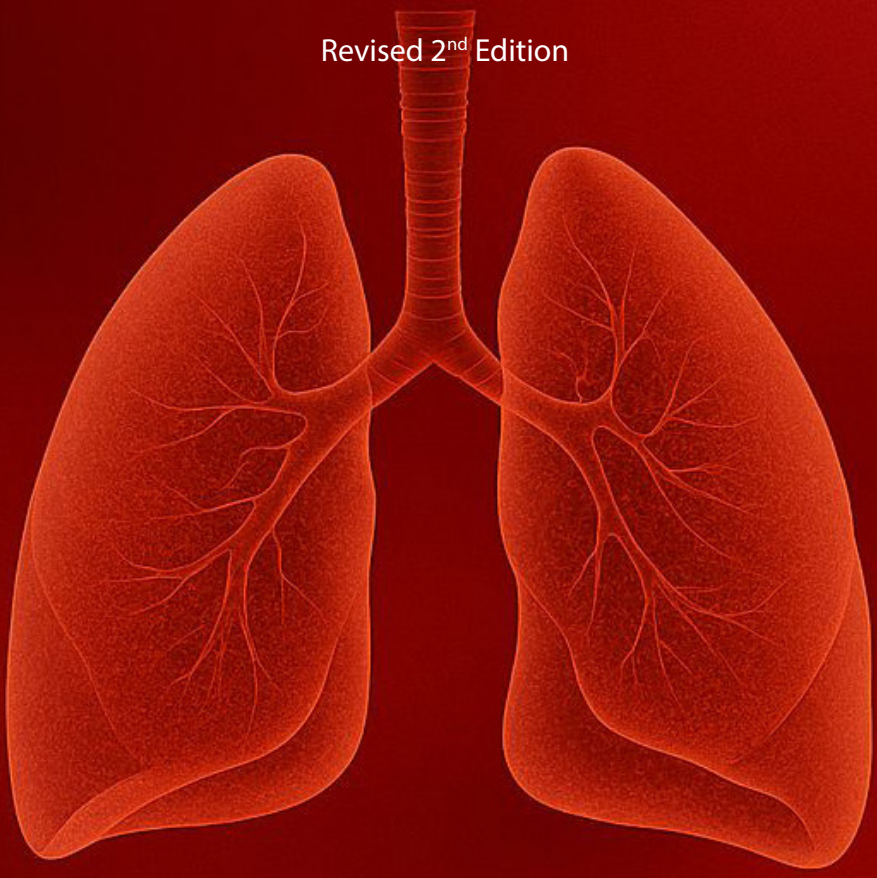
MULTIDISCIPLINARY APPROACH TO GRANULOMATOUS LUNG DISEASES

Revised 2nd Edition



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PREFACE

Granulomatous lung diseases are a complex group of conditions that develop due to infectious and non-infectious causes, requiring the combined evaluation of clinical, radiological, and pathological findings in the diagnostic and treatment process. Therefore, the diagnostic process often necessitates interdisciplinary collaboration.

Multidisciplinary Approach to Granulomatous Lung Diseases, prepared as the first comprehensive and multidisciplinary reference book in Turkey to address granulomatous lung diseases with a holistic approach. This book, prepared with contributions from experienced specialist physicians in the field, covers a wide range of topics from the etiology and pathogenesis of granulomatous lung diseases to radiological, pathological, and laboratory findings, differential diagnosis, and clinical case examples.

Each chapter has been meticulously written in light of current literature and clinical experience, providing a guiding reference for diagnostic difficulties frequently encountered in practice. We believe this book will be a useful guide for physicians working in the fields of pulmonology, radiology, pathology, rheumatology, and internal medicine, both academically and in clinical practice.

We sincerely thank all our colleagues who contributed to the preparation of this book, and the MediHealth Academy Publishing team who supported us throughout the publication process.

With kind regards,

Berna Akıncı Özyürek, Prof., MD

Maşide Arı, Assoc. Prof., MD

Ankara, 2026

SECTION I

INTRODUCTION TO GRANULOMATOUS LUNG DISEASES

CHAPTER 1

APPROACH TO GRANULOMATOUS LUNG DISEASES

Hüsra TETİK MANAV

ABSTRACT

Granulomatous lung diseases (GLD) are a heterogeneous group of disorders characterized by the presence of granulomas, arising from infectious and non-infectious causes. The diagnosis of GLD requires an integrated evaluation of clinical findings, laboratory parameters, immunological assessments, chest radiography, high-resolution computed tomography (HRCT) findings, positron emission tomography (PET) findings, bronchoalveolar lavage (BAL), and histopathological data obtained by transbronchial needle aspiration, cryobiopsy, or lung biopsy. A granuloma is defined as an organized inflammatory infiltrate formed by the clustering of inflammatory cells, activated macrophages (epithelioid histiocytes), multinucleated giant cells, and lymphocytes, representing the immune system's attempt to contain a foreign antigen that it is unable to eliminate. The fundamental trigger for granuloma formation is the presence of a foreign antigen. This antigen may originate from microorganisms, inorganic substances, tumor-derived antigens, or autoantigens. Granulomatous inflammation is a distinctive and complex form of chronic inflammation that typically develops in response to persistent pathogenic or foreign agents. Granulomatous lung diseases are classified as infectious or non-infectious.

INTRODUCTION

Granulomatous lung diseases (GLD) are a heterogeneous group of diseases characterized by the presence of granulomas, which develop due to infectious and non-infectious causes. Among infectious causes, mycobacterial and fungal infections are the most common, while non-infectious causes include exposure to harmful particles, hypersensitivity pneumonitis, disorders related to genetic mutations, and certain autoimmune diseases. Since the etiology involves many different diseases, establishing a specific diagnosis is critical for accurate and appropriate treatment.[1-3]

In the diagnosis of GLD, clinical findings, laboratory parameters, immunological assessments, chest radiography, high-resolution computed tomography (HRCT), positron emission tomography (PET), and histopathological data obtained through procedures such as bronchoalveolar lavage (BAL), transbronchial needle aspiration, cryobiopsy, or lung biopsy should be evaluated collectively. In addition, genetic testing may enhance diagnostic accuracy.

Conventional chest radiography is typically the first imaging modality used; however, its findings are often nonspecific. Radiographic features such as lymphadenopathy, a reticulonodular pattern, or

diffuse infiltrative opacities in the hilar region may raise suspicion for GLD but are not diagnostic, necessitating further evaluation with advanced imaging techniques. HRCT provides detailed visualization of pulmonary parenchymal changes associated with granulomatous inflammation. Through HRCT, patterns such as the distribution of parenchymal nodules, mosaic perfusion, ground-glass opacities, septal thickening, fibrotic alterations, cavitation, and air trapping can be assessed. Certain HRCT findings provide valuable information regarding differential diagnosis—for instance, upper lobe–predominant micronodules with a perilymphatic distribution are commonly seen in sarcoidosis, and centrilobular nodules with mosaic attenuation are observed in hypersensitivity pneumonitis.

Some granulomatous diseases demonstrate overlapping radiological features. For example, conditions such as sarcoidosis, infectious granulomatosis (including tuberculosis and atypical mycobacterial infections), and granulomatosis with polyangiitis may present with similar imaging patterns. Furthermore, granulomatous lymphocytic interstitial lung disease (GLILD), which occurs in association with certain immunodeficiency syndromes such as common variable immunodeficiency (CVID), may closely resemble sarcoidosis radiologically. Specifically, mycobacterial and fungal infections, sarcoidosis, vasculitis, hypersensitivity pneumonitis, environmental exposure–related diseases (e.g., berylliosis, silicosis), and CVID-associated GLILD can all exhibit similar HRCT findings. In such cases, correlating clinical, radiological, and pathological data is essential.

Additionally, imaging features of certain granulomatous diseases may mimic those of malignant conditions, in which case a biopsy is required to confirm the diagnosis. Nevertheless, when radiological findings are evaluated in conjunction with clinical and laboratory data, a reliable diagnosis can often be made without the need for invasive procedures. HRCT and PET-CT, in particular, can reduce the necessity for invasive diagnostic approaches when interpreted alongside appropriate clinical and laboratory findings.

The diagnosis of granulomatous lung diseases still relies heavily on the histopathological evaluation of affected lung tissue. Currently, transbronchial cryobiopsy (TBCB) has been shown to provide a higher diagnostic yield than transbronchial forceps biopsy (TBFB) in the assessment of interstitial lung diseases. Lung biopsies are critical for identifying key histological features such as granuloma architecture, necrosis, vasculitis, or lymphoid hyperplasia. However, imaging alone is insufficient for definitive diagnosis. A multidisciplinary approach—integrating clinical, laboratory, immunological, radiological, and histopathological data—is essential for accurate diagnosis and appropriate management [2,4-12] This section will discuss the mechanisms and types of granuloma formation, the cellular response in granulomatous inflammation, and the classification of granulomatous lung diseases.

GRANULOMA FORMATION MECHANISMS

A granuloma is defined as an organized inflammatory infiltrate composed of clustered inflammatory cells, activated macrophages (epithelioid histiocytes), multinucleated giant cells, and lymphocytes, formed in response to a persistent foreign antigen that the immune system is unable to eliminate. Despite the frequent observation of necrosis and multinucleated giant cells within granulomas, the classification of a structure as a granuloma does not require their presence. In well-formed granulomas, epithelioid cells are arranged in compact, organized structures; however, in some cases, they may appear more diffusely distributed, forming what are termed "poorly formed" or "loose granulomas." These loosely structured granulomas are typically encountered in conditions such as hypersensitivity pneumonitis (HP), granulomatosis with polyangiitis (GPA), foreign body reactions, and lymphocytic interstitial pneumonia. Although the precise mechanisms underlying granuloma formation are not fully understood, it is generally accepted as a protective immune response. Granulomas may develop in various tissues throughout the body, most commonly in the lungs, lymph nodes, and skin.[2,9,13]

SECTION IV

DIAGNOSTIC EVALUATION IN GRANULOMATOUS LUNG DISEASES: RADIOLOGICAL, PATHOLOGICAL, AND LABORATORY FINDINGS

CHAPTER 1

RADIOLOGICAL FINDINGS IN GRANULOMATOUS LUNG DISEASES

Bilge Sezin AKHAN, Hakan ERTÜRK

ABSTRACT

Granulomatous lung diseases comprise a heterogeneous group of disorders with infectious and non-infectious etiologies, often demonstrating overlapping imaging features. Granuloma formation represents an immune response to persistent antigens, and when radiologic findings are interpreted in conjunction with clinical and laboratory data, the need for invasive diagnostic procedures such as biopsy can be substantially reduced. Although chest radiography serves as a basic screening tool, high-resolution computed tomography (HRCT) is the cornerstone imaging modality for diagnosis, disease staging, and treatment follow-up in granulomatous lung diseases, while positron emission tomography–CT (PET-CT) plays a complementary role in selected cases for assessing disease activity and extent. In tuberculosis, nontuberculous mycobacterial infections, and fungal diseases, findings such as consolidation, cavitation, 'tree-in-bud pattern', and lymph node characteristics provide important diagnostic clues, whereas perilymphatic micronodules, bilateral symmetric hilar lymphadenopathy, and characteristic signs such as the galaxy sign are more typical of sarcoidosis and berylliosis. Pulmonary Langerhans cell histiocytosis is characterized by an upper-lobe–predominant nodular–cavitary–cystic spectrum, with the 'cheerios and octopus signs' serving as distinctive imaging features. In hypersensitivity pneumonitis, inspiratory and expiratory HRCT demonstrating air trapping—particularly the 'three-density pattern' in fibrotic disease—has high diagnostic specificity. Granulomatous vasculitides, including eosinophilic granulomatosis with polyangiitis(EGPA) and granulomatosis with polyangiitis (GPA), commonly exhibit migratory consolidations, cavitary nodules, 'halo or reverse halo signs', and airway involvement, while organizing pneumonia is typified by migratory subpleural consolidations and perilobular fibrosis. A systematic assessment of nodule distribution, cavitary characteristics, lymph node morphology, and airway involvement constitutes thefoundation for accurate and effective differential diagnosis of granulomatous lung diseases.

INTRODUCTION

Granulomatous lung diseases consist of infectious and non-infectious conditions with diverse imaging features. Granulomas form as the immune system attempts to isolate persistent agents. Diagnosis can be challenging but combining radiology with clinical and lab data often reduces the need for biopsy. This section summarizes key imaging techniques, common CT patterns, and signs useful for differential diagnosis.

While typical for sarcoidosis, similar appearances can occur in tuberculosis, silicosis, and occasionally in malignant lung diseases.[7-9]

The cluster sign consists of tightly grouped, separate micronodules without a central nodule *(Figure 17)*. It can look like ground-glass opacity but is coarser and irregular, with causes similar to those of the galaxy sign.[10]

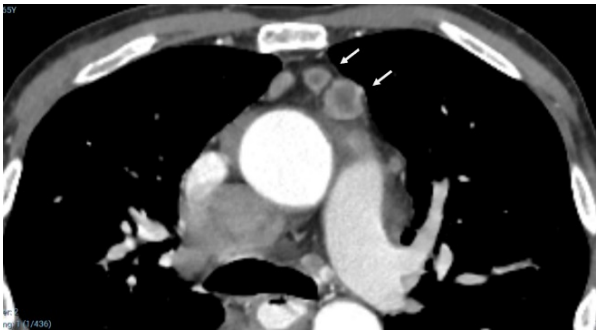

Figure 20. CT image of a patient with tuberculosis showing mediastinal lymph nodes (arrows) characterized by central necrosis and peripheral contrast enhancement, typical of tuberculous lymphadenopathy.

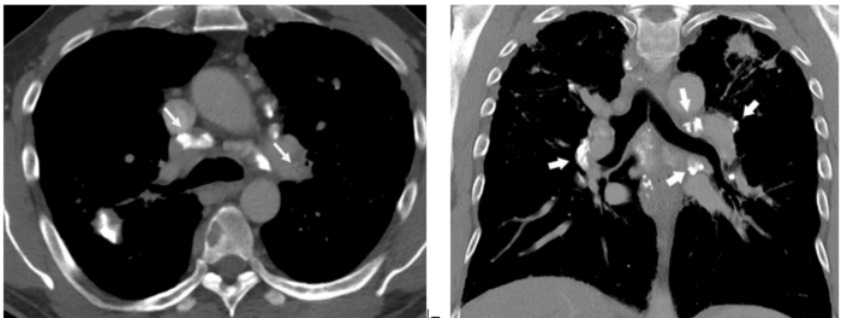

Figure 21. Calcified mediastinal lymph nodes (white arrows) observed after treatment in a patient with tuberculosis lymphadenopathy.

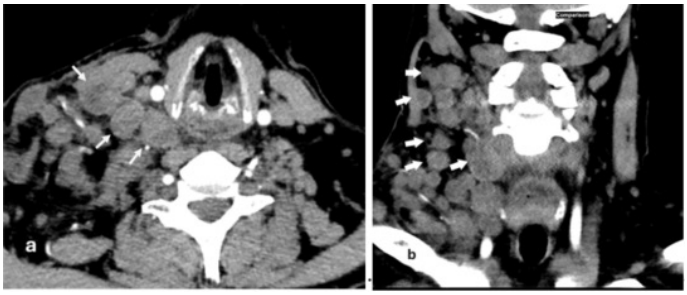

Figure 22. Axial (a) and coronal (b) CT images of a patient with cervical tuberculous lymphadenitis (scrofula) show multiple enlarged right cervical lymph nodes with central necrotic areas, indicative of caseating granulomatous inflammation.

CHAPTER 2

PATHOLOGIC FINDINGS IN GRANULOMATOUS LUNG DISEASES

Nesrin GÜRÇAY

ABSTRACT

Granulomatous lung diseases comprise a diverse group of entities unified by granuloma formation but differing significantly in etiology and histopathologic features. From a diagnostic pathology perspective, accurate classification relies primarily on granuloma architecture, the presence or absence of necrosis, associated inflammatory patterns, and vascular involvement. This chapter reviews the histopathologic characteristics of necrotizing and non-necrotizing pulmonary granulomas, emphasizing key morphologic findings in infectious conditions—particularly mycobacterial and fungal infections—as well as major non-infectious diseases such as sarcoidosis, hypersensitivity pneumonitis, and granulomatous vasculitides. The role of special histochemical stains and ancillary techniques in identifying infectious agents is highlighted. Practical morphologic clues that assist in differential diagnosis are discussed to support accurate interpretation of lung biopsies in routine surgical pathology practice.

1. CLASSIFICATION OF GRANULOMAS

Definition of Granuloma

Granulomas are characterized as localized clusters of epithelioid histiocytes. Epithelioid histiocytes are distinguished from ordinary histiocytes by their elongated, irregularly shaped nuclei and indistinct cell borders. The presence of lymphocytes, multinuclear giant cells, and necrosis is not

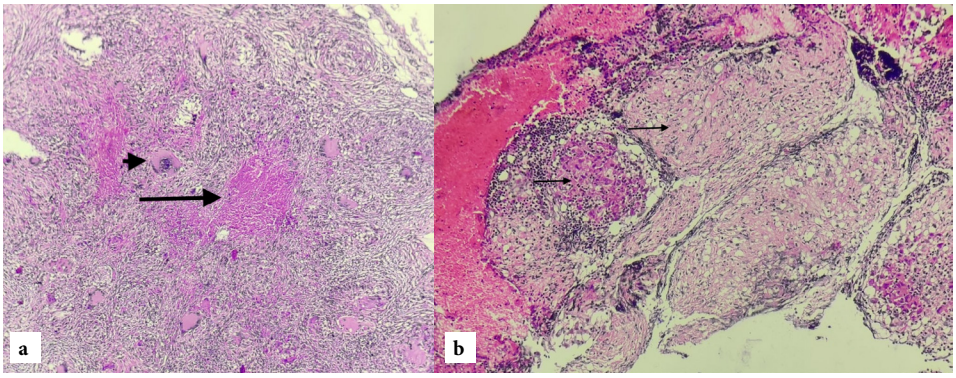

Figure 1. a. Necrotizing granuloma. Necrosis (arrow), multinuclear giant cell (arrowhead) (hematoxylin-eosin, original magnification X200). b. Non-necrotizing granuloma. Clustering of epithelioid histiocytes (arrow) (hematoxylin-eosin, original magnification X200).