

Lung Disease Related to Collagen Vascular Disease

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Abstract: Collagen vascular disease is one of the most common causes of chronic infiltrative lung disease. Patterns of lung injury from collagen vascular disease include nonspecific interstitial pneumonia (NSIP), usual interstitial pneumonia, organizing pneumonia, bronchiectasis, obliterative bronchiolitis, and pulmonary arterial hypertension. The prevalence of each entity varies according to the specific disease entity. NSIP and pulmonary hypertension are common in scleroderma, whereas usual interstitial pneumonia, bronchiectasis, and obliterative bronchiolitis are commonly found in rheumatoid arthritis. In systemic lupus erythematosus, pleural effusions and pulmonary hemorrhage are the salient features. In polymyositis, a combination of organizing pneumonia and NSIP is characteristic. Sjögren syndrome is characterized by bronchiectasis and lymphoid interstitial pneumonia, often associated with thin-walled cysts. Ankylosing spondylitis is associated with upper lobe fibrosis, and may be complicated by mycetoma.

Key Words: lungs, computed tomography, collagen vascular disease, rheumatoid arthritis, scleroderma

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Involvement of the respiratory system is common in the collagen vascular diseases and results in significant morbidity and mortality. Many of these diseases are characterized by the presence of a specific type of autoantibody, which may greatly assist specific diagnosis (Table 1). Lung injury from collagen vascular disease can affect each portion of the lung, the pleura, alveoli, interstitium, vasculature, lymphatic tissue, and airways both large and small (Table 2). Commonly, more than 1 compartment is involved (Fig. 1). Most of the parenchymal manifestations of collagen vascular disease are similar to those found in idiopathic interstitial pneumonias³ (see the article by Drs Silva and Muller in this issue), and can be classified using the same system.¹ Although there is some overlap, each collagen vascular disease is associated with a characteristic pattern of pulmonary involvement (Table 2). The lung disease associated with collagen vascular disease may precede the clinical presentation of the collagen disease, sometimes by more than 5 years (Fig. 12).

A careful evaluation of the chest radiograph and chest computed tomography (CT) in patients with parenchymal abnormalities can yield some useful clues to the presence of collagen vascular disease. Joint abnormalities (shoulder or acromioclavicular) suggest rheumatoid arthritis (RA). A dilated esophagus should suggest scleroderma or 1 of its variants (Figs. 7, 8). An enlarged pulmonary artery (out of

TABLE 1. Autoantibodies Associated With Specific Collagen Vascular Diseases

Disease	Associated autoantibodies
Rheumatoid arthritis	Rheumatoid factor, anti-CCP
Scleroderma	Anticentromere antibody (limited PSS) Anti-SCL-70 Anti-ribonuclear protein
Mixed connective tissue disease	Anti-Jo-1
Dermatomyositis/ polymyositis	Anti-double-stranded (ds) DNA and anti-Sm
Systemic lupus erythematosus	Anti-nuclear factor (less specific) Anti-phospholipid antibodies
Sjögren syndrome	Anti-SS-A (Ro) Anti-SS-B (La)

proportion to the extent of lung parenchymal abnormality) may be seen in many types of collagen vascular disease, particularly scleroderma. Soft tissue calcifications may be seen in dermatomyositis or scleroderma. Pleural effusions, pericardial abnormality, or esophageal abnormalities are statistically more common in individuals with lung fibrosis related to collagen vascular disease than in those with idiopathic fibrosing interstitial pneumonia.⁴

RA

Most patients with RA have abnormalities on high-resolution chest CT. CT-detected abnormalities are often not associated with symptoms. In unselected patients with RA, the most common findings are bronchial wall thickening (12% to 92%), bronchial dilation (30% to 40%), parenchymal micronodules (15% to 20%), reticular abnormality (10% to 20%), pleural opacity (16%), ground glass opacity (15% to 25%), honeycombing (10%), and consolidation (5%).^{5,6} Pleural effusion may also be identified. Bronchiectasis is usually cylindrical in type, and is commonly, although not always, associated with CT and physiologic evidence of small airways disease.⁷

There is a recognized association between rheumatoid disease and obliterative bronchiolitis (constrictive bronchiolitis)^{8–12} in which bronchioles are destroyed and replaced by scar tissue. The characteristic CT finding is mosaic perfusion (Fig. 1) with expiratory air trapping (Fig. 2)^{13–16} often associated with evidence of mild bronchial dilation. Follicular bronchiolitis is a second type of small airway disorder recognized in rheumatoid lung disease.^{17–21} It is characterized by lymphoid aggregates, with or without germinal centers, lying in the walls of bronchioles and possibly compressing their lumens.²² Follicular bronchiolitis probably produces a reticular or reticulonodular pattern on the chest radiograph.¹⁷ The major CT

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TABLE 2. Pulmonary Complications of Collagen Vascular Diseases^{1,2}

Pattern	RA	SLE	MCTD	Scleroderma	PM/DM	Sjögren Syndrome
UIP pattern	++	+	+	++	+	+
NSIP pattern	+	+	++	++++	++	+
Organizing pneumonia	++	+	+	+	++	
Pulmonary hypertension	+	+	+	++		+
Bronchiectasis	++					++
Obliterative bronchiolitis	++	+				

The frequency of a particular complication is denoted by the number of “+” signs.

“+” indicates that the entity is relatively uncommon, whereas “++++” indicates a frequent clinical association. Empty cells indicate that the entity is not described or rare.

MCTD indicates mixed connective tissue disease; NSIP, nonspecific interstitial pneumonia; PM/DM, polymyositis/dermatomyositis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; UIP, usual interstitial pneumonia.

finding is centrilobular nodules, often associated with peribronchial nodules, and with areas of ground glass abnormality.^{19,22}

Airways disease seems to be the earliest manifestation of RA in the lung. In a study of 34 patients with early RA (duration < 1 y), CT showed expiratory air trapping in 69%, bronchiectasis in 58%, and ground glass opacity in 35%.²³ An interesting recent study²⁴ evaluated CT findings in 14 asymptomatic first-degree relatives of individuals with known RA. Six of the 7 individuals who had positive RA-related antibodies (anti-cyclic citrullinated peptide) had expiratory air trapping, compared with none of the 7 antibody-negative subjects. This intriguing finding suggests that the airways or the lung may be involved very early in

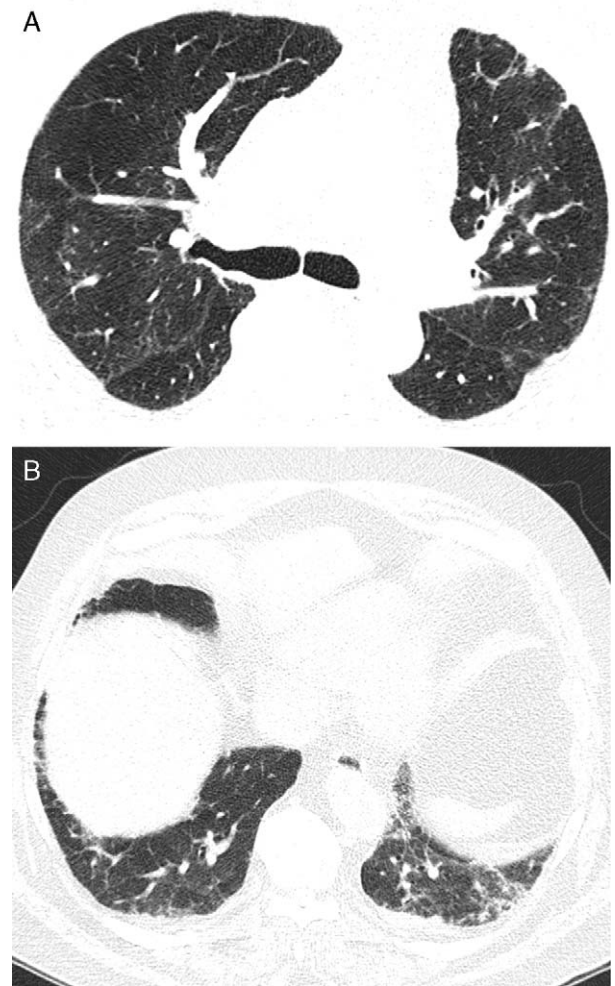


FIGURE 1. Obliterative bronchiolitis and lung fibrosis in a patient with RA. A, CT through the midlungs shows mosaic attenuation indicating obliterative bronchiolitis. B, CT through the lower lungs shows basal ground glass and reticular abnormality suggesting lung fibrosis.

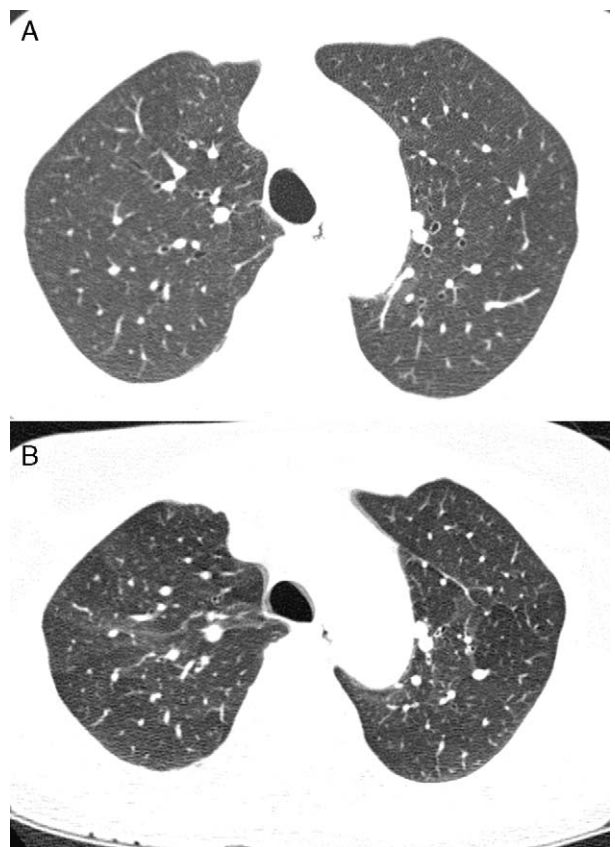


FIGURE 2. Obliterative bronchiolitis in RA. A, Inspiratory CT shows minimal mosaic attenuation. B, Expiratory CT shows moderate multilobular air trapping.

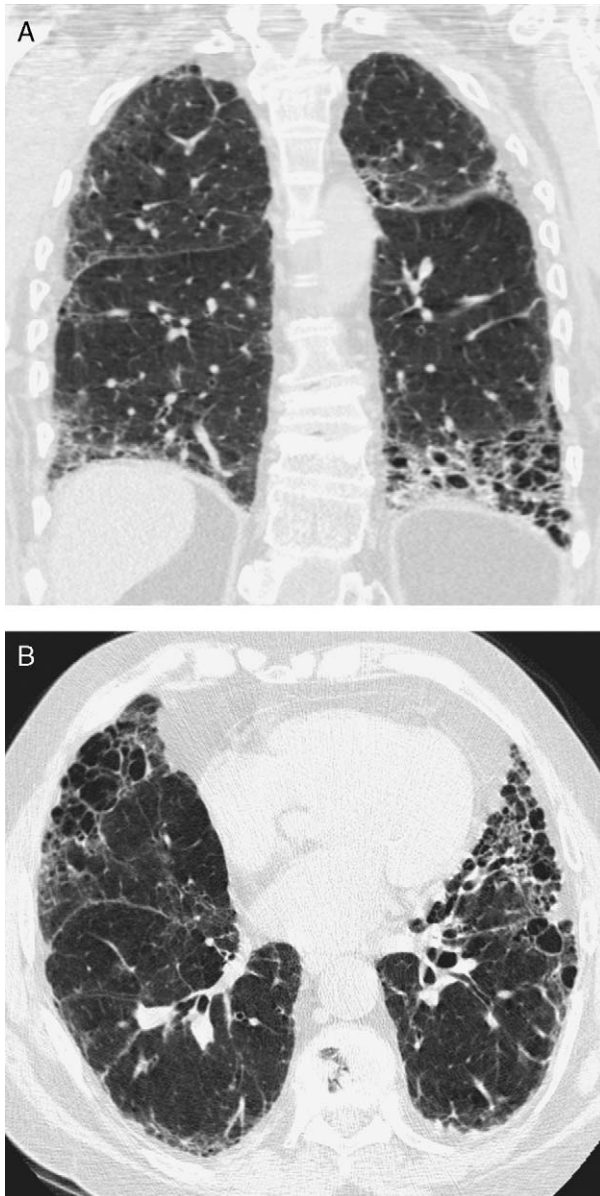


FIGURE 3. UIP in RA. A and B, Coronal and axial CT images show typical pattern of basal predominant, peripheral predominant reticular abnormality, and honeycombing.

the evolution of RA. The relatively high prevalence of air trapping in individuals with RA emphasizes the importance of obtaining expiratory images in patients with RA, as inspiratory CT is often normal or near-normal in patients with obliterative bronchiolitis (Fig. 2).

Rheumatoid lung fibrosis is substantially more common in men than in women.^{25,26} The 2 most common patterns of lung fibrosis in RA are usual interstitial pneumonia (UIP) (Fig. 3) and nonspecific interstitial pneumonia (NSIP).^{27,28} organizing pneumonia (OP) may also be seen.^{17,18,29-31} A few cases of desquamative interstitial pneumonia have been described.^{18,26} CT findings in interstitial pneumonia associated with RA are similar to those of the idiopathic variety.³²⁻³⁴ However, associated



FIGURE 4. Methotrexate toxicity in a patient with RA. CT shows patchy basal ground glass and reticular abnormality.

nodules, mosaic attenuation, pulmonary arterial enlargement, and pleural abnormality may provide a clue to the underlying diagnosis (Fig. 1). In a study of 63 patients with rheumatoid lung disease,²⁸ 26 had a CT pattern suggestive of UIP, 19 had a pattern of NSIP, 11 had a bronchiolitis pattern, and 5 had an OP pattern. These CT patterns were in agreement with the histology in 13 of the 17 who underwent biopsy.

Necrobiotic nodules, similar to subcutaneous rheumatoid nodules, may uncommonly occur in the lung. They are usually round, well defined, and may cavitate. The entity of Caplan syndrome (multiple, large-rounded nodules seen on the chest radiographs of coal miners with RA) now seems to be very rare, with only 1 published case report since 1965.^{35,36}

Pulmonary hypertension commonly occurs in patients with RA, but is usually mild.³⁷ Other complications of RA include lymphoma, and lung cancer.³⁸ Many of the available treatments for RA, including gold, methotrexate, and D-penicillamine have been implicated in the development of infiltrative lung disease. Low-dose methotrexate may be associated with subacute hypersensitivity pneumo-

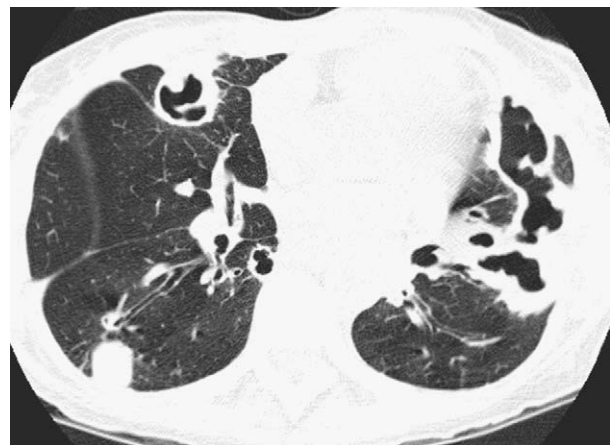


FIGURE 5. Mycobacterial infection (*Mycobacterium avium* complex) in a patient with RA treated with infliximab. CT shows large irregular cavities and 2 noncavitary nodules.

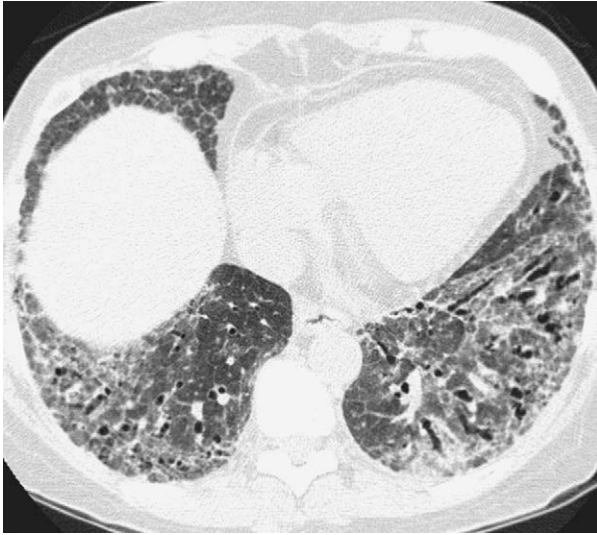


FIGURE 6. NSIP pattern in scleroderma. CT through the lower lungs shows basal predominant ground glass abnormality with fine reticular abnormality and marked traction bronchiectasis indicating fibrosis.

nitis in 2% to 5% of cases (Fig. 4).^{39,40} Preexisting radiographic evidence of interstitial lung disease (ILD) probably predisposes to the development of methotrexate pneumonitis in patients with RA.⁴¹

The new generation of biologic agents used to treat RA has resulted in a new array of potential pulmonary side effects. The most important of these is impaired immunity related to the use of anti-tumor necrosis factor- α antibodies (etanercept, infliximab, and adalimumab), which results in a substantially increased incidence of tuberculosis (sometimes disseminated or extra-articular) and nontuberculous mycobacterial infection (Fig. 5).⁴² Fungal and pneumocystis infection may also occur. Screening chest radiographs are usually obtained when anti-tumor necrosis factor- α antibody treatment is planned. Mycobacterial or fungal infection should be strongly suspected when new parenchymal abnormalities are identified in these patients.

SCLERODERMA (PROGRESSIVE SYSTEMIC SCLEROSIS)

Parenchymal lung involvement is very common in patients with scleroderma. At autopsy, the lungs are abnormal in at least 80% of cases.⁴³ Lung fibrosis is the most common pattern of abnormality, with NSIP being much more common than UIP.^{44,45} However, pulmonary hypertension is also common, either as an isolated finding or in association with lung fibrosis. Pulmonary hypertension is particularly common in patients with limited scleroderma (CREST syndrome).⁴⁶ Esophageal dilation is found in up to 80% of cases on CT.⁴⁷

CT findings in scleroderma reflect the dominant NSIP histology, and are characterized by confluent ground glass opacification and fine reticular pattern, often posterior and subpleural, usually associated with traction bronchiectasis and bronchiolectasis (Fig. 6).^{48,49} Honeycombing, when present, is usually mild.⁵⁰ However, patients with honeycombing on initial CT are probably more likely to progress

on serial evaluation (Fig. 7).⁴⁹ The lung fibrosis associated with scleroderma is associated with a much better prognosis than that found in idiopathic lung fibrosis,^{51–53} most likely due, in part, to the predominant NSIP histology. In a large treatment study, the extent of lung fibrosis identified on baseline CT was an important independent predictor of physiologic progression, and of response to treatment.⁵⁴

Pulmonary arterial hypertension usually causes enlargement of the main and proximal pulmonary arteries on chest radiograph or CT (Fig. 8A); however, normal-sized pulmonary arteries do not exclude the diagnosis, and the presence of pericardial thickening or fluid in patients with scleroderma is also a strong predictor of echocardiographic pulmonary hypertension (Fig. 8B).⁵⁵ There is an increased prevalence of lung cancer in scleroderma, with relative risk of malignancy ranging from 1.8 to 6.5.^{56,57} Lung cancer in this condition often occurs in individuals with lung fibrosis (Fig. 9).

SYSTEMIC LUPUS ERYTHEMATOSUS

Pleuritis is the most common pleuropulmonary manifestation of lupus, found in 40% to 60% of patients

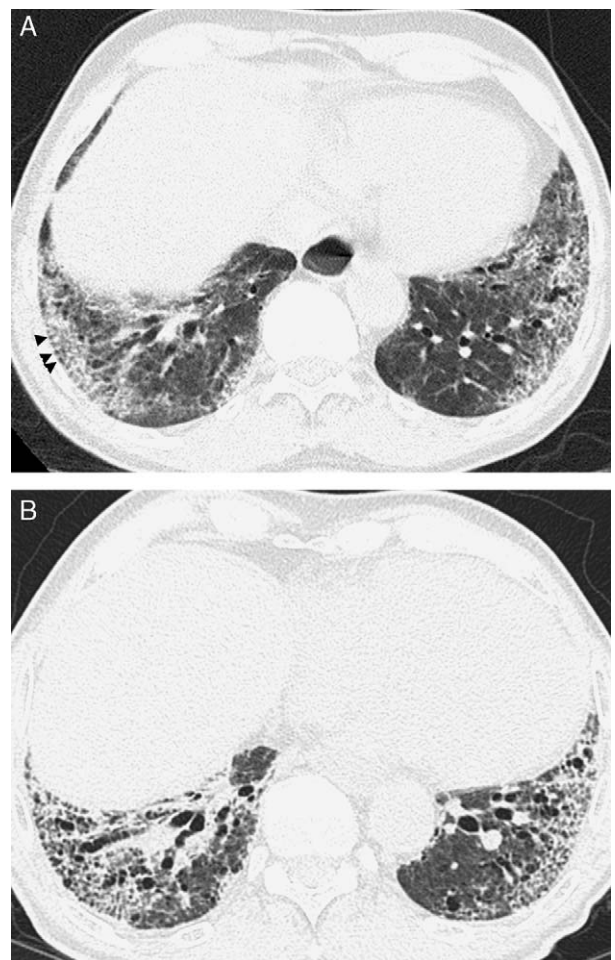


FIGURE 7. Progressive lung fibrosis in scleroderma. A, Initial CT shows moderate basal reticular abnormality with fine subpleural honeycombing (arrowheads). The esophagus is moderately dilated. B, CT 7 months later shows marked progression of fibrosis, traction bronchiectasis, and honeycombing.

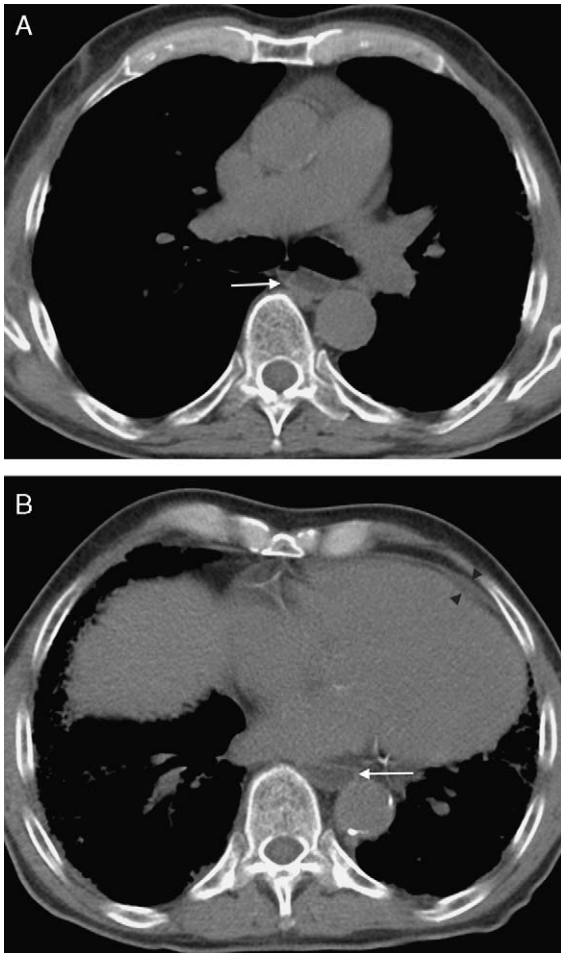


FIGURE 8. Pulmonary hypertension in scleroderma. A, CT shows marked dilation of main pulmonary artery, measuring 3.5 cm. B, CT at a lower level shows cardiomegaly, with prominence of the right ventricle, and a small amount of pericardial fluid or thickening (arrowheads). Note the dilated, fluid-filled esophagus on both images (arrows).



FIGURE 9. Lung cancer in a patient with lung fibrosis related to scleroderma. CT shows a 4-cm mass in the fibrotic left lower lobe.

with systemic lupus erythematosus (SLE),⁵⁸⁻⁶⁰ and may or may not be associated with pleural effusion. Although pulmonary infection is said to be the most common pulmonary complication of lupus,⁶¹ acute pulmonary hemorrhage is also an important pulmonary complication of this condition,⁶² characterized radiologically by diffuse or patchy consolidation and ground glass abnormality (Fig. 10). Acute lupus pneumonitis is a poorly defined entity, characterized by a variable degree of respiratory impairment accompanied by focal or diffuse pulmonary consolidation, occurring in patients with lupus.⁶² It is now believed that most cases previously identified as lupus pneumonitis probably represented acute interstitial pneumonia with or without pulmonary hemorrhage.⁶³

Fibrotic ILD is less common in SLE than in the other collagen vascular diseases.⁶⁴ UIP or NSIP may occur. CT abnormalities in SLE are often relatively mild and nonspecific, with linear thickened interlobular septa and parenchymal bands being most common.^{65,66} Other complications of lupus may include diaphragmatic dysfunction

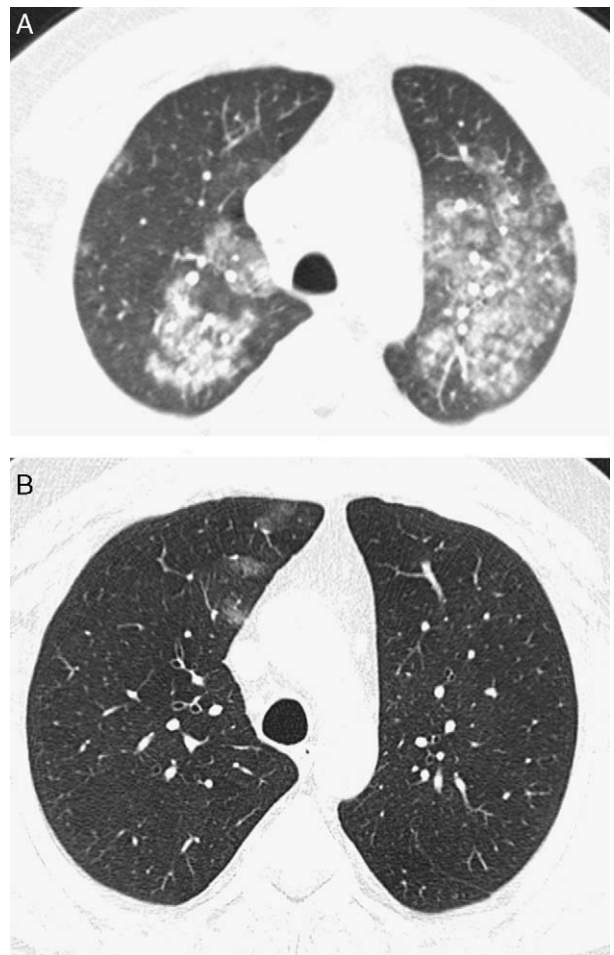


FIGURE 10. Recurrent pulmonary hemorrhage in a patient with systemic lupus erythematosus. A, CT shows bilateral upper lobe consolidation with "acinar" centrilobular nodularity, on account of pulmonary hemorrhage. B, CT 1 year later shows patchy ground glass abnormality, indicating recurrent hemorrhage.

(Fig. 11),⁶⁷ pulmonary hypertension,⁶⁸ and pulmonary thromboembolism, which may be related to antiphospholipid antibodies.⁶³ Diaphragmatic dysfunction, thought to be due to a diaphragmatic myopathy, is manifested by reduced lung volumes (“shrinking lungs”) (Fig. 11).

POLYMYOSITIS/DERMATOMYOSITIS

The presence of ILD in polymyositis/dermatomyositis (PM/DM) correlates strongly with the presence of anti-Jo-1.^{69,70} About 50% to 70% of patients who are anti-Jo-1 positive have ILD⁷¹ whereas the frequency of ILD falls to about 10% if antibodies are absent. ILD may antedate myositis in patients with anti-Jo-1 antibodies.⁷² The most common pathologic findings are NSIP^{73–76} and OP,^{77–79}

often occurring in combination. As with other collagen vascular disease, the occurrence of interstitial pneumonia may precede the development of clinical myositis (Fig. 12). Lung disease associated with PM/DM or with the antisynthetase syndrome, a closely related entity, is often associated with a characteristic CT appearance, characterized by confluent ground glass opacity and consolidation in the lower lobes, superimposed on a background of reticular abnormality with traction bronchiectasis (Fig. 13).^{77,80,81} This pattern reflects the characteristic histologic combination of organizing pneumonia and fibrotic NSIP.^{77,81} On serial evaluation, the changes of consolidation, ground glass abnormality, reticular abnormality, and traction bronchiectasis may all be partially reversible with treatment.^{76,77,80} Consolidation may also progress to reticular abnormality (Fig. 12).

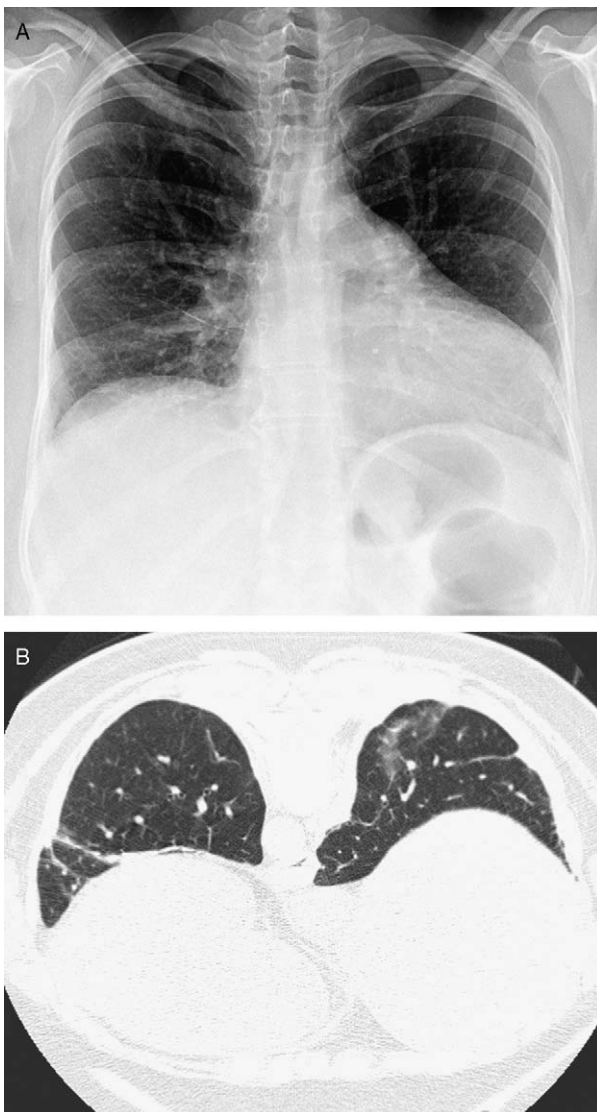


FIGURE 11. Shrinking lungs in a patient with lupus erythematosus. A, Chest radiograph shows markedly reduced lung volumes. The heart is moderately enlarged. B, Prone CT image shows band-like basal opacity that may represent atelectasis.

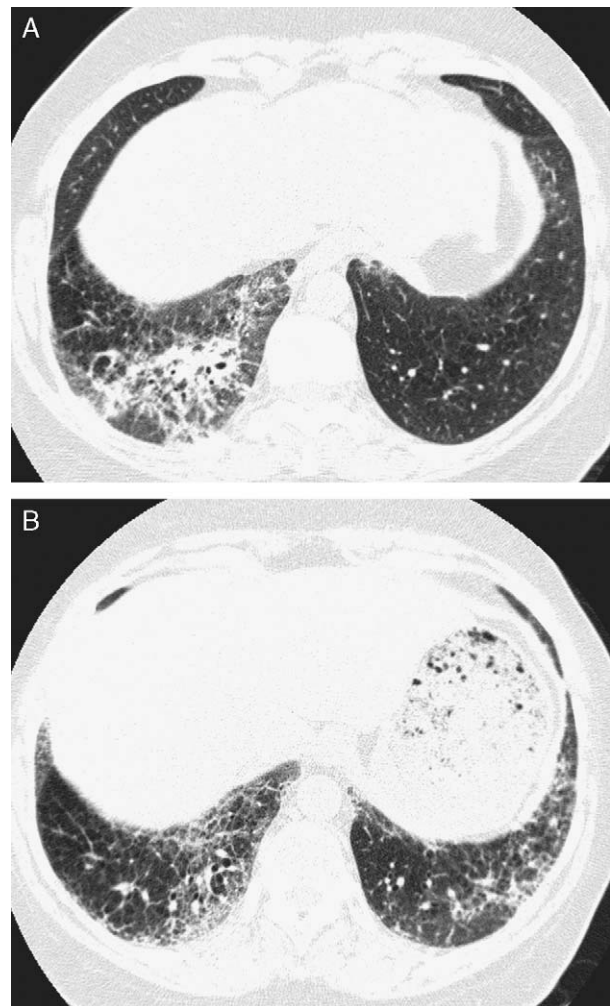


FIGURE 12. OP and NSIP in a patient who subsequently developed polymyositis. A, Initial CT shows focal consolidation and ground glass abnormality in the right lower lobe with mild bronchial dilation, compatible with OP. B, CT obtained 1 year later shows bibasal reticular abnormality with traction bronchiectasis, compatible with NSIP. One year later, the patient developed clinical polymyositis.

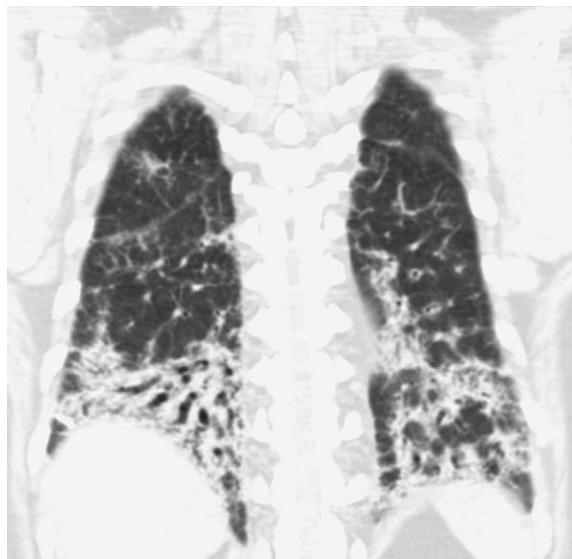


FIGURE 13. Typical findings in lung disease related to polymyositis. Coronal reconstruction from CT shows confluent basal predominant consolidation associated with marked traction bronchiectasis. This combination of findings is quite highly suggestive of polymyositis.

SJÖGREN SYNDROME

CT provides substantial information regarding the pattern of pulmonary involvement by Sjögren syndrome.⁸² The patterns may be divided into airway abnormality, interstitial fibrosis, pulmonary hypertension, and patterns suggestive of lymphoid interstitial pneumonia (LIP).⁸² In a study by Franquet et al,⁸³ of 50 consecutive patients with primary Sjögren syndrome, 17 of 50 patients (34%) had CT abnormalities. Overall, changes were the most common in the lower zones. Airway-related abnormalities were common (11 of 17) and consisted of bronchial wall thickening, bronchiectasis (Fig. 14), bronchiolectasis, tree in bud pattern, and air-trapping. Septal or nonseptal lines occurred in a similar number of individuals (11 of 17). Other findings included patchy ground glass opacity (7 of 17), nodules (5 of 17), honeycombing (4 of 17), and consolidation (1 of 17). Nodules more than 10 mm in diameter were caused by lymphoma. Although cysts were not described in this series, cystic abnormality is common in other series.⁸⁴ Small airway disease was manifest by a mosaic attenuation pattern and expiratory air trapping.^{83,85}

LIP occurring in Sjögren syndrome is characterized by ground glass abnormality on account of the homogenous lymphocytic infiltration.⁸⁶ Peribronchovascular, centrilobular, and subpleural nodules may also be seen, and cysts measuring 5 to 30 mm are often present (Fig. 14).⁸⁴ Similar cysts may be found in follicular bronchiolitis.⁸⁵ These changes are ascribed to bronchiolar obstruction on the basis of lymphocytic wall infiltration. Cysts are helpful in distinguishing LIP from lymphoma.⁸⁷ Lymphoma should be suspected if consolidation, large nodules (> 1 cm) or effusions are present.⁸⁷ However, similar large “pseudoalveolar” poorly defined nodules were found in 4 patients with combined amyloidosis and LIP.⁸⁸ In contrast to other

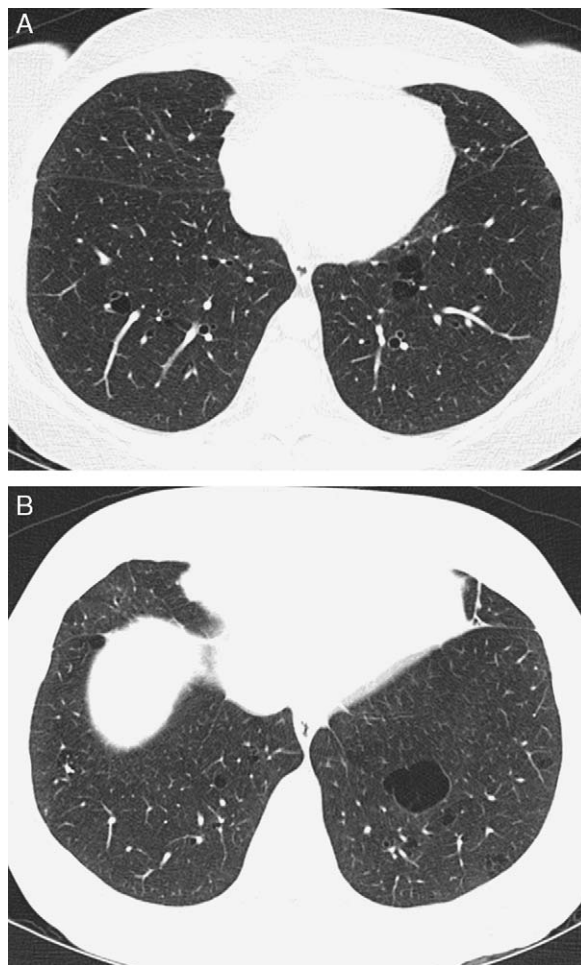


FIGURE 14. Cysts and bronchiectasis in a patient with Sjögren syndrome. A and B, CT through the lower lungs shows mild cylindrical bronchiectasis, and multiple thin-walled peribronchovascular cysts. The cystic abnormality is strongly suggestive of LIP.

cystic lung diseases, such as lymphangioleiomyomatosis, the cysts of LIP show peribronchovascular and lower lung predominance (Fig. 14).

MIXED CONNECTIVE TISSUE DISEASE

Mixed connective tissue disease (MCTD) is an overlap syndrome that is a distinct clinicopathological entity.⁸⁹ The principal characteristics are the presence of (1) features of SLE, scleroderma, PM/DM, occurring together or evolving sequentially during observation; and (2) antibodies to an extractable nuclear antigen (RNP).⁸⁹

Pulmonary involvement is common in MCTD. A study of 144 unselected patients found CT evidence of infiltrative lung disease in 67%.⁹⁰ Many affected patients are asymptomatic.⁹¹ The pulmonary abnormalities resemble those seen in SLE, SS, and PM/DM.⁶¹ Thus, pleural thickening and pleural and pericardial effusions are common.⁹¹ Ground glass attenuation is the most common parenchymal abnormality.^{90,92} The CT pattern corresponds most closely to NSIP (Fig. 15). Less common findings



FIGURE 15. NSIP and bronchiectasis in a patient with mixed connective tissue disease. Coronal CT reconstruction shows basal predominant ground glass abnormality. Focal bronchiectasis is present in the superior segment of left lower lobe.

include honeycombing, consolidation, and poorly defined centrilobular nodules.

Other important complications of MCTD include pulmonary arterial hypertension⁹³⁻⁹⁵ and esophageal dysmotility.⁹⁴

ANKYLOSING SPONDYLITIS

Pleuropulmonary involvement is a rare complication of ankylosing spondylitis, found in 1.3% of 2080 patients in 1 series.⁹⁶ It almost always involves males, with long duration of disease.⁹⁷ The radiologic changes⁹⁶ consist of nodular and linear opacity and/or pleural thickening that begin in the lung apices. The apical opacities progress slowly with increasing apical nodularity and pleural thickening, elevation of the hila, and the development of multiple thin-walled or thick-walled cysts or cavities (Fig. 16).^{96,98,99} These apical changes usually progress slowly,⁹⁹ but they can remain stable for many years. Pleural calcification may occur. The cavities that develop within the fibrotic lung may be colonized by a variety of fungi and nontuberculous mycobacteria,^{61,96} most commonly mycetomas containing *Aspergillus fumigatus* (Fig. 17).^{99,100} Colonization rates with *Aspergillus* have varied between 19%⁹⁶ and 50% to 60%.^{99,101} Hemoptysis is common in patients with mycetoma, and may be life-threatening.

SUMMARY

In evaluating an individual with suspected or known collagen vascular disease, the radiologist should be aware that specific patterns of lung injury tend to track with

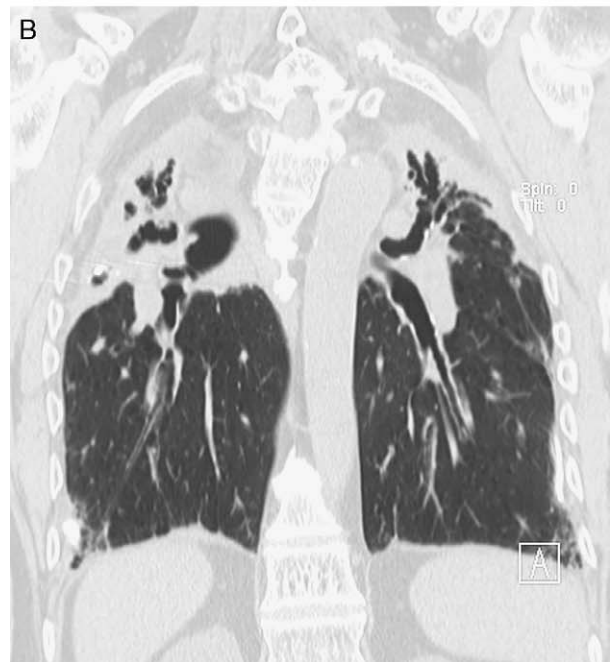


FIGURE 16. Upper lobe fibrosis in ankylosing spondylitis. Chest radiograph (A) and coronal chest CT reconstruction (B) show marked bilateral upper lobe volume loss with dense fibrotic consolidation, and associated air bronchograms. There is dense apical pleural thickening and multifocal pleural calcification. The cystic appearing abnormality seen at the right apex on the chest radiograph represents a dilated, distorted upper esophagus, probably because of the upper lobe fibrosis.

specific disease entities. A systematic approach, evaluating each compartment of the lung (airway, interstitium, pleura, pulmonary vasculature) may be helpful. Complications of treatment, including infection, should be specifically considered, particularly in rheumatoid arthritis.

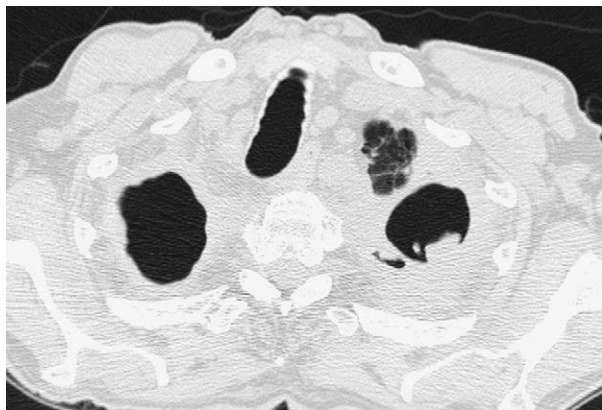


FIGURE 17. Mycetoma in ankylosing spondylitis. CT shows bilateral upper lobe cavities, with a filling defect in the left upper lobe cavity.

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