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IMAGING (D MINTZ, SECTION EDITOR)

Cardiopulmonary Manifestations of Collagen Vascular Diseases

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Abstract
Purpose of Review The study aimed to illustrate the cardiopulmonary findings of the following collagen vascular diseases on cross-sectional imaging: rheumatoid arthritis, scleroderma (progressive systemic sclerosis), systemic lupus erythematosus, the inflammatory myopathies (polymyositis/dermatomyositis), and Sjögren's syndrome.
Recent Findings Although collagen vascular diseases can affect any part of the body, interstitial lung disease and pulmonary hypertension are the two most important cardiopulmonary complications and are responsible for the majority of morbidity and mortality in this patient population. Interstitial pneumonia with autoimmune features (IPAF) is a newly described entity that encompasses interstitial lung disease in patients with clinical, serologic, or morphologic features suggestive of but not diagnostic of collagen vascular disease; these patients are thought to have better outcomes than idiopathic interstitial pneumonias.
Summary Interstitial lung disease and pulmonary hypertension determine the prognosis in collagen vascular disease patients. IPAF is a new term to label patients with possible collagen vascular disease-related interstitial lung disease. Collagen vascular disease patients are at increased risk for various malignancies.

Keywords Collagen vascular diseases · Interstitial lung disease · Pulmonary hypertension · Connective tissue diseases · Cardiac magnetic resonance imaging

Introduction

The collagen vascular diseases are a heterogeneous group of disorders with autoimmune features that can affect multiple systems and cause end-organ damage. The most frequently encountered collagen vascular diseases are scleroderma (progressive systemic sclerosis), rheumatoid arthritis, systemic lupus erythematosus (SLE), the inflammatory myopathies (polymyositis and dermatomyositis (PM/DM)), and Sjögren's syndrome. Mixed connective tissue disease (MCTD) has features of multiple overlapping collagen vascular diseases and will not be discussed in this article.

Collagen vascular diseases can involve any component of the cardiopulmonary system including the airways (small and large); lung alveoli, interstitium, and lymphatics; pleura; chest wall; heart; and the vasculature. Though the specific disease pattern varies with each entity, pulmonary hypertension and interstitial lung disease are the two most frequent intrathoracic manifestations of collagen vascular diseases and responsible for the bulk of morbidity and mortality in these patients.

Traditionally, collagen vascular diseases were imaged with chest radiography, but now computed tomography (CT) and high-resolution computed tomography (HRCT) have become widely available and led to improved understanding of the patterns of cardiopulmonary involvement.

This article is part of the Topical Collection on *Imaging*

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Pulmonary Manifestations of Collagen Vascular Diseases

Collagen vascular diseases may present with interstitial lung disease (ILD), which overlaps the histological and radiological patterns described for idiopathic interstitial pneumonias (IIPs): usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), diffuse alveolar damage (DAD), and lymphoid interstitial pneumonia (LIP) (Table 1) [1–3]. Although the actual ILD pattern and frequency varies with each collagen vascular disease, scleroderma, inflammatory myopathies, and rheumatoid arthritis have the highest association with ILD, while systemic lupus erythematosus is rarely associated with it (Table 2) [4–7].

Interestingly, ILDs associated with collagen vascular diseases have a better prognosis than their IIP counterparts. This may be because NSIP is the most common ILD pattern in collagen vascular disease (41%), whereas UIP is the most common pattern in idiopathic interstitial pneumonias. NSIP pattern, in general, has a better prognosis than a UIP pattern [5, 8]. More focused studies have shown collagen vascular disease patients with a UIP pattern to have similar or slightly better survival than idiopathic UIP or idiopathic pulmonary fibrosis (IPF) [9–11].

Rheumatoid Arthritis

Interstitial lung disease and airways disease are the predominant pulmonary manifestations of rheumatoid arthritis. Rheumatoid arthritis-related interstitial lung disease (RA-ILD) occurs in 30–60% of rheumatoid arthritis patients, with clinically significant disease in only 10% [12, 13]. UIP, NSIP, OP, and follicular bronchiolitis can all occur in rheumatoid arthritis, but UIP and NSIP are the most frequent histologic patterns, with UIP being more common on HRCT (Table 3, Fig. 1) [4, 6, 14].

Airways disease—including small and large airways—is common in rheumatoid arthritis and may be the earliest pulmonary manifestation; this includes bronchiectasis, constrictive bronchiolitis (bronchiolitis obliterans), and follicular bronchiolitis. Constrictive bronchiolitis results from bronchiolar destruction with replacement by scar tissue; CT shows mosaic attenuation and expiratory air trapping [4, 15]. Follicular bronchiolitis results from compression of bronchiolar lumen by lymphoid aggregates; CT imaging depicts these as ill-defined centrilobular nodules, with mosaic attenuation and air trapping (Fig. 2) [5]. Pleural effusions may be present in up to 5% of rheumatoid arthritis patients but are frequently unilateral [16]. Necrobiotic nodules (rheumatoid nodules) are another feature of rheumatoid arthritis but are extremely rare. On CT, these appear as well defined, round nodules that may cavitate (Fig. 3). Histologically, necrobiotic nodules are similar to the rheumatoid nodules found in the subcutaneous tissues. It is worth remembering that it is much more common for atypical infections (fungal, mycobacterial) to cause lung nodules in rheumatoid patients and should be in the differential diagnosis for necrobiotic nodules.

Table 1 HRCT findings of idiopathic interstitial pneumonias (IIPs)

Idiopathic interstitial pneumonia (IIP)	HRCT findings[a]	Distribution
Usual interstitial pneumonia (UIP)	Reticular abnormality, traction bronchiectasis and bronchiolectasis, honeycombing, architectural distortion	Subpleural Basal
Nonspecific interstitial pneumonia (NSIP)	Confluent ground-glass opacity, reticular abnormality (typically less than ground-glass opacity), traction bronchiectasis Rare: cysts and micronodules	Peripheral or peribronchovascular Basal Subpleural sparing[b]
Organizing pneumonia (OP)	Consolidation, ground-glass opacity, macro-nodules; "atoll" sign	Peripheral or peribronchovascular Basal Patchy Migratory
Diffuse alveolar damage (DAD)	Consolidation, ground-glass opacity	Bilateral symmetric Basal
Lymphoid interstitial pneumonia (LIP)	Ground-glass opacity, cysts	Basal or diffuse

[a] HRCT findings as defined in the Fleischner Society: glossary of terms for thoracic imaging [3]

[b] Subpleural sparing is not sensitive but a very specific feature of NSIP

Table 2 Prevalence of interstitial lung disease in collagen vascular diseases [4–6, 60]

Collagen vascular disease	ILD prevalence (%)	Predominant ILD patterns
Rheumatoid arthritis	5–20	Pathology: follicular bronchiolitis (35%); NSIP (41%); UIP (12%) [*N* = 17]
		CT: UIP (41%); NSIP (30%); OP (8%) [*N* = 63]
Scleroderma	70–80	NSIP (75%); UIP (8%); OP (1%) [*N* = 80]
Systemic lupus erythematosus	5	UIP (50%); NSIP (50%) [*N* = 2]
Polymyositis/dermatomyositis	30	NSIP (53%); OP (38%); UIP (8%) [*N* = 13]
Sjögren's syndrome	10	Pathology: chronic bronchiolitis (80%); NSIP (20%) [*N* = 5]
		CT: LIP

ILD interstitial lung disease, *CT* computed tomography, *UIP* usual interstitial pneumonia, *NSIP* nonspecific interstitial pneumonia, *OP* organizing pneumonia, *LIP* lymphoid interstitial pneumonia, *N* number of cases in referenced studies

Scleroderma (Progressive Systemic Sclerosis)

Scleroderma (progressive systemic sclerosis) involves the pulmonary system in up to 80% of cases [17]. Interstitial lung disease is the most common pulmonary manifestation, NSIP being the predominant ILD pattern [18]. UIP and OP are far less common. As with idiopathic interstitial pneumonias, scleroderma patients with an NSIP pattern have a better prognosis than those with a UIP pattern. Some patients earlier in the disease course may only have mild ground-glass opacity on HRCT, but half of these patients will eventually progress to overt lung fibrosis [19]. Esophageal dilatation—secondary to esophageal dysmotility—is present in up to 80% on CT and can be a clue to the etiology when confronted with an NSIP pattern on HRCT (Fig. 4). Bronchiectasis and bronchiolectasis can be out of proportion to the overall NSIP pattern, perhaps secondary to repeated episodes of micro-aspiration. Pulmonary hypertension (discussed later) is the second most common cardiopulmonary manifestation of scleroderma and can occur with or without concomitant interstitial lung disease.

Systemic Lupus Erythematosus

Pleuritis is the most common pulmonary manifestation of SLE—seen in 40–60% of patients—and can result in pleural effusions (Fig. 5) [4]. Community-acquired pneumonia is the most frequent parenchymal manifestation of SLE and results in ground-glass opacity and consolidation on CT [20, 21]. Acute pneumonitis and alveolar hemorrhage are two rare complications of SLE that can be life-threatening; these can also present with consolidation and ground-glass opacity on CT imaging and can be difficult to distinguish (Fig. 6). Pulmonary hemorrhage is more likely to have a crazy-paving pattern on CT and may show a more rapid resolution of CT abnormalities [22]. Unlike rheumatoid arthritis and scleroderma, interstitial lung disease is rare in SLE and affects less than 5% of patients [23]; both UIP and NSIP have been reported and most likely develop after an episode of acute pneumonitis [22]. Interestingly, SLE patients can develop diaphragmatic paralysis resulting in *shrinking lung syndrome* where the diaphragm appears elevated and adjacent lung atelectasis is present [24].

Table 3 Pulmonary manifestations of collagen vascular diseases [4]

Collagen vascular disease	UIP	NSIP	OP	LIP	Other
Rheumatoid arthritis	+++	+	+	–	Bronchiectasis; bronchiolitis
Scleroderma	+	+++	+	–	Bronchiectasis > reticulation
Systemic lupus erythematosus	+	+	+	+	ILD is rare; pneumonitis; alveolar hemorrhage; pleuritis
Polymyositis/dermatomyositis	+	+++	+++	–	
Sjögren's syndrome	–	+	–	+++	

The greater the number of "+" signs, the greater the relative frequency of a particular interstitial lung disease pattern

UIP usual interstitial pneumonia, *NSIP* nonspecific interstitial pneumonia, *OP* organizing pneumonia, *LIP* lymphoid interstitial pneumonia, *ILD* interstitial lung disease

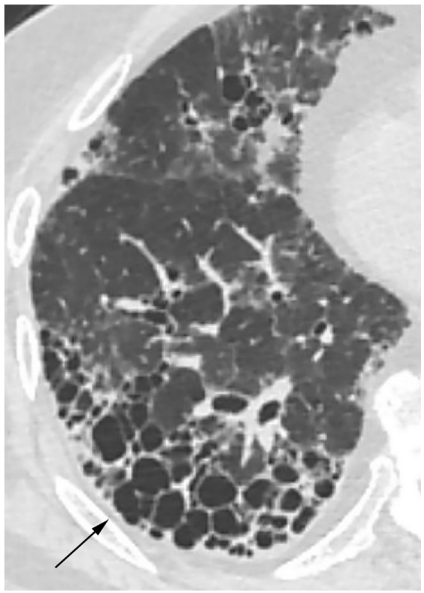

Fig. 1 HRCT of a patient with rheumatoid arthritis shows subpleural and basal predominant honeycombing (*arrow*), reticular abnormality, and mild traction bronchiolectasis consistent with a UIP pattern. HRCT high-resolution computed tomography, UIP usual interstitial pneumonia

The Inflammatory Myopathies (Polymyositis/Dermatomyositis)

PM/DM constitute the majority of the inflammatory myopathies. As with other collagen vascular diseases, interstitial lung disease can precede the diagnosis of myositis. Anti-Jo antibodies, when present, have a higher association with ILD—the incidence of ILD is 50–70% of those positive for anti-Jo as opposed to 10% in those who are anti-Jo negative [25]. NSIP and OP are the most common ILD patterns and can be present in combination (Fig. 7) [4]. On CT, these appear as lower lobe-predominant

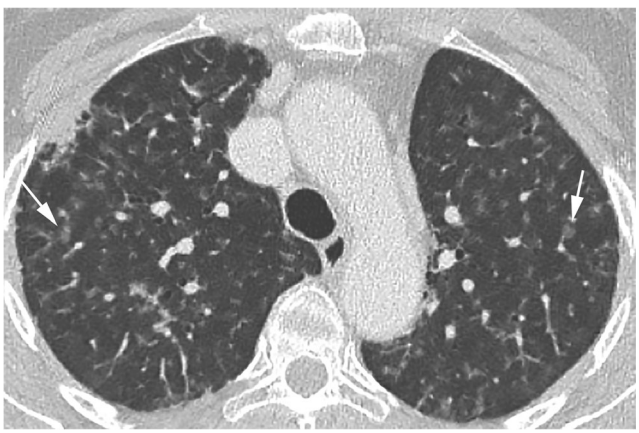

Fig. 2 HRCT of a rheumatoid arthritis patient with follicular bronchiolitis demonstrates ill-defined centrilobular ground-glass nodules (*arrow*). HRCT high-resolution computed tomography

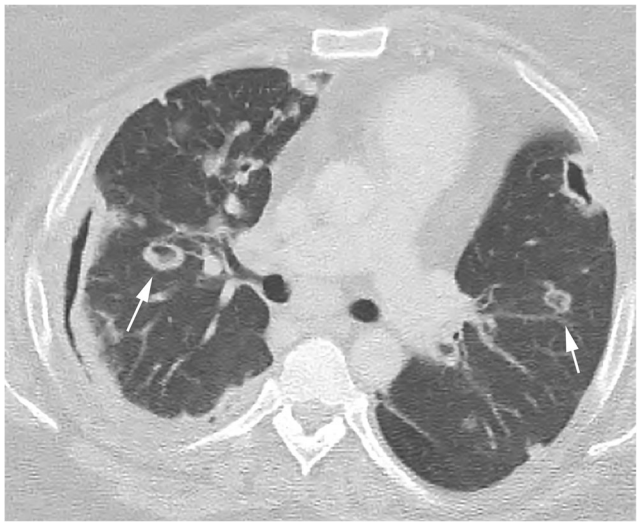

Fig. 3 CT of a rheumatoid arthritis patient demonstrates multiple, bilateral pulmonary nodules, some of which show cavitation (*arrows*). Lung biopsy confirmed necrobiotic nodules. CT computed tomography

confluent ground-glass opacity and traction bronchiectasis on a background of reticular abnormality [26, 27]. Interestingly, some of these findings can reverse with corticosteroid treatment, perhaps due to the underlying component of organizing pneumonia [28]. PM/DM patients can also develop hypoventilation and atelectasis due to diaphragmatic dysfunction and can aspirate due to pharyngeal muscle weakness, a disease feature that can confound pulmonary CT findings.

Anti-synthetase syndrome (AS) is a recently recognized inflammatory myopathy characterized by the presence of antibodies against aminoacyl-tRNA synthetase

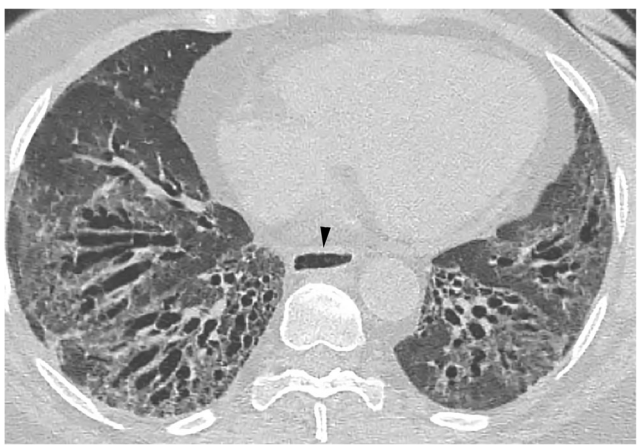

Fig. 4 HRCT of a patient with scleroderma shows basal predominant ground-glass opacity, reticular abnormality, and traction bronchiectasis consistent with an NSIP pattern. The esophagus is also patulous (*arrowhead*). Note that bronchiectasis is out of proportion to the remaining fibrotic changes. HRCT high-resolution computed tomography, NSIP nonspecific interstitial pneumonia

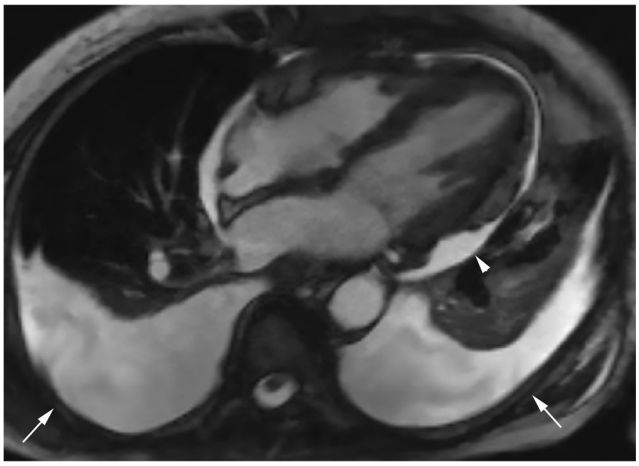

Fig. 5 T2-weighted cardiac MRI exam of an SLE patient with serositis shows a small pericardial effusion (*arrowhead*) and moderate bilateral pleural effusions (*arrows*). MRI magnetic resonance imaging, SLE systemic lupus erythematosus

enzyme. AS has a high association with ILD, arthritis, Raynaud phenomenon, and mechanic's hands. The HRCT appearance is similar to PM/DM with NSIP and OP, being the predominant patterns [29•].

Sjögren's Syndrome

Pulmonary findings can be present on CT in up to 30% of patients with Sjögren's syndrome with interstitial lung disease and airway abnormalities being the two most common. Interstitial lung disease frequently manifests as LIP, a benign lymphoproliferative disorder characterized by lymphocytic infiltration of the interstitium. On HRCT, LIP can present with ground-glass opacity, thin-walled cysts, and tiny nodules (Fig. 8) [30]. Up to one third of patients with Sjögren's syndrome can have airways disease—bronchiectasis, bronchial wall thickening, and air trapping (mosaic attenuation) [22].

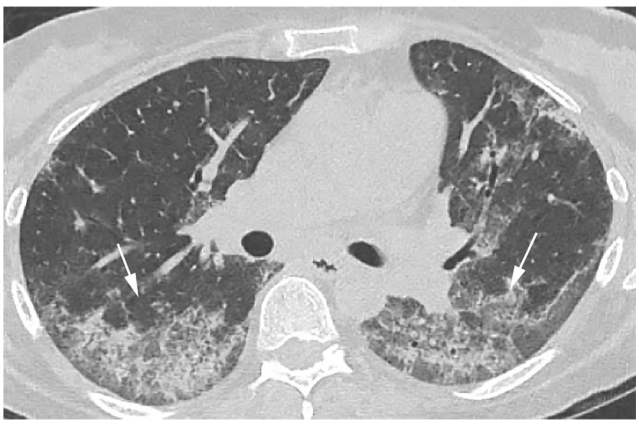

Fig. 6 HRCT of an SLE patient with acute pneumonitis shows bilateral, patchy areas of ground-glass opacity mixed with reticular abnormality (*arrows*). HRCT high-resolution computed tomography, SLE systemic lupus erythematosus

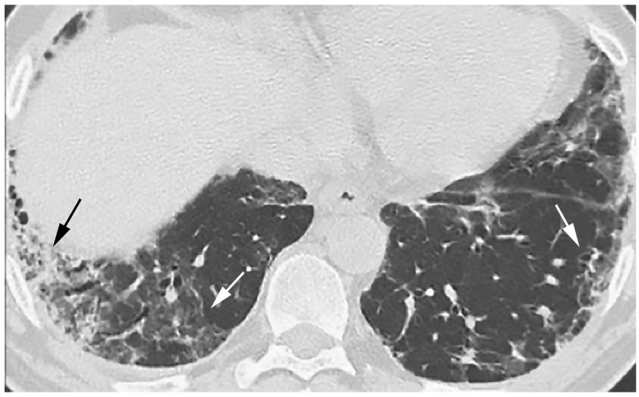

Fig. 7 HRCT of a patient with dermatomyositis shows ground-glass opacity and reticular abnormality in both lower lobes (*white arrows*) compatible with an NSIP pattern. Note that there are additional patchy areas of consolidation (*black arrow*) compatible with OP. HRCT high-resolution computed tomography, NSIP nonspecific interstitial pneumonia, OP organizing pneumonia

Interstitial Pneumonia With Autoimmune Features

Interstitial lung disease can precede the clinical diagnosis of collagen vascular disease in up to 25% of patients, which can go unrecognized for up to 5 years. Recently, an international Taskforce introduced the term "interstitial pneumonia with autoimmune features (IPAF)" to include patients with interstitial lung disease and features suggestive of but not diagnostic of a collagen vascular disease

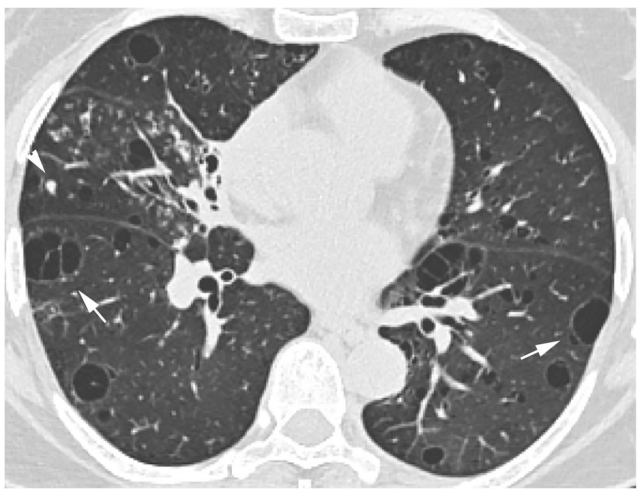

Fig. 8 HRCT of a patient with Sjögren's syndrome shows multiple scattered cysts in both lungs (*white arrows*) and a few additional tiny nodules (*arrowhead*), compatible with an LIP pattern. HRCT high-resolution computed tomography, LIP lymphoid interstitial pneumonia

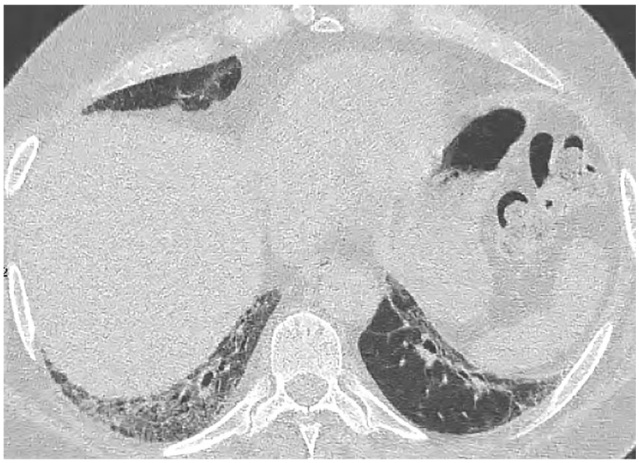

Fig. 9 HRCT of a 67-year-old woman with lower lobe-predominant ground-glass opacity, reticular abnormality, and traction bronchiectasis is compatible with NSIP pattern. The patient initially presented with muscle weakness, which was suspicious for an inflammatory myopathy but had negative serology. Five years after her initial CT, she developed anti-Jo antibodies and was diagnosed with antisynthetase syndrome. HRCT high-resolution computed tomography, NSIP nonspecific interstitial pneumonia

[31•]. IPAF encompasses patients with a diagnosis of interstitial lung disease (on HRCT or surgical lung biopsy) that exhibit a combination of features from three domains: a clinical domain consisting of specific extra-thoracic features, a serologic domain consisting of specific autoantibodies, and a morphologic domain consisting of specific chest imaging, histopathologic, or pulmonary physiologic features. The importance of this new term is highlighted by studies showing improved survival in IPAF patients when compared with their idiopathic interstitial pneumonia counterparts [32, 33]. Some IPAF patients may later meet the diagnostic criteria for a specific collagen vascular disease (Fig. 9). Using this new classification, one series retrospectively reclassified 7% of their patients with idiopathic interstitial pneumonias as IPAF [34].

Cardiovascular Manifestations of Collagen Vascular Diseases

Pulmonary Hypertension

Pulmonary hypertension (PH) is defined as a mean resting pulmonary artery pressure of ≥ 25 mmHg at rest and a pulmonary capillary wedge pressure of ≤ 15 mmHg measured during a right heart catheterization [35, 36]. Pulmonary hypertension is the second most common cause of morbidity and mortality in collagen vascular disease patients, the first being interstitial lung disease (Table 4). Collagen vascular disease patients with combined ILD and Pulmonary Arterial Hypertension (PAH) have a worse prognosis than those with PH alone—47 vs 28% 3-year survival [37].

The exact pathophysiological mechanism of pulmonary hypertension in collagen vascular diseases is not completely understood but is likely related to intrinsic pulmonary arteriopathy with vascular remodeling. The most recent NICE classification for pulmonary hypertension groups it into category 1: Pulmonary Arterial Hypertension (PAH) due to histological similarities with idiopathic PH [38]. It should be recognized that other factors may also contribute to developing pulmonary hypertension in collagen vascular diseases: capillary network destruction in those with interstitial lung disease, thromboembolic disease due to hypercoagulability in SLE patients, and pulmonary venous hypertension secondary to left ventricular dysfunction [36].

PH associated with collagen vascular disease is the second most common cause of PH—idiopathic PH is the first. The former has a worse prognosis: the 1-year mortality for PH associated with collagen vascular disease is 30% while that for idiopathic PH is 15% [39, 40]. In the West (USA, UK, and Germany), scleroderma is the most common collagen vascular disease associated with PH, seen in up to 18% of

Table 4 Cardiovascular manifestations of collagen vascular diseases

Collagen vascular disease	PH	Myocardial enhancement	Pericardial effusion	Other
Rheumatoid arthritis	+	–	–	Aortic aneurysm
Scleroderma	+++	+	+	CAD, GAVE
Systemic lupus erythematosus	++	++	++	Aortic dissection, CAD, PE
Polymyositis/dermatomyositis	+	++	+	
Sjögren's syndrome	–	–	–	

The greater the number of "+" signs, the greater the relative frequency of a particular interstitial lung disease pattern. The sign "–" means no reported association

PH pulmonary hypertension, *CAD* coronary artery disease, *GAVE* gastric antral vascular ectasia, *PE* pulmonary embolism

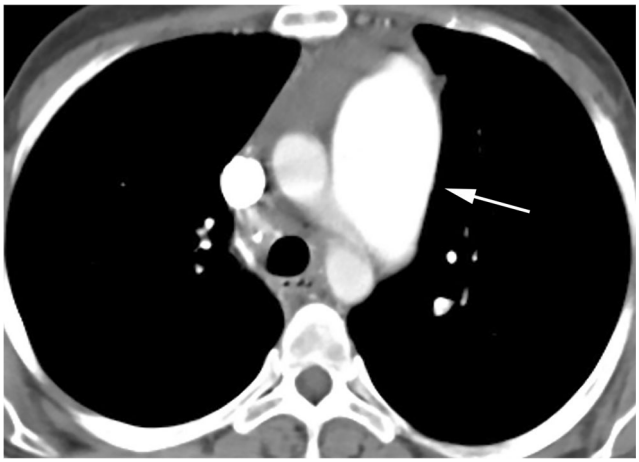

Fig. 10 Contrast-enhanced CT of a scleroderma patient with pulmonary hypertension demonstrates enlarged main pulmonary artery (*arrow*). CT computed tomography

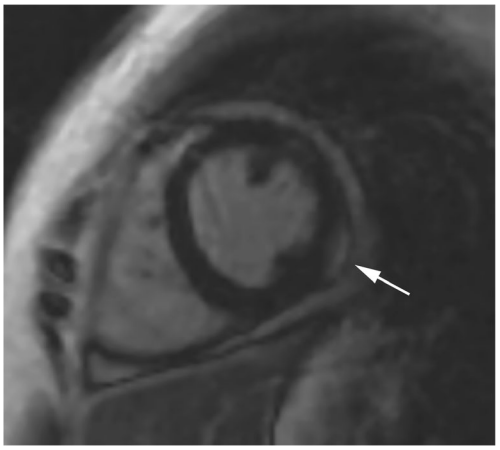

Fig. 12 Contrast-enhanced cardiac MRI of a scleroderma patient shows delayed sub-epicardial hyperenhancement in the inferolateral left ventricle wall (*arrow*). MRI magnetic resonance imaging, SLE systemic lupus erythematosus

cases [23, 41–43]. In the East, SLE is the most common cause of pulmonary hypertension, present in up to 23% of SLE patients [44]. Pulmonary hypertension can also occur in rheumatoid arthritis patients but is typically mild [45]. It is rare for patients with the inflammatory myopathies (PM/DM) and Sjögren's syndrome to develop pulmonary hypertension.

PH in collagen vascular disease is often first diagnosed on annual surveillance echocardiography; however, secondary signs can be apparent on cross-sectional imaging. CT or MR imaging can show a dilated main pulmonary arterial trunk (> 2.9 cm) (Fig. 10) and enlarged main, segmental, and lobar pulmonary arteries. In cases with elevated right heart pressures, the right heart can be enlarged, with a prominent azygous-hemiazygous venous system and reflux of administered intravenous contrast into the inferior vena cava and hepatic veins. Cardiac MR imaging is typically used to follow these patients as it can accurately assess right ventricular size and function, a major prognostic indicator in PH and an independent predictor of mortality [46].

Primary Cardiac Involvement

Scleroderma, SLE, and the inflammatory myopathies (PM/DM) have the highest incidence of cardiac involvement.

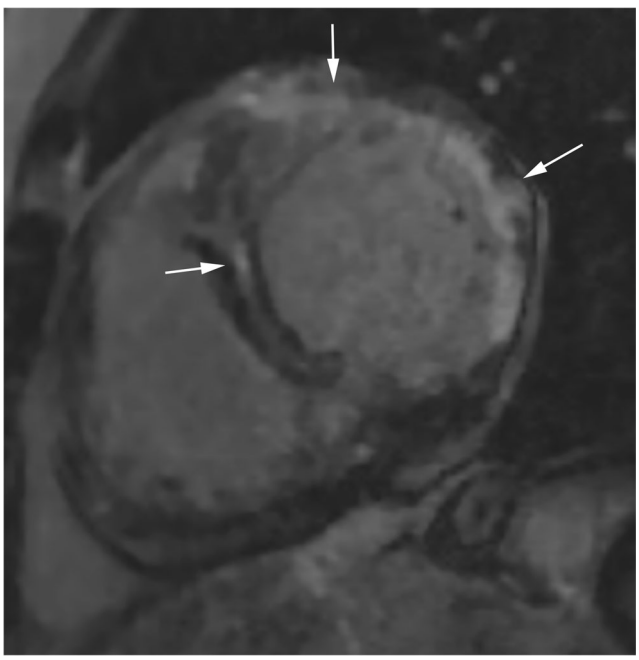

Fig. 11 Contrast-enhanced cardiac MRI of an SLE patient shows patchy areas of delayed hyperenhancement in a nonvascular distribution (*arrows*). MRI magnetic resonance imaging, SLE systemic lupus erythematosus

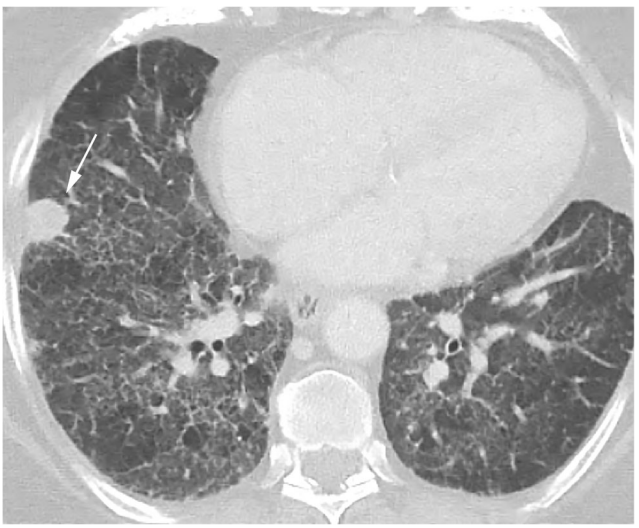

Fig. 13 HRCT of a scleroderma patient with pulmonary fibrosis (extensive reticular abnormality) shows a right middle lobe nodule lung nodule (*arrow*), which was biopsy-proven to represent lung cancer. HRCT high-resolution computed tomography

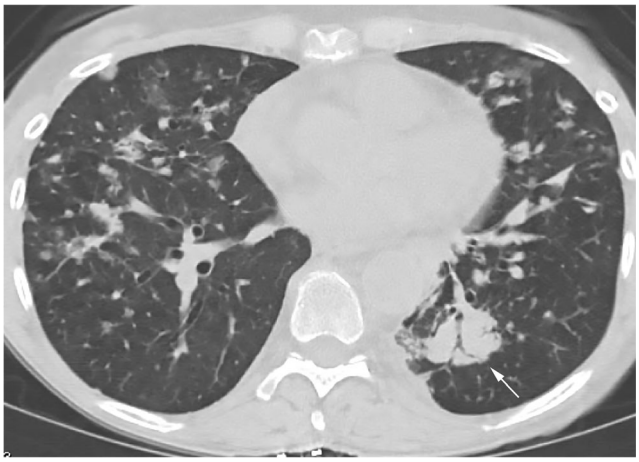

Fig. 14 HRCT of a patient with Sjögren's syndrome shows scattered bilateral pulmonary nodules. There is a dominant mass with internal air bronchogram in the left lower lobe, which was proven to represent diffuse large B cell lymphoma

On contrast-enhanced cardiac MR imaging, these typically manifest as delayed myocardial hyperenhancement in a nonvascular distribution.

Cardiac involvement can be present in 3–15% of SLE patients and usually occurs in combination with pericarditis [47]; these are best seen on contrast-enhanced MR imaging (Fig. 11). SLE patients also have a four to eight times increased risk of developing coronary artery disease and are also more prone to developing aortic dissections and aneurysms [48]. Interestingly, the incidence of pulmonary embolism is also higher in SLE [49]. Coexistent systemic lupus erythematosus and sarcoidosis have been described in multiple reports, but it is unclear if there is an actual causal association or if both result from a common immunopathologic mechanism.

Although scleroderma patients can develop cardiac failure as a result of pulmonary arterial hypertension, intrinsic cardiac abnormalities are also common and can be seen with cardiac MRI as areas of enhancement denoting myocarditis or fibrosis (Fig. 12). Pericarditis can also occur and may manifest as pericardial effusion on imaging [50]. Scleroderma patients also have an increased risk of coronary artery disease [51]. Cardiac involvement is very common in inflammatory myopathies and is a major cause of mortality in these patients—the incidence varies from 6 to 75% [52•, 53]. These patients can also develop cardiac arrhythmias, pericarditis, and myocarditis. Rheumatoid arthritis typically does not have an increased association with myocarditis or pericarditis. However, the risk of aortic aneurysms is increased in these patients [54]. Primary cardiac involvement is rare in Sjögren's syndrome. When present, it is limited to asymptomatic pericardial effusions [55].

Other Thoracic Findings

Mediastinal Lymph Node Enlargement

Mediastinal lymph node enlargement is common to many of collagen vascular diseases and frequently detected on CT or MRI. Scleroderma has the highest association with mediastinal lymphadenopathy, which can be seen in up to 70% of patients, especially if they also have interstitial lung disease [56]. That being said, mediastinal lymphadenopathy can also be secondary to other processes such as aspiration, infection, neoplasm, or sarcoidosis, all of which are common to collagen vascular diseases.

Malignancy

Collagen vascular disease patients are at increased risk of various malignancies. The incidence of malignancy in scleroderma patients is estimated to range from 3.6 to 10.7% [57]. The risk of lung cancer is increased in patients with scleroderma, rheumatoid arthritis, systemic lupus erythematosus, and the inflammatory myopathies (PM/DM); lung cancer is the most frequently reported malignancy in scleroderma patients, accounting for 39% of all cancers [57]. On CT, lung cancer may first appear as a spiculated or lobulated nodule or a single focus of consolidation on a background of lung fibrosis (Fig. 13). Hematologic malignancies (lymphoma and leukemia) have an increased incidence in scleroderma, rheumatoid arthritis, and SLE patients [58]. Sjögren's syndrome patients have an increased risk of developing pulmonary lymphoma. These can appear as nodules or masses, which are frequently larger than 1 cm and can contain internal air bronchograms (Fig. 14) [59].

Conclusion

Collagen vascular diseases are a variety of disorders with the potential to affect any component of the cardiopulmonary system. The exact pattern of cardiopulmonary findings varies with the different disorders, but interstitial lung disease and pulmonary hypertension are common to most and are responsible for the bulk of morbidity and mortality in these patients. HRCT is invaluable in illustrating the interstitial lung disease pattern in these patients, while cardiac MRI can identify cardiac involvement and pulmonary hypertension. The risk of various malignancies is also increased with collagen vascular diseases and should be remembered.

Compliance with Ethical Standards

Conflict of Interest Drs. Hamza Jawad, Sebastian McWilliams, and Sanjeev Bhalla declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Recently published papers of particular interest have been highlighted as:
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