

Pulmonary Manifestations of Systemic Diseases

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This chapter provides a review of pulmonary manifestations associated with systemic diseases, particularly focusing on sarcoidosis, connective tissue diseases (CTDs), and vasculitis. The role of imaging, especially high-resolution computed tomography (HRCT), is highlighted as a key tool in diagnosing and managing these conditions. Pulmonary sarcoidosis, the most common manifestation in systemic diseases, presents varied CT findings from typical perilymphatic nodules to complex fibrotic changes, with prognosis often related to the extent of pulmonary involvement. The chapter also covers CTD-related lung disease, including conditions such as rheumatoid arthritis, systemic sclerosis, and polymyositis/dermatomyositis, where the extent and type of lung involvement often dictate prognosis. It emphasizes that while imaging findings can suggest CTD, diagnosis is primarily reliant on serological and clinical criteria, highlighting the multidisciplinary approach needed for accurate diagnosis and management. Furthermore, pulmonary vasculitis, including ANCA-associated vasculitis and Goodpasture's syndrome, presents with distinct imaging features that may guide treatment decisions. The chapter underscores the importance of early detection and consistent monitoring of lung disease in patients with systemic conditions to improve patient outcomes, with specific attention to the prognostic value of imaging patterns in these diseases.

Keywords:

Pulmonary sarcoidosis, Advanced fibrosis, CTD-related lung disease, Vasculitis, Imaging, Lung disease in systemic disorders

Learning Objectives

- To learn about typical and atypical imaging findings of sarcoidosis
- To get familiar with imaging findings of pulmonary manifestations of connective tissue diseases and their meaning within the multidisciplinary diagnostic work-up
- To learn about imaging findings important for prognosis and management of patients with connective tissue diseases
- To know about the type and role of pulmonary imaging findings in patients with (small vessel) vasculitis

5.1. Introduction

The diagnosis of systemic diseases involves an analysis of their characteristic clinical manifestations in multiple organ systems. Clinical features are often correlated with serologic abnormalities, radiologic findings, and, in some cases, histopathology. Systemic diseases may affect a variety of different compartments of the thorax including the lungs, pleura, pericardium, lymph nodes, vessels, and heart.

The role of imaging in systemic diseases varies depending on the specific disorder. Sarcoidosis is an example that computed tomography (CT) can establish the diagnosis in an appropriate clinical

context. On the other hand, connective tissue disease is often diagnosed primarily using clinical and serologic findings, and the role of CT is to establish type and extent of lung involvement. The finding of an NSIP pattern can trigger the diagnostic search for an underlying systemic disease (“NSIP is just the beginning of a diagnostic work-up”). Further, imaging plays an important role in following lung abnormalities over time and evaluating patients with worsening or acute symptoms.

In the following we will focus on the more common systemic disorders that develop pulmonary abnormalities such as sarcoidosis, connective tissue diseases, and vasculitis. Because a comprehensive review of the lung manifestations of all systemic diseases is not possible, selected rare disorders such as inflammatory bowel disease, amyloidosis, Erdheim–Chester disease, and IgG4-related sclerosing disease are not included.

5.2. Pulmonary Sarcoidosis [1–6]

Sarcoidosis is an inflammatory, multisystemic disease of unknown origin with a wide range of clinical manifestations. The disease can affect virtually any organ, most frequently the lungs and the lymphatic system but also eyes, skin, heart, abdominal organs, or the neural system.

The histological hallmarks are noncaseating epithelioid cell granulomas. It is thought that a dysregulated immune response against certain environmental antigens results in sustained granulomatous inflammation and failure to clear the offending antigen. The triggering antigen varies according to race, geography, and individual genetic background.

Morbidity and mortality are closely related to pulmonary manifestations occurring in >90% of patients. The CT appearance of pulmonary sarcoidosis varies greatly and is known to masquerade many other diffuse infiltrative lung diseases, conversely several diseases can resemble classical sarcoidosis.

5.2.1. Diagnosis

The disease may occur at any age, but mostly affects individuals between 20 and 40 years of age and only rarely occurs in people over 65 years of age. The prognosis is mostly good with disease resolution often occurring in <2 years and mortality between 1% and 5%.

The American Thoracic Society (ATS) published an official clinical guideline for diagnosis and detection of sarcoidosis in 2020. The guideline lists clinical and radiological features “highly probable” and “probable” for the diagnosis of sarcoidosis (Table 5.1, modified from the ATS document, focusing on lung and heart). Histological lymph-node sampling—to be obtained by endobronchial ultrasound-guided (EBUS) transbronchial biopsy—is *not* recommended in patients with high clinical suspicion. Whether to obtain histological sampling in patients with bilateral hilar lymphadenopathy and no clinical symptoms is left to the decision of the clinician.

5.2.2. Radiology

CT pulmonary findings in sarcoidosis include small, well-defined nodules in a characteristic “perilymphatic distribution,” often located near the subpleural surface, major fissures, interlobular septa, and vessels. These nodules may appear throughout both lungs, especially in the upper and middle zones, or cluster in perihilar and peribronchovascular regions with peripheral sparing.

Confluence of granulomas can create larger nodules (1–4 cm, “galaxy sign”) or ill-defined opacities (up to 10 cm, alveolar sarcoidosis) (see Fig. 5.1).

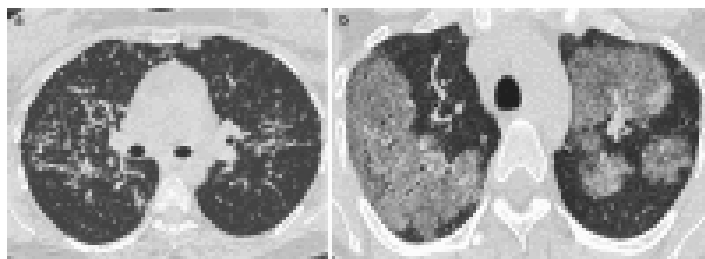


Fig. 5.1

Two patients with sarcoidosis: (a) a typical pattern of nodules in a perilymphatic distribution; (b) an atypical pattern with very small confluent nodules described as “alveolar sarcoidosis”

Lymphadenopathy is commonly seen in a subcarinal, right paratracheal, aortopulmonary, and symmetric hilar distribution. In advanced stages, lymph node calcifications may appear in an eggshell or “icing sugar” pattern. Up to 20–30% of patients develop irreversible pulmonary fibrosis (stage IV), with features like architectural distortion, traction bronchiectasis, honeycombing, and upper lobe volume loss. Perihilar conglomerate masses often reflect areas of fibrosis.

Airway abnormalities include compression from lymphadenopathy, traction bronchiectasis, and granuloma-induced bronchial wall thickening, affecting both large and small airways. Lobular air trapping, often seen on expiratory CT, results from small airway involvement.

A Delphi consensus identified seven CT phenotypes, differentiating non-fibrotic from likely fibrotic subtypes, though further research is needed to validate these categories. While sarcoidosis may show characteristic HRCT features allowing for a confident diagnosis, it can also present with atypical imaging, especially in advanced fibrotic stages, making differentiation from other fibrosing diseases difficult.

Diseases with imaging features that overlap with sarcoidosis (modified from [2])

5.2.3. Clinical Course, Prognosis, and Treatment

Managing sarcoidosis is challenging due to its unpredictable course and uncertain treatment strategies. Treatment decisions are based on the risk of organ failure and the impact on the patient’s quality of life. Many cases resolve spontaneously without systemic treatment. Granulomatous inflammation is believed to cause fibrosis in sarcoidosis, with “smoldering sarcoidosis” referring to ongoing inflammation that may lead to further fibrosis despite the absence of acute symptoms.

FDG-PET is useful for assessing granulomatous activity in patients with persistent symptoms and no serological inflammation, and can help predict pulmonary deterioration and monitor treatment response. Diet-based suppression of myocardial FDG uptake can help detect cardiac sarcoidosis activity.

A small percentage of sarcoidosis patients with pulmonary fibrosis exhibit usual interstitial pneumonia (UIP) histology and progressive fibrotic interstitial lung disease (ILD). While antifibrotic therapy may benefit those with UIP, it is unclear if patients with sarcoidosis and adequate anti-granulomatous treatment benefit from this.

Complications include aspergilloma and pulmonary hypertension. Mycetomas, common in stage IV sarcoidosis, can cause life-threatening hemoptysis requiring urgent intervention. Pulmonary hypertension occurs in advanced fibrosis or can be caused by mediastinal fibrosis, lymphadenopathy, or sarcoid vasculopathy. An integrated clinical–radiological staging system has been proposed to identify high-risk patients, incorporating lung function, fibrosis extent, and pulmonary artery-to-aorta diameter ratios to predict prognosis.

Key Point for Pulmonary Sarcoidosis

- Awareness of atypical imaging findings in sarcoidosis is crucial, as the disease can resemble other pulmonary conditions. Certain imaging features, such as solitary parenchymal abnormalities without lymphadenopathy and signs of fibrosis, suggest a worse prognosis and influence treatment decisions.

5.3. Connective Tissue Diseases [7]

Connective tissue diseases (CTDs) are primarily diagnosed based on clinical symptoms and physical examination, supported by the presence of specific autoantibodies. Imaging plays a key role in assessing lung involvement but is less useful for primary diagnosis due to overlapping findings among CTDs. Diagnosis typically involves an interdisciplinary team, including pulmonologists, rheumatologists, immunologists, radiologists, and sometimes pathologists.

Different lung connective tissue diseases and their main serum markers, clinical features, and radiological patterns (modified from [7])

Lung abnormalities may appear before other clinical symptoms, sometimes by more than 5 years, and imaging can suggest a CTD even if clinical criteria are not met. CTD can affect various compartments of the thorax, including the lungs, pleura, pericardium, lymphatics, vasculature, and heart, with more than one area often involved. Respiratory system involvement is common and leads to significant morbidity and mortality. Lung manifestations of CTD often resemble idiopathic interstitial pneumonias and are classified using the same system.

Lung biopsies are rarely performed in patients with known CTD, so high-resolution CT is often used to identify the dominant pattern of injury. This imaging pattern helps guide treatment and prognosis, as certain patterns are more commonly associated with specific CTDs, although multiple patterns may be present in the same patient.

5.3.1. Rheumatoid Arthritis (RA) [8–11]

RA is the most common connective tissue disease, characterized by erosive and inflammatory joint disease, primarily affecting distal joints. Extra-articular manifestations include subcutaneous nodules, skin ulcers, pericarditis, splenomegaly, and various pulmonary conditions. Anti-cyclic citrullinated peptide (CCP) antibodies are specific to RA and often correlate with disease severity.

Up to 80% of RA patients show abnormalities on high-resolution chest CT, often asymptomatic. Pulmonary involvement spans multiple compartments, including airway changes (bronchial wall thickening, dilation), parenchymal alterations (reticulation, ground-glass opacity, honeycombing), and pleural thickening/effusion. Airways disease is usually the earliest lung manifestation. Bronchiectasis, air trapping, and obliterative bronchiolitis are common, with air trapping leading to mosaic

attenuation on CT. Follicular bronchiolitis is another small airway disorder recognized in rheumatoid lung disease, presenting with centrilobular nodules and ground-glass opacity.

Although RA is more frequent in women, lung fibrosis (UIP or NSIP) is more common in men, with UIP being the most prevalent pattern. CT findings in RA-associated interstitial pneumonia can resemble idiopathic forms but clues such as nodules, arterial enlargement, or pleural abnormalities help distinguish RA. UIP in RA typically shows a subpleural, basilar distribution, and features such as the “anterior upper lobe,” “exuberant honeycombing,” and “straight-edge” signs are suggestive of CTD-related UIP (an example is shown in Fig. 5.2).

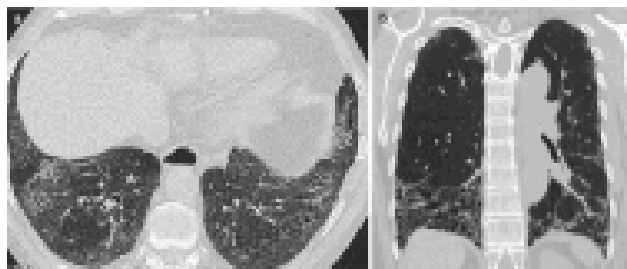


Fig. 5.2

(a) Patient with systemic sclerosis (SSc) with a uniform NSIP pattern and a dilated esophagus; (b) patient with rheumatoid arthritis (RA) with a UIP pattern: note the sharp horizontal demarcation of the honeycombing, described as “straight edge-sign” ([more...](#))

Risk factors for progression of RA-ILD include extent and UIP pattern, smoking history, older age, and male gender. Antifibrotic treatments may benefit some patients with progressive RA-UIP (INBUILD trial). RA patients can develop large nodules that may cavitate, potentially causing pneumothorax, and must be differentiated from malignancies. Pleural thickening and effusion are common, with chronic thickening leading to lung entrapment.

Pulmonary issues may stem from RA itself or its treatments, such as immune-modulating drugs that raise the risk of infections and drug toxicity. Methotrexate, a first-line treatment, is linked to rare cases of hypersensitivity pneumonitis. Biologic agents, particularly anti-TNF α antibodies, significantly increase the risk of tuberculosis and other infections. Complications in RA include pulmonary hypertension (PH), lymphoma, and lung cancer.

Key Point for Rheumatoid Arthritis (RA)

- Pulmonary manifestations of RA, particularly airway disease and interstitial fibrosis (UIP, NSIP), are common and often asymptomatic, with UIP being the most severe and a major determinant of prognosis.

5.3.2. Systemic Sclerosis (SSc) [12–15]

Systemic sclerosis is characterized by fibroblast dysfunction and excessive extracellular matrix deposition, leading to microvascular damage and progressive skin and organ fibrosis. Lung involvement is common in scleroderma patients. The ACR-EULAR classification criteria for SSc include pulmonary hypertension (PH) and interstitial lung disease (ILD) alongside skin thickening, fingertip lesions, telangiectasia, abnormal nailfold capillaries, Raynaud’s phenomenon, and scleroderma-related antibodies such as anticentromere (ACA) and anti-Scl-70 antibodies.

Lung abnormalities are present in over 80% of autopsies, with NSIP being the dominant pattern (>90%), and PH is frequently seen, especially in limited scleroderma (CREST syndrome). Esophageal dilation, related to gastroesophageal reflux, is found in 80% of cases and increases the risk of ILD. CT findings mirror NSIP histology, with ground glass opacity in cellular NSIP and irregular reticulation and traction bronchiectasis in fibrotic NSIP (Fig. 5.2). Subpleural sparing and limited honeycombing are key features. Progression to “end-stage lung disease” is marked by the replacement of ground glass with honeycombing.

Specific CT findings in SSc include the “straight-edge” sign, showing clear boundaries between fibrosis and unaffected lung (more often present in SSc than RA), and the “Four Corners” sign, indicating parenchymal changes in the anterolateral regions of the mid-upper lobes and the posterolateral regions of the lower lobes. SSc-related lung fibrosis often has a better prognosis than idiopathic lung fibrosis, with fibrotic changes sometimes remaining stable for years.

Pulmonary arterial hypertension (PAH) in SSc can cause pulmonary artery enlargement, though normal artery size does not exclude the diagnosis. Pericardial thickening or fluid is also predictive of PAH. CREST patients may develop PAH due to pulmonary capillary hemangiomatosis (PCH) without lung fibrosis. Scleroderma also increases the risk of lung cancer, especially in those with fibrosis, with malignancy risks ranging from 1.8 to 6.5.

Key Point for Systemic Sclerosis (SSc)

- Lung involvement is common in systemic sclerosis, with NSIP as the predominant pattern. SSc-related lung fibrosis often has a better prognosis compared to idiopathic pulmonary fibrosis, but pulmonary hypertension represents a serious complication.

5.3.3. Systemic Lupus Erythematosus (SLE) [16, 17]

SLE can affect multiple organs, including joints, skin, kidneys, serosa, blood vessels, and the central nervous system, leading to a wide range of clinical symptoms, such as rheumatological, dermatological, respiratory, and renal issues. It primarily affects young women. Serological markers may include antinuclear antibodies (ANA), anti-dsDNA, hypocomplementemia, and anti-Ro/anti-SS-A antibodies.

Pleuritis is the most common pleuropulmonary manifestation, occurring in 40–60% of cases, sometimes with pleural effusion. Fibrotic interstitial lung disease is less frequent in SLE (1–15%) compared to other connective tissue diseases. Pulmonary infection is the most common lung complication, while acute pulmonary hemorrhage and acute lupus pneumonitis (ALP) are also significant. ALP, which may present with active lupus nephritis, is characterized by pulmonary consolidation and can resemble severe infection or ARDS.

Other lung complications include diaphragmatic dysfunction, pulmonary hypertension, and thromboembolism, potentially linked to antiphospholipid antibodies. Diaphragmatic dysfunction, caused by myopathy, results in reduced lung volumes and “shrinking lungs” with platelike atelectasis.

Key Point for Systemic Lupus Erythematosus (SLE)

- Systemic lupus erythematosus (SLE) commonly affects multiple organs, with pleuritis as the most frequent pleuropulmonary manifestation, while serious complications such as acute lupus pneumonitis and pulmonary hemorrhage can occur.

5.3.4. Polymyositis/Dermatomyositis (PM/DM) and Antisynthetase Syndrome (ASSD) [18–20]

Polymyositis and dermatomyositis are characterized by proximal muscle weakness, systemic involvement, and skin manifestations, classified as idiopathic inflammatory myopathies (IIMs). These may also include antisynthetase syndrome (ASSD). Diagnostic criteria include symmetric muscle weakness, elevated muscle enzymes like creatine kinase (CK), and signs of myositis and skin involvement.

The presence of ILD in PM/DM correlates strongly with the presence of anti-Jo-1 (anti-histidyl-tRNA synthetase). About 50–70% of patients who are anti-Jo-1 positive have ILD, whereas the frequency of ILD falls to about 10% if antibodies are absent. ILD may antedate myositis in patients with anti-Jo-1 antibodies. The clinical course is very variable, ranging from subclinical to rapidly progressive.

Common pathological findings are NSIP and organizing pneumonia (OP), often combined. CT scans show confluent ground-glass opacity and consolidation in the lower lobes, with traction bronchiectasis reflecting NSIP and OP (Fig. 5.3). While consolidation often improves with treatment, fibrosis typically persists. OP may appear independently and is more widespread in IIMs. Diffuse alveolar damage can also occur, presenting acutely with symmetric bilateral ground-glass opacity or consolidation.

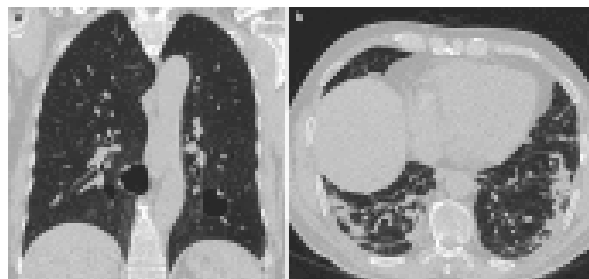


Fig. 5.3

(a) Patient with Sjögren’s syndrome and a lymphocytic interstitial pneumonia (LIP) characterized by thin-walled cysts. Note the small solid nodules in the cyst walls and the bronchiectasis in the right lower lobe. (b) Patient with antisynthetase ([more...](#))

Patients with PM/DM have an increased risk of malignancy, particularly breast, lung, ovary, and stomach cancers, with up to 20% diagnosed within 1 year.

Key Point for Polymyositis/Dermatomyositis (PM/DM)/Antisynthetase Syndrome (ASSD)

- PM/DM and ASSD share common clinical features and may be more appropriately summarized under the term idiopathic inflammatory myopathies (IIMs). The most common pulmonary findings include NSIP and OP or a combination of both. The serological marker anti-Jo-1 (anti-histidyl-tRNA synthetase) is the hallmark of ASSD.

5.3.5. Sjögren Syndrome (SS) [21–23]

Sjögren syndrome (SS), or “sicca syndrome,” is a chronic autoimmune disease targeting the exocrine glands, causing xerostomia and xerophthalmia. SS is classified as primary or secondary, depending on its association with other connective tissue diseases such as RA, SLE, and SSc. Diagnosis is based on a weighted score of five items, including salivary gland biopsy, anti-Ro/SSA antibodies, and tests for eye and salivary gland function. A score of 4 or more confirms the diagnosis according to ACR-EULAR 2016 criteria.

Pulmonary involvement in SS is divided into airway abnormalities, interstitial fibrosis, pulmonary hypertension, and lymphoid interstitial pneumonia (LIP). Airway-related issues such as bronchial wall thickening, bronchiectasis, and air trapping are common. NSIP (28–60%) is the most frequent pattern of parenchymal lung disease, followed by LIP (up to 20%), which presents with ground-glass opacity and cysts caused by lymphocytic infiltration. LIP can also involve perilymphatic or centrilobular nodules, but the presence of cysts will help differentiate it from lymphoma.

LIP increases the risk of MALT lymphoma, which is suspected if large nodules, consolidation, or mediastinal lymphadenopathy appear. Unlike other cystic lung diseases, LIP-related cysts are fewer, mainly in peribronchovascular regions, and show lower lung predominance (Fig. 5.3).

Key Point for Sjögren Syndrome (SS)

- Sjögren syndrome (SS) is a chronic autoimmune disease affecting the exocrine glands, often involving pulmonary complications such as airway abnormalities and interstitial lung disease (primarily NSIP and LIP). LIP increases the risk of developing MALT lymphoma, making early detection critical.

5.3.6. Mixed Connective Tissue Disease [24, 25]

Mixed connective tissue disease (MCTD) is an overlap syndrome characterized by features of systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and polymyositis/dermatomyositis (PM/DM), either occurring simultaneously or evolving over time. A key marker of MCTD is the presence of antibodies to extractable nuclear antigen (RNP). Pulmonary involvement is common, affecting more than 60% of patients, though many remain asymptomatic. Lung abnormalities resemble those seen in SLE, SSc, and PM/DM, with pleural thickening, effusions, and ground-glass attenuation being frequent. The most common CT pattern observed is NSIP, while honeycombing and poorly defined nodules are less common.

Complications in MCTD can include pulmonary arterial hypertension and esophageal dysmotility, which may lead to recurrent aspiration in the lungs. The presence of anti-Ro52 antibodies is associated with more severe lung fibrosis, similar to that seen in SSc-related interstitial lung disease. While pulmonary progression in MCTD is generally slow, the associated conditions can significantly impact the respiratory system over time.

Key Point for Mixed Connective Tissue Disease (MCTD)

- MCTD presents with overlapping features of SLE, SSc, and PM/DM, often involving pulmonary abnormalities such as ground-glass attenuation and NSIP, with complications including pulmonary hypertension and esophageal dysmotility.

5.3.7. Interstitial Pneumonia with Autoimmune Features (IPAF) [26, 27]

Increasing attention is being given to patients with interstitial lung disease (ILD) who display some, but not all, characteristics of a connective tissue disease (CTD). Previously referred to as undifferentiated CTD (UCTD) or lung-dominant CTD, the accepted term is now interstitial pneumonia with autoimmune features (IPAF). This classification is for patients with interstitial pneumonia on CT or biopsy, where known causes of ILD have been excluded, but criteria for a defined CTD are not met.

An ERS/ATS task force outlined criteria for diagnosing IPAF. Patients must exhibit features in two of three domains: (1) a clinical domain with extrathoracic signs such as arthritis, Raynaud's

phenomenon, or mechanic's hands; (2) a serologic domain with specific autoantibodies; and (3) a morphologic domain with CT or histopathologic features suggestive of CTD. Imaging patterns include NSIP, organizing pneumonia, and multicompartiment involvement, such as unexplained pleural or pericardial effusions, small airways disease, or pulmonary vasculopathy.

Key Point for Interstitial Pneumonia with Autoimmune Features (IPAF)

- IPAF refers to a subset of patients who exhibit clinical, radiological, or serological markers suggestive of a connective tissue disease (CTD) but do not meet the full criteria for a specific CTD. The most common pattern observed is NSIP. Diagnosis is based on a multidomain approach to provide consistent and meaningful data on the clinical progression of this patient group in the future.

5.4. Pulmonary Vasculitis/Diffuse Alveolar Hemorrhage [28–31]

Vasculitis is a systemic inflammatory process that damages blood vessels, leading to ischemic or hemorrhagic changes. The 2012 Chapel Hill classification categorizes vasculitis by the size of affected vessels: large vessels (aorta and its branches), medium vessels (main visceral arteries), and small vessels (capillaries, venules, arterioles). The recent Diagnostic and Classification Criteria in Vasculitis (DCVAS) project led to new ACR/EULAR criteria (2022) for GPA, MPA, and EGPA. These criteria now emphasize ANCA specificity, shifting from a phenotype-based to a serology-based approach. Classification requires meeting a weighted threshold score (GPA 5, MPA 5, EGPA 6).

Pulmonary involvement is most common in small vessel vasculitis (SVV), which includes ANCA-associated vasculitis (AAV) such as microscopic polyangiitis, granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA). Immune-complex SVV, such as Goodpasture disease, also affects the lungs. Symptoms and signs of pulmonary vasculitis include diffuse alveolar hemorrhage (DAH), lung nodules, and pulmonary–renal syndrome. Secondary vasculitis can occur with connective tissue diseases such as RA, SLE, and systemic sclerosis, as well as sarcoidosis. The distinction between primary and secondary vasculitis is becoming less clear as more causes are discovered, such as drug-induced immune complex vasculitis.

DAH is a clinical syndrome characterized by hemoptysis, diffuse infiltrates, and a drop in hematocrit. It occurs in both primary and secondary small vessel vasculitis, such as GPA, MPA, EGPA, and Goodpasture disease. DAH must be distinguished from other causes of pulmonary hemorrhage, such as coagulation disorders, drug-induced hemorrhage, and ARDS-associated bleeding.

5.4.1. ANCA-Associated Granulomatous Vasculitis with Polyangiitis (GPA, Formerly Wegener's Disease)

GPA is the most common ANCA-associated vasculitis (AAV), primarily affecting the sinuses, kidneys, and lungs, presenting as a triad of upper airway disease (sinusitis, otitis, subglottic stenosis), lower respiratory symptoms (hemoptysis, chest pain, dyspnea), and glomerulonephritis (hematuria, azotemia). Patients may initially show limited symptoms, but any organ can be affected over time. The leading cause of death is renal failure. Up to 80% of patients are ANCA-positive, mostly PR3-ANCA. Histologically, GPA shows necrotizing granulomatous vasculitis of small to medium vessels.

Common pulmonary findings include multiple nodules or masses of varying size, with or without a CT halo sign, often in subpleural areas. Lesions, which can cavitate, range up to 10 cm but are usually smaller. Peripheral wedge-shaped consolidations, diffuse ground-glass opacities, and fibrotic changes may also occur. Cavitating nodules can become superinfected, and a reverse halo sign suggests organizing pneumonia. Tracheal and bronchial thickening occurs in 70% of cases, often affecting the subglottic trachea, with possible airway narrowing causing atelectasis.

GPA is marked by rapid progression of nodules and airspace opacities. Differential diagnoses include neoplasms, infections, and other granulomatous or airway diseases like amyloidosis and relapsing polychondritis.

Key Point for GPA (Formerly Wegener's Disease)

- GPA (formerly Wegener's disease) is an ANCA-associated vasculitis affecting the sinuses, kidneys, and lungs, often presenting with nodules, cavitations, and airway involvement.

5.4.2. Eosinophilic Granulomatosis with Polyangiitis (EGPA; Formerly Churg Strauss)

EGPA, a small vessel vasculitis, primarily affects patients with **asthma** and is marked by significant serum eosinophilia. It shares clinical, radiological, and pathological features with GPA and eosinophilic pneumonia. Multiple organs may be involved, including the heart (47%), skin (40%), musculoskeletal system (50%), and peripheral nerves (75%). Renal involvement and pulmonary hemorrhage are less common. About 30% of cases are ANCA-positive, mainly MPO-ANCA or c-ANCA, with higher positivity in active disease. Biopsy is recommended if ANCA is negative and accessible lesions are present. Histology shows small vessel vasculitis, eosinophilic infiltrates, and granulomas.

EGPA typically presents in three phases—asthmatic, eosinophilic, and vasculitic—with the asthmatic phase often preceding the vasculitic phase by 8–10 years. Pulmonary findings occur in 70% of cases, with transient, multifocal consolidations or ground glass opacities, often resembling eosinophilic pneumonia when subpleural. Pleural effusions are seen in a third of cases due to cardiomyopathy or pleuritis, and airway abnormalities include wall thickening, dilation, and centrilobular nodules. Differential diagnoses include eosinophilic pneumonia, organizing pneumonia, and airway diseases such as MPA, SLE, and infection bronchiolitis.

Key Point for Eosinophilic Granulomatosis with Polyangiitis (EGPA)

- EGPA primarily affects **asthma** patients, presenting with eosinophilia and multisystem involvement, including lungs, heart, skin, and peripheral nerves. Common pulmonary findings include transient consolidations, ground-glass opacities, and airway abnormalities, with **asthma** being an obligatory symptom during the disease course.

5.4.3. Microscopic Polyangiitis (MPA)

Microscopic polyangiitis (MPA) is a systemic necrotizing small vessel vasculitis without granulomatous inflammation, commonly causing pulmonary–renal syndrome. Rapidly progressive glomerulonephritis occurs in up to 90% of cases, with pulmonary involvement in 30–50%. Over 75% of patients are ANCA positive, predominantly MPO-ANCA (35–65%).

MPA is defined by the combination of glomerulonephritis and diffuse alveolar hemorrhage (DAH). Imaging shows patchy, bilateral, or diffuse airspace opacities, which may appear as consolidations or ground-glass opacities depending on the amount of alveolar bleeding. DAH is typically more

pronounced in perihilar areas, sparing the lung apices and costophrenic angles. A halo around a consolidation or nodule indicates hemorrhage, and interlobular lines (crazy paving) appear during resorption. Fibrotic interstitial lung disease, with honeycombing and bronchiectasis, is seen more frequently in MPA than in GPA.

Key Point for Microscopic Polyangiitis (MPA)

- MPA is a systemic small vessel vasculitis, often presenting with rapidly progressive glomerulonephritis and diffuse alveolar hemorrhage. Pulmonary involvement includes patchy airspace opacities and, in some cases, fibrotic interstitial lung disease, with most patients being MPO-ANCA positive.

5.4.4. Anti-glomerular Basement Membrane (Anti-GBM) Disease

Anti-GBM disease, an immune complex small vessel vasculitis (SVV), is characterized by antibodies targeting the glomerular basement membrane, leading to necrotizing glomerulonephritis and acute renal failure, typically diagnosed via renal biopsy. Diffuse alveolar hemorrhage (DAH) occurs in 40–60% of cases, while isolated pulmonary involvement is rare. “Goodpasture syndrome” refers to glomerulonephritis with pulmonary hemorrhage, regardless of cause, while “Goodpasture disease” refers specifically to DAH, glomerulonephritis, and anti-GBM antibodies.

Serology shows c-ANCA or p-ANCA positivity in 30% of cases and anti-GBM antibodies in over 90%. Young men are more commonly affected, though elderly women may also develop the disease. Pulmonary involvement is often linked to lung injury, such as from smoking or drug use. Imaging reveals diffuse or patchy ground-glass opacities or consolidations due to DAH, usually resolving within days. Recurrent episodes can lead to fibrosis, traction bronchiectasis, and honeycombing.

Key Point for Anti-GBM Disease

- Anti-GBM disease causes necrotizing glomerulonephritis and diffuse alveolar hemorrhage, with pulmonary involvement often linked to prior lung injury, and recurrent episodes may lead to fibrosis.

Key Point for Vasculitis

- Pulmonary manifestations are mainly caused by small vessel vasculitis such as GPA, EGPA, and MPA. Hallmark is the association with the serological marker ANCA. Imaging findings are mostly nonspecific. Diffuse hemorrhage is seen in all of them, mostly in MPA. GPA demonstrates with (cavitating nodules) and airway-wall thickening.

5.5. Summary and Take Home Points

- Pulmonary manifestations of systemic diseases are characterized by a wide spectrum of imaging patterns.
- While in sarcoidosis, typical HRCT findings (perilymphatic nodular pattern and/or symmetric lymphadenopathy) are diagnostic, CT findings in connective tissue diseases are always only part of a multidisciplinary diagnostic work-up that is largely based on serum markers. Similarly, in vasculitis, the diagnosis is mainly based on serological findings.

- Nevertheless, CT is important for the assessment of extent and monitoring of pulmonary disease. This is especially important, since in many diseases patient prognosis is determined by lung involvement.

Key Points

- Pulmonary sarcoidosis exhibits a wide spectrum of imaging features, with advanced fibrosis indicating a worse prognosis.
- In CTD-related lung disease, HRCT patterns like UIP and NSIP are common, and multidisciplinary management is crucial.
- Vasculitis affecting the lungs can present with diffuse hemorrhage, cavitating nodules, and airway thickening, with serological markers aiding diagnosis.
- Imaging plays a central role in the follow-up and management of lung disease in systemic disorders, impacting prognosis and therapeutic decisions.

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