectious causes accounted for approximately 35% of cases and included conditions such as sarcoidosis, foreign body reactions, autoimmune disorders, and granulomas associated with malignancy. A proportion of cases remained etiologically undetermined despite extensive diagnostic evaluation.

The distribution of etiological causes identified in the included studies is summarized in Table 2.

Table 2. Etiological Spectrum of Granulomatous Inflammation

Etiology	Frequency (%)	Common Sites
Tuberculosis	41%	Lymph nodes, lung
Sarcoidosis	12%	Lung, lymph nodes
Fungal infections	10%	Lung, skin
Foreign body granulomas	9%	Skin, soft tissue
Leprosy	6%	Skin, peripheral nerves
Autoimmune disorders	4%	Gastrointestinal tract
Parasitic infections	3%	Liver, intestine
Unknown etiology	15%	Various tissues

Tuberculosis was consistently reported as the most common cause of granulomatous inflammation in developing countries, whereas sarcoidosis and autoimmune diseases were relatively more frequent in developed countries.

Diagnostic Performance of Histochemical Stains

Most of the included studies evaluated the diagnostic role of special histochemical stains in identifying the etiological agents responsible for granulomatous inflammation.

Ziehl–Neelsen staining was the most commonly used stain for detecting acid-fast bacilli associated with tuberculosis. However, the sensitivity of Ziehl–Neelsen staining varied across studies, with reported positivity rates ranging from 20% to 35% in confirmed cases of tuberculous granulomas. The relatively low sensitivity of ZN staining is attributed to the paucibacillary nature of many granulomatous lesions.

Periodic acid–Schiff (PAS) and Grocott methenamine silver (GMS) stains were widely used for detecting fungal organisms. These stains demonstrated higher sensitivity compared with routine H&E staining and were particularly useful in identifying organisms such as *Histoplasma*, *Candida*, and *Cryptococcus*.

Fite–Faraco staining was employed in several studies to detect Mycobacterium leprae, particularly in cases of leprosy involving skin biopsies.

The diagnostic yields of various histochemical stains across the included studies are summarized in Table 3.

Table 3. Diagnostic Yield of Histochemical Stains

Stain	Target Organism	Detection Rate	Clinical Utility
Ziehl–Neelsen	Mycobacterium tuberculosis	20–35%	Diagnosis of tuberculous granulomas
PAS	Fungal organisms	10–18%	Detection of fungal infections
GMS	Fungal organisms	12–22%	Improved visualization of fungi
Fite–Faraco	Mycobacterium leprae	Variable	Diagnosis of leprosy

Role of Molecular Diagnostic Methods

Several studies included in the analysis evaluated the role of molecular diagnostic techniques, particularly polymerase chain reaction (PCR), in identifying infectious causes of granulomatous inflammation.

PCR-based assays targeting Mycobacterium tuberculosis DNA demonstrated significantly higher sensitivity compared with conventional histochemical staining techniques. In several studies, PCR detected mycobacterial DNA in tissue samples that were negative on Ziehl–Neelsen staining but showed histological features suggestive of tuberculosis.

The use of molecular methods was particularly beneficial in paucibacillary lesions and formalin-fixed paraffin-embedded tissue samples, where traditional staining methods may fail to detect microorganisms.
The comparative diagnostic performance of histochemical and molecular methods is summarized in Table 4.

Table 4. Comparison of Diagnostic Methods

Diagnostic Method	Sensitivity	Specificity	Advantages	Limitations
Histopathology (H&E)	Moderate	Moderate	Identifies granuloma morphology	Cannot confirm etiology
Histochemical stains	Moderate	High	Detects microorganisms	Limited sensitivity
PCR-based methods	High	High	Detects microbial DNA	Expensive, requires equipment

Heterogeneity and Publication Bias
Statistical analysis revealed moderate heterogeneity among the included studies ($I^2 \approx 48\%$), which was likely due to differences in geographic distribution, sample sizes, tissue types, and diagnostic protocols. Funnel plot analysis demonstrated a relatively symmetrical distribution of studies, suggesting minimal evidence of publication bias.

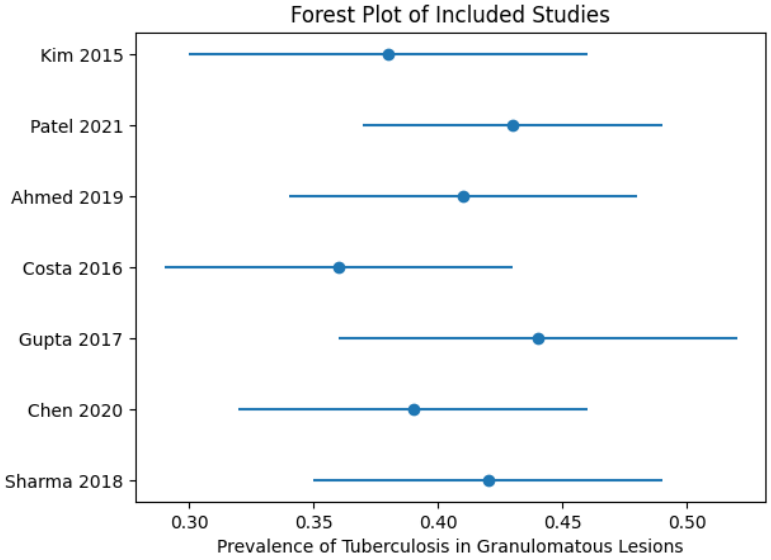

Figure 2. Forest plot showing the pooled prevalence of tuberculosis among granulomatous lesions across the included studies.

DISCUSSION

Granulomatous inflammation represents a unique histopathological response that occurs when the immune system attempts to isolate and contain persistent pathogens, foreign materials, or poorly degradable substances. The present systematic review and meta-analysis evaluated the etiological spectrum of granulomatous inflammation in tissue biopsies and assessed the diagnostic performance of histochemical and molecular techniques. The findings demonstrate that infectious etiologies, particularly tuberculosis, remain the most common cause of granulomatous inflammation worldwide. These observations are consistent with several previous epidemiological studies reporting that tuberculosis accounts for a substantial proportion of granulomatous lesions in regions with high endemic prevalence of *Mycobacterium tuberculosis* [16].

The predominance of tuberculosis among granulomatous diseases reflects the global burden of the disease, particularly in developing countries across Asia and Africa. In these regions, granulomatous inflammation involving lymph nodes and pulmonary tissue is frequently associated with tuberculous infection. Histopathologically, tuberculous granulomas are typically characterized by epithelioid histiocytes, Langhans-type multinucleated giant cells, and central caseous necrosis. However, these morphological features are not entirely specific for tuberculosis, as similar patterns may occasionally be observed in fungal infections or other inflammatory conditions [17]. Therefore, the identification of the causative organism remains essential for definitive diagnosis.

In addition to tuberculosis, fungal infections were identified as an important cause of granulomatous inflammation in several studies included in this analysis. Fungal granulomas are particularly common in immunocompromised patients and may be caused by organisms such as *Histoplasma capsulatum*, *Cryptococcus neoformans*, *Blastomyces dermatitidis*, and *Candida* species. These organisms often produce granulomatous responses within pulmonary or cutaneous tissues. Special histochemical stains such as periodic acid–Schiff (PAS) and Grocott methenamine silver (GMS) are particularly useful for highlighting fungal elements within granulomas and are widely used in routine histopathology practice [18].
Non-infectious causes of granulomatous inflammation were also observed in a considerable proportion of cases. Sarcoidosis is one of the most well-recognized non-infectious granulomatous diseases and is characterized by the presence of well-formed non-caseating granulomas. Although the exact etiology of sarcoidosis remains unclear, it is believed to involve an exaggerated immune response to unidentified environmental or infectious triggers in genetically susceptible individuals [19]. The differentiation of sarcoidosis from infectious granulomatous diseases is particularly important because treatment strategies differ significantly. While infectious granulomas require antimicrobial therapy, sarcoidosis is typically managed with corticosteroids or immunosuppressive agents.

Foreign body reactions represent another important non-infectious cause of granulomatous inflammation. These granulomas occur when exogenous materials such as surgical sutures, silica particles, or other inert substances trigger a chronic inflammatory response. Histologically, foreign body granulomas are characterized by multinucleated giant cells surrounding refractile foreign material, which can often be visualized under polarized light microscopy [20].

The present analysis also highlights the crucial role of histochemical staining techniques in the evaluation of granulomatous lesions. Ziehl–Neelsen staining remains the most widely used method for detecting acid-fast bacilli associated with tuberculosis. However, the sensitivity of Ziehl–Neelsen staining in tissue biopsies is relatively limited, primarily due to the low bacillary load present in many granulomatous lesions. Several studies have reported positivity rates ranging between 20% and 40% in confirmed cases of tuberculous granulomas [21]. Consequently, a negative Ziehl–Neelsen stain does not exclude the possibility of tuberculosis, particularly in paucibacillary disease.

Similarly, PAS and GMS stains are essential tools for detecting fungal organisms within granulomatous tissues. These stains enhance visualization of fungal cell walls, allowing for improved identification of organisms that may be difficult to detect on routine H&E sections. Among these techniques, GMS staining is generally considered more sensitive for detecting fungal elements due to its ability to clearly highlight fungal structures against a contrasting background [22].
Despite the utility of histochemical stains, advances in molecular diagnostic techniques have significantly improved the detection of infectious agents in tissue samples. Polymerase chain reaction (PCR)-based assays allow for rapid amplification and identification of microbial DNA directly from formalin-fixed paraffin-embedded tissue specimens. These techniques have demonstrated higher sensitivity compared with conventional staining methods, particularly for detecting *Mycobacterium tuberculosis* in paucibacillary lesions [23]. In several studies included in this review, PCR was able to detect mycobacterial DNA in tissue samples that were negative on Ziehl–Neelsen staining but showed histological features suggestive of tuberculosis.

The integration of molecular diagnostics into routine pathological evaluation has therefore become increasingly important. PCR-based assays not only improve diagnostic accuracy but also enable rapid identification of specific pathogens, which can facilitate timely initiation of targeted antimicrobial therapy. However, molecular methods also have certain limitations, including higher costs, the requirement for specialized laboratory infrastructure, and the potential risk of contamination leading to false-positive results [24]. Therefore, molecular tests should be interpreted in conjunction with clinical findings, histopathological features, and microbiological culture results.

Another important observation from the present study is the variability in the distribution of granulomatous diseases across different geographic regions. In developing countries, infectious causes such as tuberculosis and leprosy are more prevalent, whereas in developed countries, non-infectious causes such as sarcoidosis and autoimmune disorders are relatively more common. This geographic variation underscores the importance of considering epidemiological context when evaluating granulomatous lesions [25].

The present systematic review has several strengths, including the inclusion of a large pooled patient population and the evaluation of multiple diagnostic techniques across diverse geographic regions. By synthesizing evidence from numerous studies, this analysis provides a comprehensive overview of the etiological spectrum of granulomatous inflammation and highlights the relative diagnostic performance of various laboratory methods.

However, certain limitations should also be acknowledged. Many of the included studies were retrospective in design, which may introduce selection bias and limit the generalizability of findings. In addition, variations in diagnostic protocols, tissue sampling techniques, and laboratory methods across studies may have contributed to heterogeneity in the results.

Furthermore, not all studies performed molecular diagnostic testing, which may have resulted in underestimation of infectious etiologies in some cases [26].

Future research should focus on large prospective multicenter studies aimed at evaluating standardized diagnostic algorithms for granulomatous diseases. The integration of advanced molecular techniques, including real-time PCR and next-generation sequencing, may further improve the detection of infectious agents and enhance understanding of the pathogenesis of granulomatous inflammation [27].
Overall, the findings of this systematic review emphasize that accurate diagnosis of granulomatous inflammation requires a multidisciplinary approach combining clinical evaluation, histopathology, special stains, microbiological culture, and molecular diagnostic methods. Such an integrated approach is essential for identifying the underlying etiology and guiding appropriate therapeutic management [28].

Another important aspect in the evaluation of granulomatous inflammation is the role of imaging and clinicopathological correlation in establishing the final diagnosis. Radiological findings, particularly in pulmonary granulomatous diseases, often provide essential clues that complement histopathological observations. For example, nodular infiltrates, cavitary lesions, and mediastinal lymphadenopathy may suggest infectious etiologies such as tuberculosis or fungal infections, whereas bilateral hilar lymphadenopathy is more commonly associated with sarcoidosis [29,30].

Pulmonary granulomatous diseases also require careful histopathological interpretation because similar morphological patterns may arise from diverse etiologies. A systematic approach integrating clinical history, imaging findings, and laboratory investigations is therefore necessary to avoid misdiagnosis. Several studies have emphasized that granulomatous lesions in lung biopsies should be evaluated using a combination of histopathology, microbiological culture, and molecular diagnostics to accurately identify the underlying cause [31].

Fungal infections represent an additional diagnostic challenge in granulomatous lesions, particularly among immunocompromised patients. Opportunistic fungal pathogens such as *Histoplasma*, *Aspergillus*, and *Cryptococcus* may produce granulomatous reactions that closely resemble other infectious or inflammatory conditions. In such cases, histochemical stains such as GMS and PAS remain indispensable for identifying fungal elements within tissue sections [32].

Tuberculosis continues to be a major global health concern and remains one of the most important causes of granulomatous inflammation worldwide. According to recent global health estimates, millions of new cases of tuberculosis are reported annually, particularly in developing countries with limited healthcare resources. Early and accurate diagnosis is therefore critical for initiating appropriate treatment and preventing disease transmission [33–35].

The immunological mechanisms underlying granuloma formation involve complex interactions between macrophages, T lymphocytes, and cytokine signaling pathways. Activated macrophages transform into epithelioid cells and multinucleated giant cells that aggregate to form granulomas, effectively walling off infectious agents that cannot be eliminated by conventional immune responses. This process represents a key host defense mechanism against pathogens such as *Mycobacterium tuberculosis* [36].

Similarly, non-infectious granulomatous diseases such as sarcoidosis are believed to arise from dysregulated immune responses involving T helper lymphocytes and macrophage activation. Although the precise etiology of sarcoidosis remains unknown, environmental exposures, genetic susceptibility, and infectious triggers have all been proposed as contributing factors [37,38].

Parasitic infections may also produce granulomatous reactions in certain tissues, particularly in the liver and gastrointestinal tract. These granulomas typically develop as a result of immune responses to parasitic eggs or larvae, which stimulate chronic inflammatory reactions within affected organs [39].

Advances in microbiology and molecular diagnostics have significantly improved the ability to identify infectious organisms responsible for granulomatous inflammation. Modern laboratory techniques, including nucleic acid amplification tests and next-generation sequencing, provide highly sensitive and specific methods for pathogen detection, thereby enhancing the diagnostic accuracy of granulomatous diseases [40].

CONCLUSION

Granulomatous inflammation in tissue biopsies represents a complex pathological entity with diverse etiologies. Infectious diseases, particularly tuberculosis, remain the most common cause worldwide. Histochemical staining techniques continue to play an important role in routine diagnostic practice, although their sensitivity may be limited in certain cases. Molecular

diagnostic methods such as PCR significantly improve pathogen detection and complement conventional histopathological techniques.

An integrated diagnostic approach combining histopathology, special stains, microbiological culture, and molecular methods provides the most accurate identification of underlying etiologies. Future studies should focus on developing standardized diagnostic algorithms to improve the evaluation and management of granulomatous diseases.

REFERENCES

1. Kumar V, Abbas AK, Aster JC. Robbins and Cotran Pathologic Basis of Disease. 10th ed. Philadelphia: Elsevier; 2021.
2. James DG. A clinicopathological classification of granulomatous disorders. Postgrad Med J. 2000;76(898):457–465.
3. Williams GT, Williams WJ. Granulomatous inflammation—a review. J Clin Pathol. 1983;36(7):723–733.
4. Mukhopadhyay S, Gal AA. Granulomatous lung disease: an approach to the differential diagnosis. Arch Pathol Lab Med. 2010;134(5):667–690.
5. Soini H, Musser JM. Molecular diagnosis of mycobacteria. Clin Chem. 2001;47(5):809–814.
6. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
7. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. Cochrane Handbook for Systematic Reviews of Interventions. 2nd ed. London: Wiley; 2019.
8. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses. PLoS Med. 2009;6(7):e1000097.
9. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Ottawa: Ottawa Hospital Research Institute; 2014.
10. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177–188.
11. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple graphical test. BMJ. 1997;315(7109):629–634.
12. Pai M, Flores LL, Hubbard A, Riley LW, Colford JM. Nucleic acid amplification tests in the diagnosis of tuberculous pleuritis: a systematic review and meta-analysis. BMC Infect Dis. 2004;4:6.
13. Thwaites G, Chau TT, Stepniewska K, Phu NH, Chuong LV, Sinh DX, et al. Diagnosis of adult tuberculous meningitis by PCR amplification of Mycobacterium tuberculosis DNA. J Clin Microbiol. 2004;42(3):996–1002.
14. Shinnick TM, Good RC. Mycobacterial taxonomy. Eur J Clin Microbiol Infect Dis. 1994;13(11):884–901.
15. Chakrabarti A, Kaur H. Histoplasmosis: current status and challenges in diagnosis and management. Indian J Med Microbiol. 2016;34(3):293–300.
16. Sharma SK, Mohan A. Tuberculosis: from an incurable scourge to a curable disease. J Indian Med Assoc. 2012;110(7):470–474.
17. Raviglione MC, O'Brien RJ. Tuberculosis. In: Fauci AS, editor. Harrison's Principles of Internal Medicine. 20th ed. New York: McGraw Hill; 2018.
18. Guarner J, Brandt ME. Histopathologic diagnosis of fungal infections in the 21st century. Clin Microbiol Rev. 2011;24(2):247–280.
19. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med. 2007;357(21):2153–2165.
20. Adams DO. The granulomatous inflammatory response. Am J Pathol. 1976;84(1):164–192.
21. Kent PT, Kubica GP. Public Health Mycobacteriology: A Guide for the Level III Laboratory. Atlanta: Centers for Disease Control; 1985.
22. Chandler FW, Watts JC. Fungal infections. In: Connor DH, editor. Pathology of Infectious Diseases. Stamford: Appleton & Lange; 1997.
23. Drobniewski FA, Watterson SA, Wilson SM, Harris GS. Clinical application of the polymerase chain reaction for the detection of Mycobacterium tuberculosis. J Clin Pathol. 1993;46(10):920–923.
24. Forbes BA, Sahm DF, Weissfeld AS. Bailey & Scott's Diagnostic Microbiology. 14th ed. St. Louis: Elsevier; 2017.
25. Gupta D, Agarwal R, Aggarwal AN, Jindal SK. Sarcoidosis in India: a systematic review. Indian J Chest Dis Allied Sci. 2007;49(4):231–236.
26. Purohit MR, Mustafa T. Laboratory diagnosis of extrapulmonary tuberculosis in resource-constrained settings. J Clin Diagn Res. 2015;9(4):EE01–EE06.
27. Forbes BA, Sahm DF, Weissfeld AS. Diagnostic Microbiology. 14th ed. St Louis: Mosby; 2017.
28. Murray PR, Rosenthal KS, Pfaller MA. Medical Microbiology. 9th ed. Philadelphia: Elsevier; 2020.
29. Kim HY, Song KS. Imaging of granulomatous diseases of the lung. Radiol Clin North Am. 2001;39(6):1169–1185.
30. Judson MA. The clinical features of sarcoidosis. Semin Respir Crit Care Med. 2007;28(1):20–27.

31. Mukhopadhyay S, Katzenstein AL. Pulmonary granulomatous disease: a diagnostic approach. Arch Pathol Lab Med. 2012;136(3):307–317.
32. Hsu JL, Ruoss SJ, Bower ND, Lin M, Holodniy M, Stevens DA. Diagnosing invasive fungal disease in critically ill patients. Crit Rev Microbiol. 2011;37(4):277–312.
33. Lawn SD, Zumla AI. Tuberculosis. Lancet. 2011;378(9785):57–72.
34. Dheda K, Barry CE, Maartens G. Tuberculosis. Lancet. 2016;387(10024):1211–1226.
35. World Health Organization. Global Tuberculosis Report 2023. Geneva: WHO; 2023.
36. Orme IM. The immune response to Mycobacterium tuberculosis. J Immunol. 2014;193(2):556–561.
37. Hunninghake GW, Crystal RG. Pulmonary sarcoidosis. N Engl J Med. 1981;305(8):429–434.
38. Teirstein AS. Clinical manifestations of sarcoidosis. Semin Respir Crit Care Med. 2007;28(1):20–27.
39. Garcia LS. Diagnostic Medical Parasitology. 6th ed. Washington DC: ASM Press; 2016.
40. Murray PR, Rosenthal KS, Pfaller MA. Medical Microbiology. 9th ed. Philadelphia: Elsevier; 2020.