RadioGraphics

Interstitial Lung Diseases Associated with Collagen Vascular Diseases: Radiologic and Histopathologic Findings[1]

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ONLINE-ONLY CME

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LEARNING OBJECTIVES

After reading this article and taking the test, the reader will be able to:

- Describe the radiologic features of various interstitial lung diseases in patients with diverse collagen vascular diseases.
- Describe the histopathologic features of interstitial lung diseases in patients with collagen vascular disease.
- Correlate the radiologic findings with the histopathologic findings.

Collagen vascular diseases that demonstrate features of interstitial lung disease include systemic lupus erythematosus, rheumatoid arthritis, progressive systemic sclerosis, dermatomyositis and polymyositis, ankylosing spondylitis, Sjögren syndrome, and mixed connective tissue disease. At histopathologic analysis, interstitial lung diseases associated with collagen vascular diseases are diverse and include nonspecific interstitial pneumonia, usual interstitial pneumonia, bronchiolitis obliterans organizing pneumonia (BOOP), apical fibrosis, diffuse alveolar damage, and lymphocytic interstitial pneumonia. Although proportions of interstitial pneumonias vary, nonspecific interstitial pneumonia accounts for a large proportion, especially in progressive systemic sclerosis, dermatomyositis and polymyositis, and mixed connective tissue disease. The more favorable prognosis in interstitial pneumonia associated with collagen vascular diseases than in idiopathic interstitial pneumonias may be explained by the larger proportion of nonspecific interstitial pneumonia than of usual interstitial pneumonia. High-resolution computed tomography seems to help characterize and determine the extent of interstitial lung disease in collagen vascular diseases.

Abbreviations: BOOP = bronchiolitis obliterans organizing pneumonia, H-E = hematoxylin-eosin

Index terms: Collagen vascular disease, 9∗.61,[2] 9∗.612, 9∗.613, 9∗.614, 9∗.8225, 9∗.8226 • Lung, CT, 60.12118 • Lung, interstitial disease, 60.213, 60.917 • Lung, radiography, 60.11

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[2]9∗ indicates vascular system, location unspecified.

Table 1
Frequency of Pulmonary Disease Involvement in Various Collagen Vascular Diseases

Pulmonary Disease	Systemic Lupus Erythematosus	Rheumatoid Arthritis	Progressive Systemic Sclerosis	Polymyositis or Dermatomyositis	Sjögren Syndrome	Mixed Connective Tissue Disease
Usual interstitial pneumonia	+	++	++	++	+	++
Nonspecific interstitial pneumonia	+	+	++++	++++	+	+++
Diffuse alveolar damage	++	+	+	+	. . .	. . .
BOOP	+	. . .	+	++	+	. . .
Lymphocytic interstitial pneumonia	. . .	. . .	. . .	. . .	+++	+
Hemorrhage	+++	. . .	. . .	. . .	. . .	. . .
Airway disease	. . .	++	. . .	. . .	++	. . .

Note.—Plus signs (+) indicate relative frequency of pulmonary disease involvement (+ = lowest frequency, ++++ = highest frequency). Empty cells (. . .) indicate no pulmonary disease involvement.

Introduction

The collagen vascular diseases constitute a group of autoimmune disorders whose common denominator is damage to components of connective tissue at a variety of sites in the body. Collagen vascular diseases that show features of interstitial lung disease include systemic lupus erythematosus, rheumatoid arthritis, progressive systemic sclerosis, polymyositis and dermatomyositis, Sjögren syndrome, mixed connective tissue disease, and ankylosing spondylitis. At histopathologic examination, interstitial lung diseases associated with collagen vascular disease are diverse and include usual interstitial pneumonia, nonspecific interstitial pneumonia, bronchiolitis obliterans organizing pneumonia (BOOP, also called cryptogenic organizing pneumonia), diffuse alveolar damage, lymphocytic interstitial pneumonia, and apical fibrosis (1–14) (Table 1). The histopathologic and radiologic findings of interstitial lung diseases associated with collagen vascular diseases (15) are identical to those of their idiopathic counterparts (16) (Table 2). However, some histopathologic findings, although not specific, are suggestive of interstitial pneumonia in association with collagen vascular disease. These findings are lymphoid hyperplasia (follicular hyperplasia) and prominent plasma cell infiltration in interstitial inflammation (16).

High-resolution computed tomography (CT) has proved to be more sensitive than chest radiography and conventional CT in the detection and characterization of various histopathologically confirmed interstitial lung diseases in patients with collagen vascular diseases (17). There is evidence that the pattern of abnormality at high-resolution CT reflects the relative proportions of fibrosis and inflammation. A reticular pattern with traction bronchiectasis at CT is associated with a predominantly fibrotic process, whereas ground-glass attenuation without a reticular pattern or traction bronchiectasis is associated with an inflammatory process (18). In this article, we show imaging findings of various interstitial lung diseases in association with diverse collagen vascular diseases and correlate these findings with histopathologic results.

Systemic Lupus Erythematosus

Systemic lupus erythematosus is characterized immunologically by the presence of autoantibodies against various nuclear antigens. It is most

Table 2
Most Common Histopathologic and Radiologic Findings in Idiopathic Interstitial Pneumonias

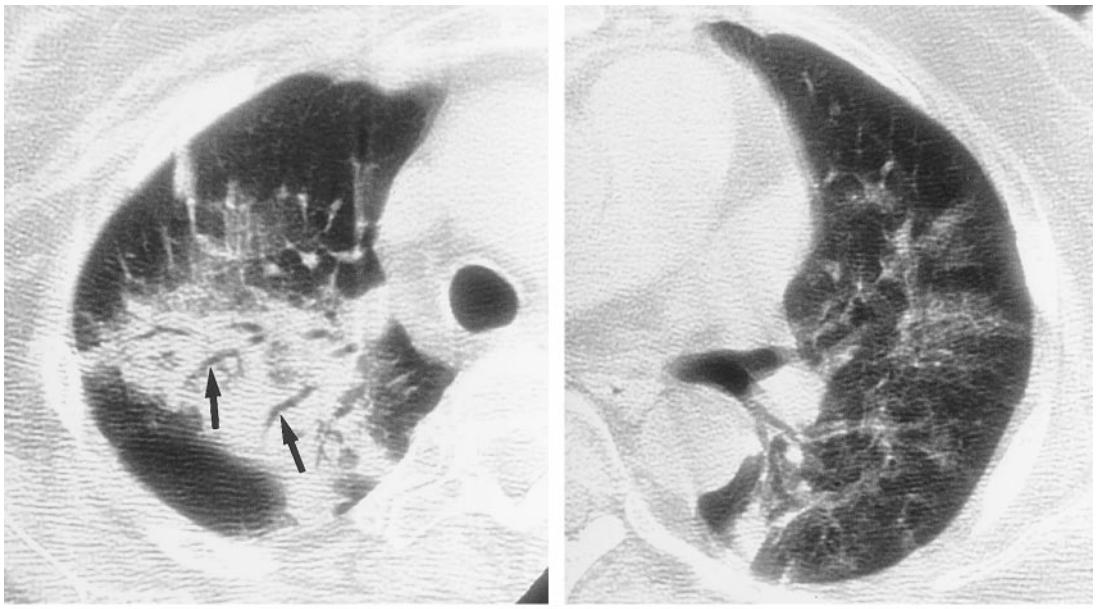
		Radiologic Findings		
Histologic Pattern	Histopathologic Findings	Common Radiographic Findings	Distribution at CT	Usual CT Findings
Usual interstitial pneumonia	Architectural destruction, fibrosis with honeycombing, fibroblastic foci; alternating areas of normal lung tissue, inflammation, fibrosis, and honeycombing (temporally heterogeneous)	Reticular abnormality with volume loss, basal	Peripheral, subpleural, basal	Irregular linear hyperattenuating areas, honeycombing, traction bronchiectasis or bronchiolectasis, architectural distortion, focal ground-glass attenuation
Nonspecific interstitial pneumonia	Varying proportion of interstitial inflammation and fibrosis, divided into cellular (inflammation) and fibrosing (fibrosis) patterns; patchy with intervening normal lung tissue; temporally uniform	Ground-glass and reticular opacity, basal	Peripheral, subpleural, basal, symmetric	Ground-glass attenuation, irregular linear hyperattenuating areas, consolidation
BOOP	Intraluminal organizing fibrosis in distal airspaces, patchy, preservation of lung architecture, temporally uniform, mild chronic interstitial inflammation	Patchy bilateral consolidation	Subpleural, peribronchovascular	Patchy consolidation or nodules
Diffuse alveolar damage	Alveolar edema, hyaline membrane, fibroblastic proliferation with little mature collagen; diffuse; temporally uniform	Progressive diffuse ground-glass appearance or consolidation	Diffuse	Consolidation, ground-glass attenuation, often with lobular sparing; traction bronchiectasis in later stages
Lymphocytic interstitial pneumonia	Infiltration of T lymphocytes, plasma cells, and macrophages; lymphoid hyperplasia; diffuse; predominantly septal	Reticular areas of increased opacity, nodules	Diffuse	Centrilobular nodules, ground-glass attenuation, septal and bronchovascular thickening, thin-walled cysts

common in young women. Pleuropulmonary involvement occurs in approximately 50%–60% of patients. Most such involvement consists of pleural disease (19). In one prospective study that included 1,000 patients, lung involvement was identified in only 3% at the onset of the disease; it developed in an additional 7% over the period of observation (20).

Pulmonary manifestations of systemic lupus erythematosus comprise both acute and chronic lesions. Acute disease includes pulmonary hemorrhage, acute lupus pneumonitis, and pulmonary edema. Chronic disease, such as interstitial pneumonitis and fibrosis, is less common than in other connective tissue disorders (17).

Histopathologic Characteristics

Acute lupus pneumonitis occurs in 1%–4% of patients (1,19). Histopathologic findings include alveolar wall damage and necrosis that lead to inflammatory cell infiltration, hemorrhage, edema, and hyaline membrane formation (Fig 1). Large vessel vasculitis has rarely been detected. Thrombi in small vessels, associated with an interstitial pneumonitis, have been well documented, although this finding is an unusual feature of acute lupus pneumonitis. The pathogenesis of these histologic changes remains controversial (17).



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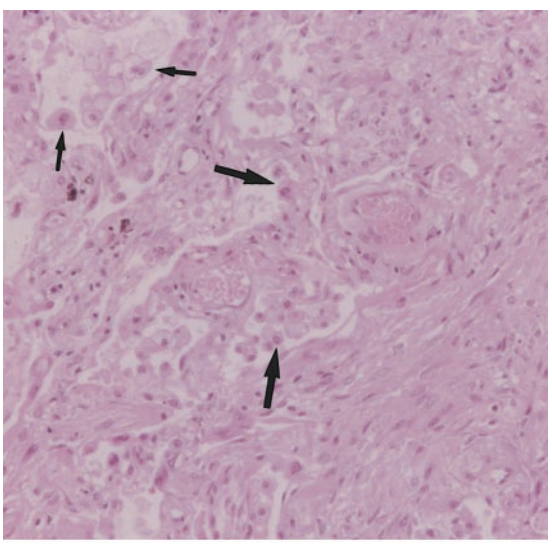

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Figure 1. Systemic lupus erythematosus and acute lupus pneumonitis in a 45-year-old man. **(a, b)** CT scans (3-mm collimation) obtained with lung windowing at the levels of the aortic arch **(a)** and lingular segmental bronchus **(b)** show airspace consolidation in the right upper lobe and ground-glass attenuation in the left upper lobe. Bronchial dilatation is seen in the consolidation in the right upper lobe (arrows in **a**). **(c)** Photomicrograph (original magnification, ×40; hematoxylin-eosin [H-E] stain) shows prominent interstitial fibroblastic proliferation and alveolar type 2 pneumocyte hyperplasia (large arrows) that cause alveolar collapse. There is also intraalveolar macrophage collection (small arrows). These findings are compatible with the organizing stage of diffuse alveolar damage.

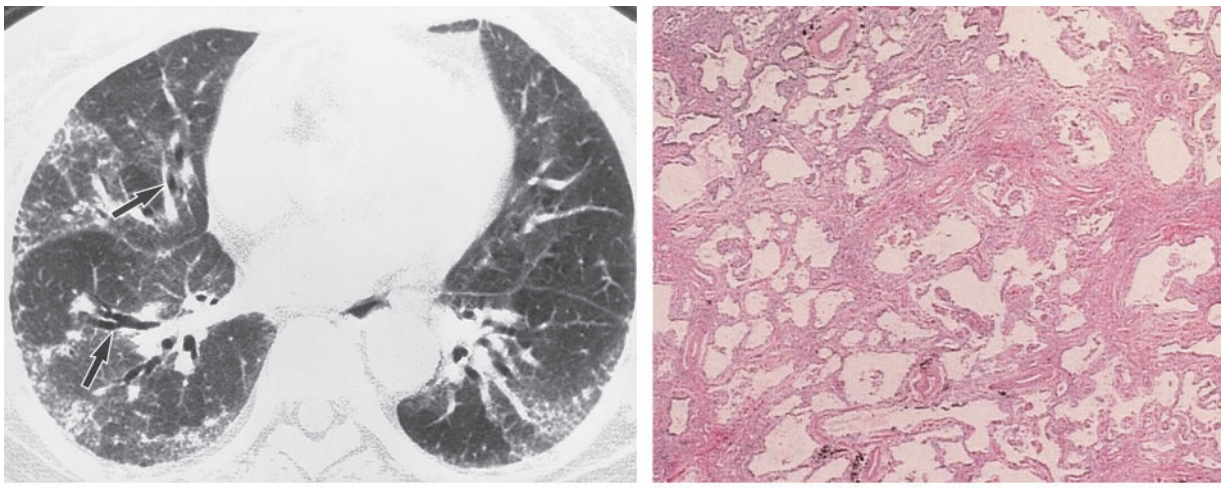
Diffuse interstitial pneumonitis and fibrosis are uncommon; in one series of 120 patients, only five (4%) had findings of interstitial lung disease (1). Histopathologic findings in such cases are those of usual interstitial pneumonia or nonspecific interstitial pneumonia (Fig 2) (2). A few cases of BOOP have been reported.

Radiologic Manifestations

Ground-glass attenuation and consolidation at high-resolution CT may reflect the presence of interstitial pneumonitis and fibrosis, acute lupus pneumonitis, hemorrhage, or, occasionally, BOOP (Figs 1–4). Radiographic evidence of interstitial fibrosis, consisting of a reticular pattern that involves mainly the lower lung zones, is seen in only about 3% of patients who have systemic lupus erythematosus. By contrast, interstitial abnormalities are seen in approximately 30% of patients at high-resolution CT (21,22). They include interlobular septal thickening (33%), irregular linear hyperattenuating areas (33%), and architectural distortion (22%) (Figs 2, 4). Such abnormalities are usually mild and focal; diffuse disease occurs in only 4% of patients (1). Honeycombing is uncommon.

Rheumatoid Arthritis

Rheumatoid arthritis is characterized by the presence of symmetric arthritis, morning stiffness, and rheumatoid factor in the blood. Pleuropulmonary complications are common and include interstitial pneumonitis and fibrosis, rheumatoid (necrobiotic) nodules, BOOP, bronchiectasis,



a. b.

Figure 2. Systemic lupus erythematosus and nonspecific interstitial pneumonia (fibrosing pattern) in a 67-year-old woman. **(a)** Thin-section (1-mm collimation) CT scan obtained at the level of the inferior pulmonary vein shows ground-glass attenuation and irregular linear hyperattenuating areas in the subpleural areas of both lower lung zones, as well as traction bronchiectasis (arrows). **(b)** Photomicrograph (original magnification, ×12; H-E stain) shows uniform interstitial fibrous thickening with infiltration of a few mononuclear cells.

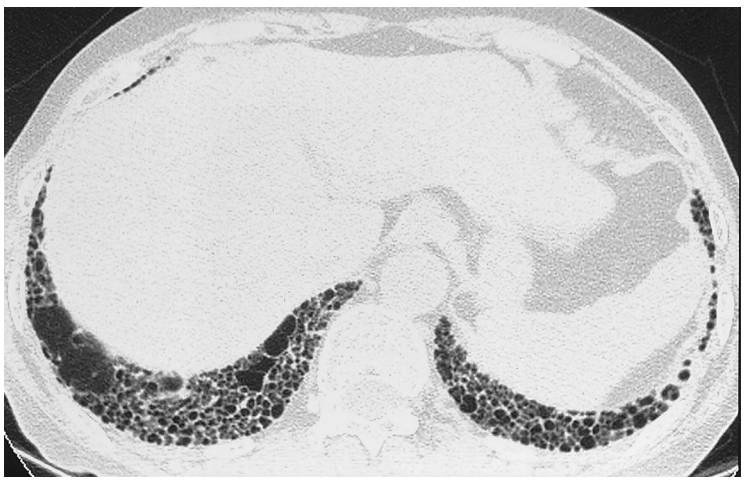


Figure 3. Systemic lupus erythematosus and BOOP in a 23-year-old woman. Thin-section (1-mm collimation) CT scan obtained at the level of the liver dome shows subpleural consolidation and ground-glass attenuation in the basal areas of both lungs.

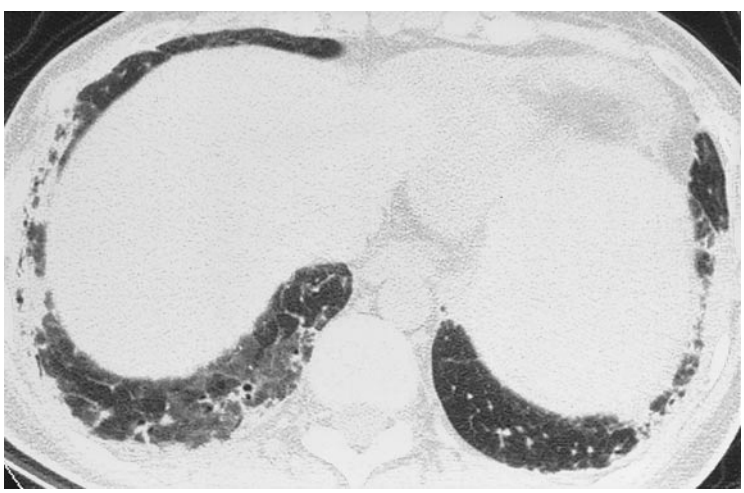


Figure 4. Systemic lupus erythematosus and usual interstitial pneumonia in a 51-year-old woman. Thin-section (1-mm collimation) CT scan obtained at the level of the liver dome shows subpleural honeycombing, irregular linear hyperattenuating areas, and ground-glass attenuation in the basal areas of both lungs.

obliterative bronchiolitis, follicular bronchiolitis, and pleural effusion or thickening (23,24).

Interstitial pneumonitis and fibrosis are the most common pulmonary manifestations of rheumatoid arthritis (23). In fact, pulmonary function abnormalities consistent with interstitial fibrosis have been reported in as many as 40% of patients who have rheumatoid arthritis (24); in more than one-half of these patients, however, findings at chest radiography are normal. Evidence of interstitial fibrosis is seen at chest radiography in approximately 5% of patients with rheumatoid arthritis (23,25) and at high-resolution CT in 30%–40% (24,26). The complication is seen most frequently in men between 50 and 60 years of age (27).

Histopathologic Characteristics

The majority of patients who have interstitial fibrosis associated with rheumatoid arthritis have usual interstitial pneumonia; a small percentage have histologic findings of nonspecific interstitial pneumonia (3). Nodular aggregates of lymphocytes may be prominent in both the parenchymal interstitium and in the interstitial tissue in bronchiolar walls and interlobular septa (follicular bronchiolitis) (5).

In one report, a variety of histopathologic features were seen in specimens obtained at open lung biopsy in patients with rheumatoid lung disease (5). Five different groups were identified on the basis of histologic patterns: pulmonary rheumatoid nodules, usual interstitial pneumonia, BOOP (Fig 5), lymphoid hyperplasia, and cellular interstitial infiltrates (nonspecific interstitial pneumonia). Few cases of diffuse alveolar damage have been reported (Fig 6) (28).

Radiologic Manifestations

In the early stage, the radiographic appearance consists of irregular linear hyperattenuating areas in a fine reticular pattern. The abnormality usually involves mainly the lower lung zones. With the progression of disease, the reticular pattern becomes more coarse and diffuse, and honeycombing may be seen (29).

Similar to the findings at radiography, the predominant abnormality at high-resolution CT consists of irregular linear hyperattenuating areas caused by a combination of intralobular lines and irregular thickening of interlobular septa (24). Honeycombing is seen, most markedly near the diaphragm. In a study by Akira et al (30), three predominant CT patterns were identified in 29 patients: reticulation with or without honeycombing ($n = 19$), centrilobular branching linear structures with or without bronchial dilatation ($n = 5$), and consolidation ($n = 5$). Reticulation and centrilobular branching linear structures corresponded to the histopathologic findings of usual interstitial pneumonia and BOOP, respectively. Consolidation corresponded to BOOP with or without findings of coexistent chronic eosinophilic pneumonia (Fig 5). Reticulation deteriorates rapidly, especially when it is associated with the new appearance of multifocal areas of ground-glass attenuation. Centrilobular branching linear structures show a tendency to progress to bronchiectasis. Consolidation shows a tendency to improve in one-half of patients and to evolve into honeycombing in the remaining patients at serial CT.

Interstitial lung changes are frequent and independent of disease duration. Interstitial changes are more frequent and severe in rheumatoid factor–positive patients and in patients with more severe joint involvement (31).

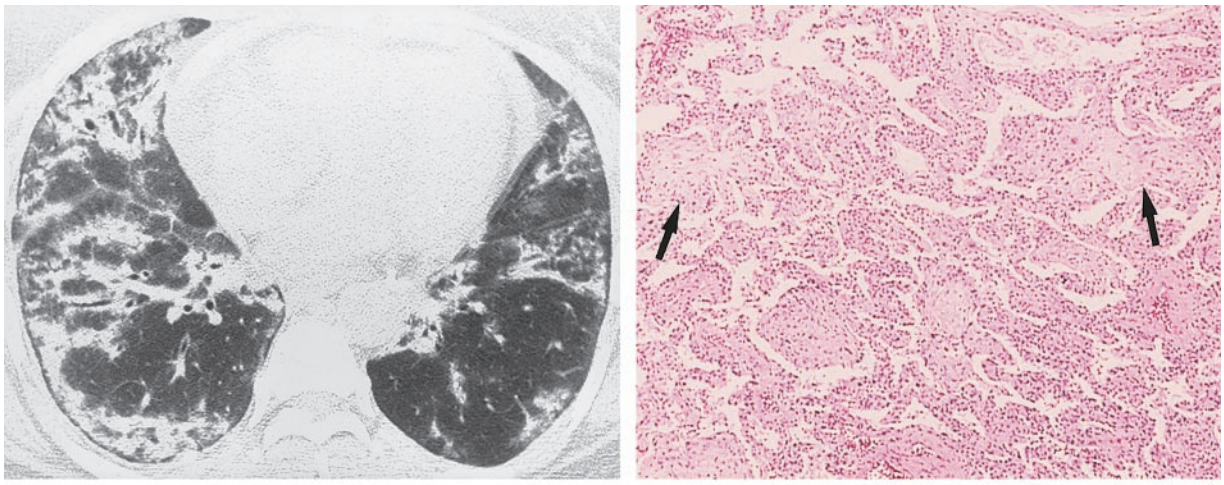
Progressive Systemic Sclerosis

Progressive systemic sclerosis (scleroderma), an uncommon disease with an estimated incidence of approximately 10 cases per million per year, is a disorder of connective tissue characterized by deposition of excessive extracellular matrix and vascular obliteration (32). It has an approximately 3:1 female predilection. Diffuse and limited forms of systemic sclerosis refer to the extent of cutaneous involvement, with a different clinical course and prognosis for each. Both types are more common in women, although the diffuse form tends to involve older women.

Pulmonary involvement is more common and more severe in systemic sclerosis than in other types of collagen vascular disease. The most common pulmonary manifestation is interstitial fibrosis, which occurs in approximately 80% of patients (32). Pulmonary fibrosis is equally likely in the limited and diffuse forms of the disease but is less severe in the limited form.

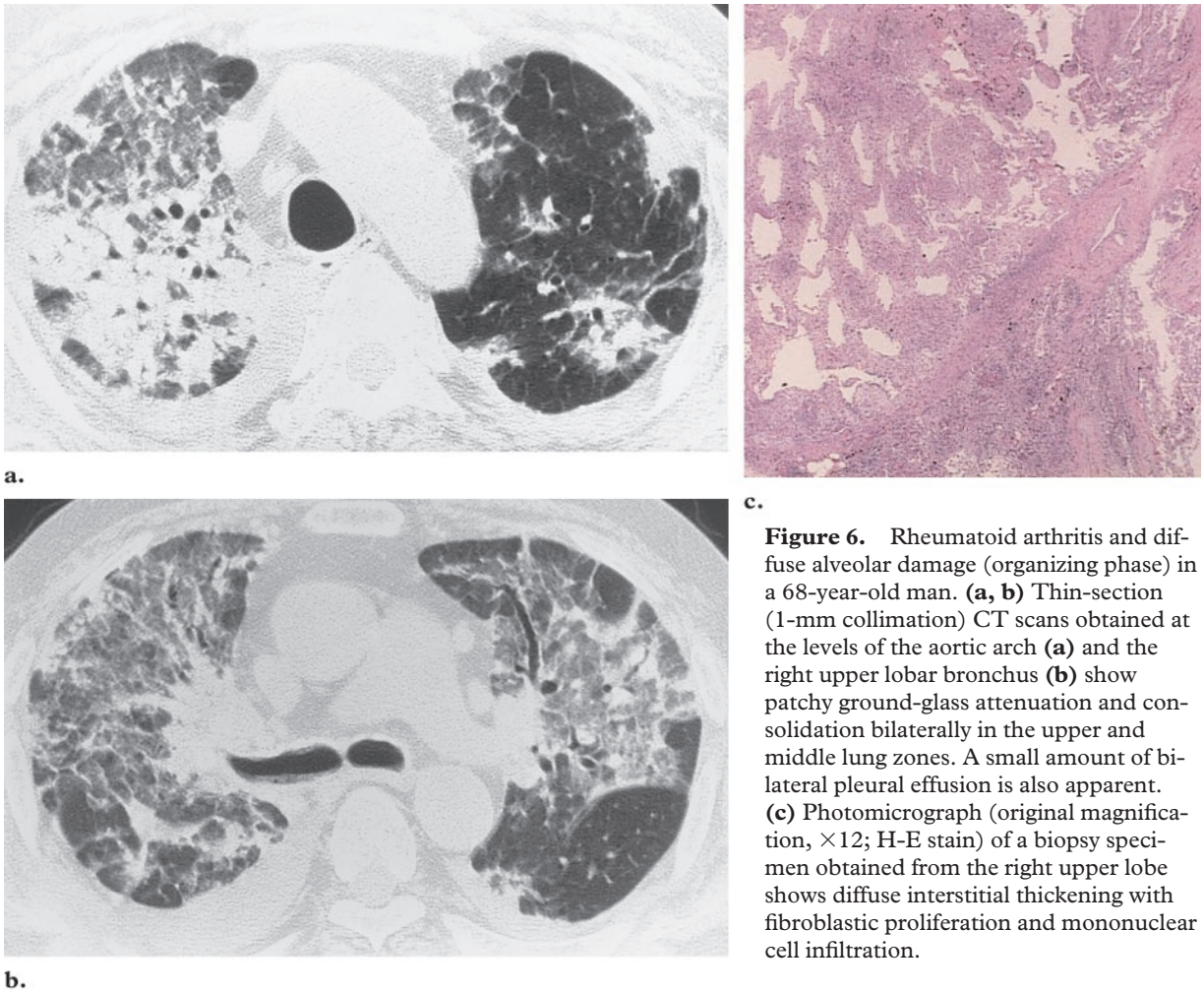
Histopathologic Characteristics

At autopsy, some degree of parenchymal interstitial fibrosis is frequently seen. The histologic features are those of nonspecific (Fig 7) or usual (Fig 8) interstitial pneumonia, the former being more common. Follicular bronchiolitis is seen occasionally. Although BOOP may be associated with scleroderma, obliterative bronchiolitis is only rarely seen with the disease (6). Diffuse alveolar damage has rarely been recognized in association with scleroderma (7).



a. b.

Figure 5. Rheumatoid arthritis and BOOP in a 68-year-old man. **(a)** Thin-section (1-mm collimation) CT scan obtained at the level of the inferior pulmonary vein shows patchy areas of ground-glass attenuation and consolidation with a subpleural or peribronchovascular distribution in both lungs. **(b)** Photomicrograph (original magnification, ×40; H-E stain) shows intraalveolar fibroblastic plugging (arrows) in alveolar spaces and alveolar ducts.



a. c.

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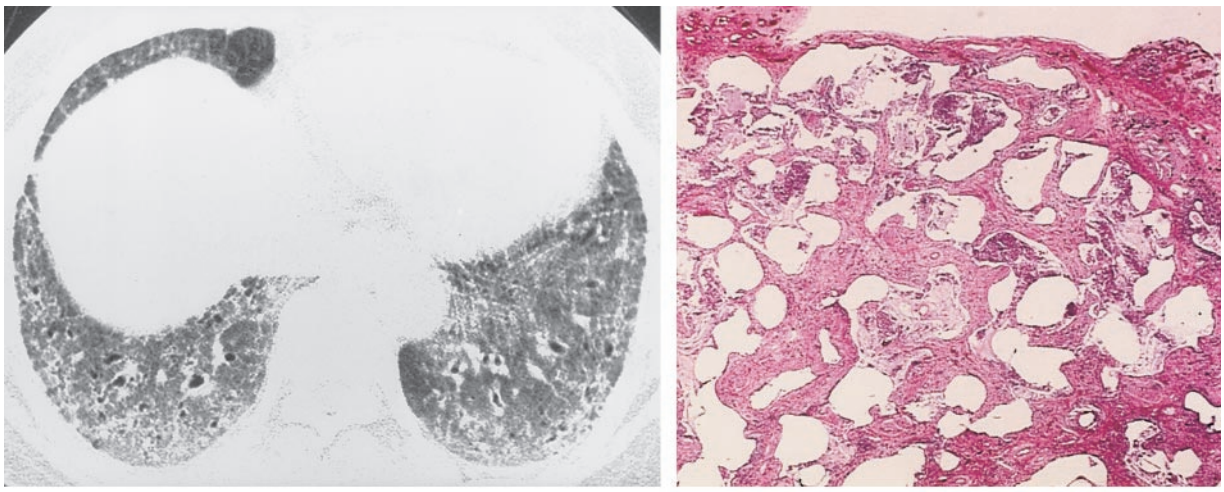
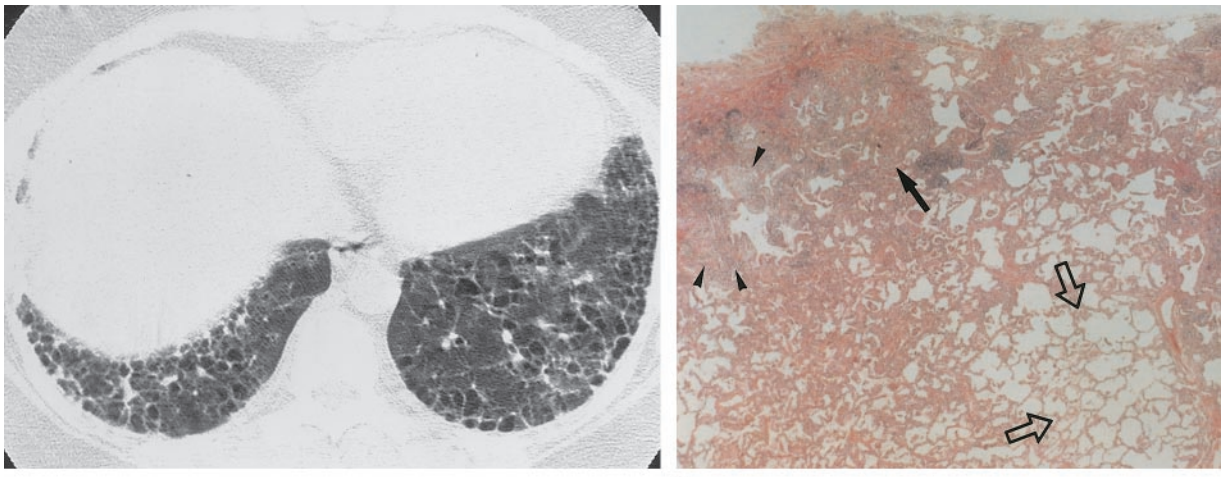
Figure 6. Rheumatoid arthritis and diffuse alveolar damage (organizing phase) in a 68-year-old man. **(a, b)** Thin-section (1-mm collimation) CT scans obtained at the levels of the aortic arch **(a)** and the right upper lobar bronchus **(b)** show patchy ground-glass attenuation and consolidation bilaterally in the upper and middle lung zones. A small amount of bilateral pleural effusion is also apparent. **(c)** Photomicrograph (original magnification, ×12; H-E stain) of a biopsy specimen obtained from the right upper lobe shows diffuse interstitial thickening with fibroblastic proliferation and mononuclear cell infiltration.



a. b.

Figure 7. Progressive systemic sclerosis and nonspecific interstitial pneumonia (group 3) in a 50-year-old woman. **(a)** Thin-section (1-mm collimation) CT scan obtained at the level of the liver dome shows patchy areas of ground-glass attenuation, irregular linear hyperattenuating areas, and traction bronchiectasis. **(b)** Photomicrograph (original magnification, ×40; H-E stain) shows diffuse uniform interstitial fibrous thickening, intraalveolar mucin, and inflammatory cell infiltration.



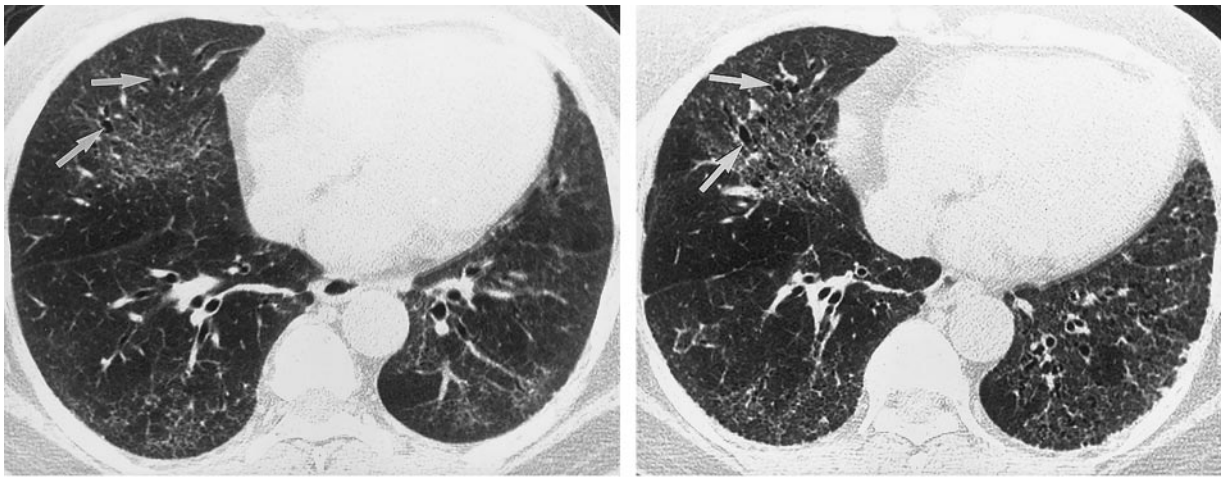
a. b.

Figure 8. Progressive systemic sclerosis and usual interstitial pneumonia in a 41-year-old woman. **(a)** Thin-section (1-mm collimation) CT scan obtained at the level of the liver dome shows honeycombing, irregular linear hyperattenuating areas, and ground-glass attenuation in the basal areas of both lungs. **(b)** Photomicrograph (original magnification, ×12; H-E stain) shows irregular interstitial fibrosis (solid arrow) with mononuclear cell infiltration and foci of fibroblastic proliferation (arrowheads). Intervening normal lung tissue is also seen (open arrows).

Radiologic Manifestations

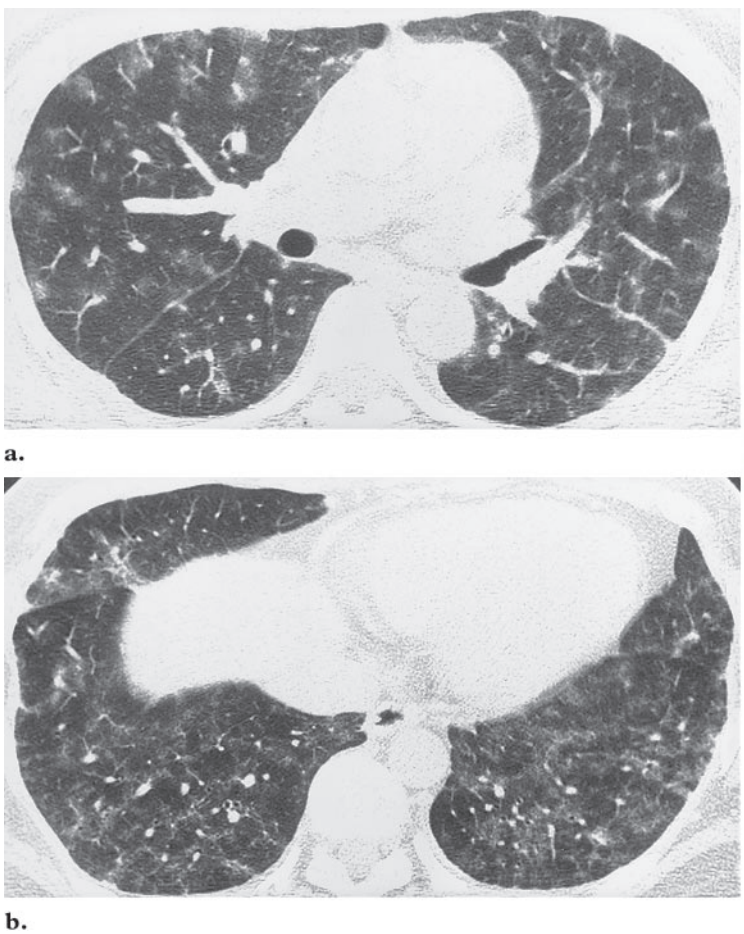
Evidence of interstitial fibrosis has been reported at chest radiography in 20%–65% of patients (32). Serial radiographs obtained over several years may show progressive loss of lung volume in addition to a worsening of the interstitial disease.

High-resolution CT frequently shows evidence of interstitial pneumonitis and fibrosis in patients who have normal or questionable radiographic findings (Figs 7–10) (33,34). The abnormalities involve mainly the lower lobes and have a predominantly peripheral and posterior distribution (35). In a recent study by Kim et al (36), findings at serial high-resolution CT were correlated with



a. b.

Figure 9. Progression of disease extent in a 51-year-old woman with progressive systemic sclerosis and nonspecific interstitial pneumonia. **(a)** Thin-section (1-mm collimation) CT scan obtained at the level of the basal segmental bronchi shows patchy distribution of irregular linear hyperattenuating areas and ground-glass attenuation with traction bronchiectasis (arrows) in both lungs. **(b)** Follow-up CT scan obtained at a similar level 54 months later shows increased extent of disease in both lungs. Traction bronchiectasis has progressed (arrows).



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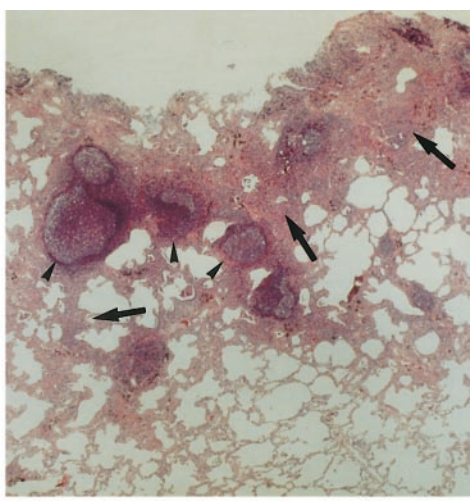
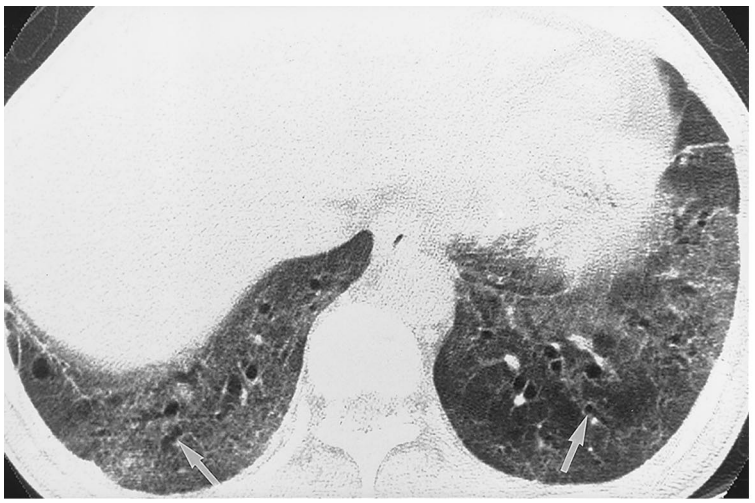


c.

Figure 10. Dermatomyositis and usual interstitial pneumonia in a 64-year-old woman. **(a, b)** Initial thin-section (1-mm collimation) CT scans obtained at the levels of the bronchus intermedius **(a)** and liver dome **(b)** show patchy areas of ground-glass attenuation and irregular linear hyperattenuating areas with random distribution in both lungs. **(c)** Photomicrograph (original magnification, ×12.5; H-E stain) shows irregular interstitial fibrosis (arrows) and mononuclear cell infiltration with subpleural predominance. Germinal center formation is also seen (arrowheads).

Figure 11. Dermatomyositis and nonspecific interstitial pneumonia in a 51-year-old man. **(a)** Thin-section (2.5-mm collimation) CT scan obtained at the level of the liver dome shows subpleural patchy areas of ground-glass attenuation and irregular linear areas of hyperattenuation. Traction bronchiectasis is also visible (arrows). **(b)** Coronal reformatted image (2-mm collimation of original axial helical CT data obtained with 2.5-mm collimation, 120 kVp, and 100 mA) of the posterior portion of the lung shows subpleural ground-glass attenuation and irregular linear hyperattenuating areas, predominantly in the lower lung zones. Traction bronchiectasis is also visible (arrows).



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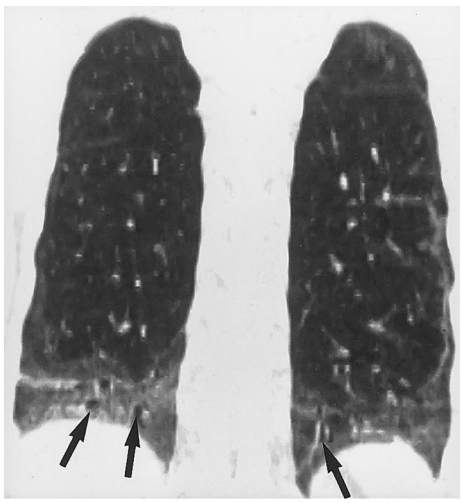


b.

the results of pulmonary function tests in 40 patients with progressive systemic sclerosis and interstitial pneumonia. The overall extent of disease and the degrees of honeycombing and ground-glass attenuation increased significantly at follow-up CT (Fig 9). Both forced vital capacity and forced expiratory volume in 1 second decreased significantly at follow-up. The increase in the extent of honeycombing at CT correlated significantly with the decrease in diffusing capacity for carbon monoxide. The average rate of progression of honeycombing in patients with idiopathic usual interstitial pneumonia is 0.4% of lung volume per month (37). According to study by Kim et al (36), the progression rate of honeycombing in patients with progressive systemic sclerosis is 0.07% of lung volume per month.

Polymyositis and Dermatomyositis

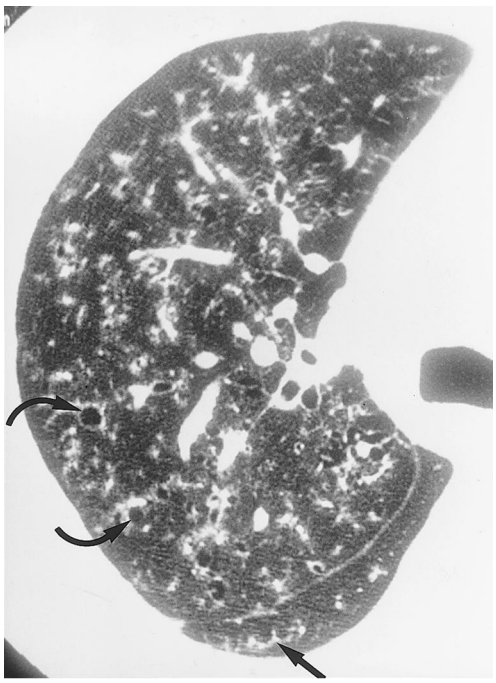
Polymyositis is an autoimmune inflammatory myopathy characterized by symmetric weakness of the limb girdle and anterior neck muscles (8). Dermatomyositis is similar to polymyositis except for the presence of a characteristic skin rash. Polymyositis and dermatomyositis have an incidence of approximately 5–10 cases per million per year (8) and occur twice as often in women as in men.

The thorax is commonly affected, generally in one or more of three forms: (*a*) hypoventilation and respiratory failure as a result of involvement of the respiratory muscles; (*b*) interstitial pneumonitis, usually with a histologic pattern of usual interstitial pneumonia (Fig 10) or nonspecific interstitial pneumonia; and (*c*) aspiration pneumonia secondary to pharyngeal muscle weakness (probably the most common pulmonary complication) (8,38).

Histopathologic Characteristics

Interstitial lung disease associated with polymyositis or dermatomyositis has a wide spectrum of histopathologic features (8,38). Three major groups can be identified on the basis of histologic patterns: BOOP, usual or nonspecific interstitial pneumonia (Figs 10, 11), and diffuse alveolar damage. Histologic appearance is useful for determining the prognosis (38). Patients with diffuse alveolar damage or usual interstitial pneumonia have a poor prognosis, with only a 33% survival rate at 5 years (39); however, patients with BOOP have an excellent prognosis. Patients with nonspecific interstitial pneumonia have a good prognosis.

Figure 12. Sjögren syndrome and lymphocytic interstitial pneumonia in a 32-year-old woman. **(a)** Thin-section (1-mm collimation) CT scan obtained at the level of the carina shows centrilobular nodules and branching linear structures (straight arrow) in the right lung. Many thin-walled cysts (curved arrows) were seen in both lungs. **(b)** Photomicrograph (original magnification, ×20; H-E stain) shows diffuse lymphocyte infiltration in the peribronchovascular interstitium and surrounding alveolar septa (arrows).



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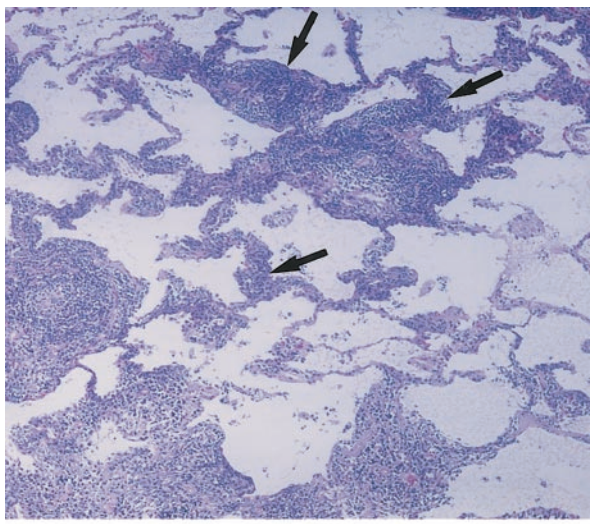

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Radiologic Manifestations

The frequency of radiographic parenchymal abnormalities is low (about 5%). The most common is a symmetric, predominantly basal reticular pattern (Figs 10, 11) that may become diffuse over time and progress to honeycombing (8). Bilateral areas of consolidation develop in some patients over a 2- to 3-week period. This abnormality usually corresponds histologically to diffuse alveolar damage or BOOP (38).

Initial high-resolution CT findings of pulmonary involvement in patients with polymyositis or dermatomyositis are prominent interlobular septa, ground-glass attenuation, patchy consolidation, parenchymal bands, irregular peribronchovascular thickening, and subpleural lines (Figs 10, 11). Honeycombing may be seen in up to 16% of patients who have abnormal chest radiographic findings or pulmonary function (40). Areas of consolidation with or without ground-glass attenuation correspond histopathologically to BOOP or organizing diffuse alveolar damage. Patchy consolidation, parenchymal bands, and irregular peribronchovascular thickening are seen to improve at sequential CT, becoming pleural irregularities, prominent interlobular septa, ground-glass attenuation, and subpleural lines on follow-up CT scans (9,41). Therefore, consolidation with patchy and subpleural distribution, parenchymal bands, and irregular peribronchovascular thickening are reversible. On occasion, areas of ground-glass attenuation with parenchymal bands or subpleural lines that represent a pathologic area of usual interstitial pneumonia may progress to honeycombing (9).

Sjögren Syndrome

Sjögren syndrome is characterized by a clinical triad of dry eyes (keratoconjunctivitis sicca), dry mouth (xerostomia), and arthritis. It is relatively common, affecting 0.1% of the general population and 3% of older adults (42). It may be primary, without features of other collagen vascular disease, or secondary in association with other collagen vascular disease, most often rheumatoid arthritis.

The most common thoracic complication, lymphocytic interstitial pneumonia (Fig 12), is followed in frequency by airway abnormalities such as follicular bronchitis, bronchiectasis, and bronchiolitis. Less common complications include interstitial pneumonitis and fibrosis, BOOP, lymphoma, pulmonary hypertension, and pleural effusion or fibrosis (42).

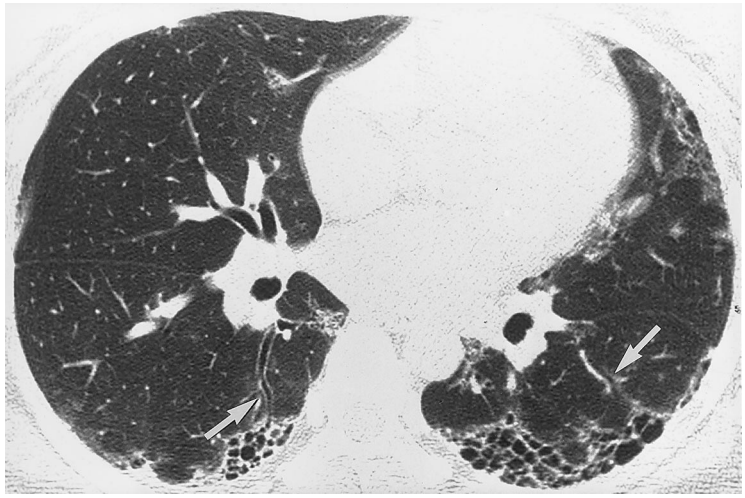

Figure 13. Sjögren syndrome and usual interstitial pneumonia in a 30-year-old woman. Thin-section (1-mm collimation) CT scan obtained at the level of the lower lobar bronchus shows subpleural ground-glass attenuation, irregular linear hyperattenuating areas, and honeycombing. Traction bronchiectasis is also visible (arrows).

Histopathologic Characteristics

Sjögren syndrome appears with a wide spectrum of interstitial lung disease, from follicular bronchiolitis to lymphocytic interstitial pneumonia and, finally, fibrosis with honeycombing (10). At histopathologic examination, lymphocytic interstitial pneumonia is characterized by a diffuse, usually bilateral, interstitial infiltration of lymphoplasma cells (2,10). It is usually most prominent in relation to bronchioles and their accompanying vessels but can be seen in the alveolar interstitium (Fig 12). Fibrosis is usually mild (10).

Radiologic Manifestations

Parenchymal abnormalities are evident at chest radiography in 10%–30% of patients (43). The most common finding, a reticulonodular pattern that involves mainly the lower lung zones, may reflect the presence of lymphocytic interstitial pneumonia or interstitial fibrosis. Franquet et al (44) made a prospective study of high-resolution CT findings in the lungs of 50 consecutive patients in whom the onset of disease occurred an average of 12 years prior to CT (range, 2–37 years). Moreover, 37 of 50 patients (74%) had no respiratory symptoms at the time of CT. The authors detected abnormalities in 17 patients (34%) at CT and in only seven patients (14%) at chest radiography. The most common findings consisted of bronchiolectasis and poorly defined centrilobular nodular or branching linear hyperattenuating areas (seen in 11 patients) (Fig 12), areas of ground-glass attenuation (seven patients), and honeycombing (four patients) (Fig 13). Honeycombing alone or both honeycombing and ground-glass attenuation suggestive of pulmonary fibrosis were bilateral, asymmetric, and present almost exclusively in the periphery of the lower lobes.

A characteristic pattern of extensive areas of ground-glass attenuation with scattered thin-walled cysts is seen in approximately 50% of patients with lymphocytic interstitial pneumonia (Fig 12) (11,45,46). Similar findings have been described in patients with this pneumonia but without Sjögren syndrome (11,12). Interstitial peribronchiolar lymphoplasmacytic infiltrates associated with overinflation of the secondary pulmonary lobule (12) in histopathologic specimens suggest that at least some of the cysts may be related to air trapping secondary to bronchiolar stenosis. Poorly defined centrilobular nodules and thickening of the bronchovascular bundles, also seen in lymphocytic interstitial pneumonia, represent expansion of the interstitial tissue by lymphoplasma cell infiltration (Fig 12) (11).

Mixed Connective Tissue Disease

The term *mixed connective tissue disease* refers to a condition in which patients have mixed features of systemic lupus erythematosus, progressive systemic sclerosis, and polymyositis. Respiratory involvement has been described in 20%–80% of patients. Common pulmonary abnormalities include interstitial pneumonitis and fibrosis, pulmonary hypertension, and pleural effusion (47).

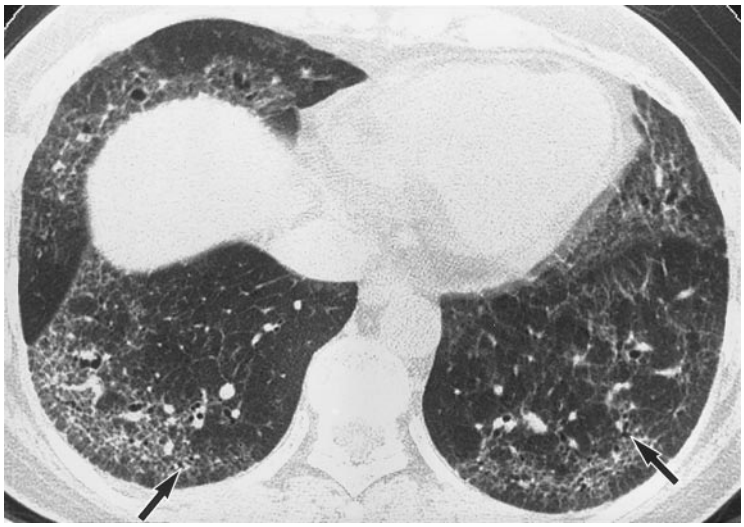

Figure 14. Mixed connective tissue disease and usual interstitial pneumonia in a 54-year-old woman. Thin-section (1-mm collimation) CT scan obtained at the level of the liver dome shows subpleural areas of ground-glass attenuation, irregular linear hyperattenuating areas, and traction bronchiectasis and bronchiolectasis (arrows).

Histopathologic Characteristics

Histopathologic findings of pulmonary involvement in mixed connective tissue disease are classified into interstitial fibrosis and vascular changes. Interstitial fibrosis has the appearance of usual or nonspecific interstitial pneumonia. Typical vascular changes consist of bland intimal proliferation of the lung arterioles, plexogenic angiopathy, and chronic pulmonary emboli (47).

Radiologic Manifestations

The frequency of pulmonary abnormalities varies considerably in different series. For example, in a retrospective study of 81 patients at the Mayo Clinic (48), an interstitial pattern was seen at chest radiography in 19%; on the other hand, careful prospective study of 34 patients in another investigation (49) showed interstitial abnormalities in 85%. The abnormalities consist of irregular linear hyperattenuating areas with a reticular pattern and involving mainly the lung bases. With the progression of disease, the fibrosis gradually extends superiorly; in the late stage, honeycombing may be identified. High-resolution CT shows a predominant subpleural distribution of fibrosis (Fig 14). Other radiologic abnormalities include areas of parenchymal consolidation that may be related to BOOP (13).

Ankylosing Spondylitis

Ankylosing spondylitis, a chronic inflammatory disease that affects mainly the joints of the axial skeleton (sacroiliac, costovertebral and apophyseal joints), affects mainly men (male predilection, 10:1). In approximately 1%–2% of patients, pleuropulmonary complications develop (14).

Histopathologic Characteristics

Histopathologic findings of interstitial lung disease in patients with ankylosing spondylitis include prominent interstitial fibrosis with hyaline and elastic degeneration of collagen, especially in the apices of the lungs. Chronic inflammatory cell infiltrations have also been reported (50).

Radiologic Manifestations

The most common pulmonary manifestation is upper lobe fibrobullous disease. At radiography, the process begins as apical pleural involvement, which is followed by apical areas of increased opacity that may progress to cavity and bulla formation. Generally, the disease begins unilaterally and later becomes bilateral.

A variety of abnormalities can be seen at high-resolution CT and include evidence of apical fibrosis, paraseptal emphysema, bronchiectasis, interstitial fibrosis, mediastinal lymph node enlargement, and tracheal dilatation (51).

Conclusions

Interstitial lung diseases are frequently seen in patients with collagen vascular disease. At histopathologic examination, these lung diseases are diverse and identical to their idiopathic counterparts. The findings include nonspecific interstitial pneumonia, usual interstitial pneumonia, BOOP, apical fibrosis, diffuse alveolar damage, and lymphocytic interstitial pneumonia. Although the proportions of interstitial pneumonias vary, the nonspecific variety accounts for a large proportion, especially in patients with progressive

systemic sclerosis, dermatomyositis, polymyositis, or mixed connective tissue disease. The more favorable prognoses in patients with interstitial pneumonia associated with collagen vascular diseases than in those with idiopathic interstitial pneumonias may be explained by the larger proportion of nonspecific than of usual interstitial pneumonia. High-resolution CT appears to help characterize and determine the extent of interstitial lung disease associated with collagen vascular diseases.

References

1. Haupt HM, Moore GW, Hutchins GM. The lung in systemic lupus erythematosus: analysis of the pathologic changes in 120 patients. Am J Med 1981; 71:791–798.
2. Colby TV. Pulmonary pathology in patients with systemic autoimmune diseases. Clin Chest Med 1998; 19:587–612.
3. Katzenstein AL, Fiorelli RF. Nonspecific interstitial pneumonia/fibrosis: histologic features and clinical significance. Am J Surg Pathol 1994; 18: 136–147.
4. Hakala M, Paakko P, Huhti E, et al. Open lung biopsy of patients with rheumatoid arthritis. Clin Rheumatol 1990; 9:452–460.
5. Yousem SA, Colby TV, Carrington CB. Lung biopsy in rheumatoid arthritis. Am Rev Respir Dis 1985; 131:770–777.
6. Bridges AJ, Hsu KC, Dias-Arias AA, Chechani V. Bronchiolitis obliterans organizing pneumonia and scleroderma. J Rheumatol 1992; 19:1136–1140.
7. Muir TE, Tazelaar HD, Colby TV, Myers JL. Organizing diffuse alveolar damage associated with progressive systemic sclerosis. Mayo Clin Proc 1997; 72:639–642.
8. Schwarz MI. The lung in polymyositis. Clin Chest Med 1998; 19:701–702.
9. Akira M, Hara H, Sakatani M. Interstitial lung disease in association with polymyositis-dermatomyositis: long-term follow-up CT evaluation in seven patients. Radiology 1999; 210:333–338.
10. Deheinzelin D, Capelozzi VL, Kairalla RA, et al. Interstitial lung disease in primary Sjögren's syndrome: clinical-pathological evaluation and response to treatment. Am J Respir Crit Care Med 1996; 154:794–799.
11. Johkoh T, Müller NL, Pickford M, et al. Lymphocytic interstitial pneumonia: thin-section CT findings in 22 patients. Radiology 1999; 212:567–572.
12. Ichikawa Y, Kinoshita M, Koga T, et al. Lung cyst formation in lymphocytic interstitial pneumonia: CT features. J Comput Assist Tomogr 1994; 18: 745–748.
13. Prakash UBS. Respiratory complications in mixed connective tissue disease. Clin Chest Med 1998; 19:733–746.
14. Lee-Chiong TL. Pulmonary manifestations of ankylosing spondylitis and relapsing polychondritis. Clin Chest Med 1998; 19:747–757.
15. Colby TV. Pulmonary pathology in patients with systemic autoimmune disease. Clin Chest Med 1998; 19:587–612.
16. American Thoracic Society. American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 2002; 165:277–304.
17. Mayberry JP, Primack SL, Müller NL. Thoracic manifestations of systemic autoimmune diseases: radiographic and high-resolution CT findings. RadioGraphics 2000; 20:1623–1635.
18. Wells AU, Hansell DM, Corrin B, et al. High-resolution computed tomography as a predictor of lung histology in systemic sclerosis. Thorax 1992; 47:508–512.
19. Murin S, Wiedemann HP, Matthay RA. Pulmonary manifestations of systemic lupus erythematosus. Clin Chest Med 1998; 19:641–665.
20. Cervera R, Khamashta MA, Font J, et al. Systemic lupus erythematosus: clinical and immunologic patterns of disease expression in a cohort of 1,000 patients. Medicine 1993; 72:113–124.
21. Bankier AA, Kiener HP, Wiesmayr MN, et al. Discrete lung involvement in systemic lupus erythematosus: CT assessment. Radiology 1995; 196: 835–840.
22. Fenlon HM, Doran M, Sant SM, Breatnach E. High-resolution chest CT in systemic lupus erythematosus. AJR Am J Roentgenol 1996; 166: 301–307.
23. Tanoue LT. Pulmonary manifestations of rheumatoid arthritis. Clin Chest Med 1998; 19:667–685.
24. Remy-Jardin M, Remy J, Cortet B, et al. Lung changes in rheumatoid arthritis: CT findings. Radiology 1994; 193:375–382.
25. Jurik AG, Davidsen D, Graudal H. Prevalence of pulmonary involvement in rheumatoid arthritis and its relationship to some characteristics of the patients: a radiological and clinical study. Scand J Rheumatol 1982; 11:217–224.
26. Gabbay E, Tarala R, Will R, et al. Interstitial lung disease in recent-onset rheumatoid arthritis. Am J Respir Crit Care Med 1997; 156:528–535.

27. Anaya JM, Diethelm L, Ortiz LA, et al. Pulmonary involvement in rheumatoid arthritis. Semin Arthritis Rheum 1995; 24:242–254.
28. Aratake K, Eguchi K, Migita K, et al. An autopsy case of rheumatoid arthritis accompanied with acute exacerbation of interstitial pneumonia. Nihon Rinsho Meneki Gakkai Kaishi 1998; 21:129–136. [Japanese]
29. Gamsu G. Radiographic manifestations of thoracic involvement by collagen vascular diseases. J Thorac Imaging 1992; 7:1–12.
30. Akira M, Sakatani M, Hara H. Thin-section CT findings in rheumatoid arthritis–associated lung disease: CT patterns and their courses. J Comput Assist Tomogr 1999; 23:941–948.
31. Muller-Leisse C, Bussmann A, Meyer O, Vorbruggen W, Genth E, Gunther RW. Pulmonary manifestations in rheumatoid arthritis: high-resolution computed tomography in correlation with the skeletal changes and laboratory chemical changes. Rofo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr 1996; 165:438–444. [German]
32. Minai OA, Dweik RA, Arroliga AC. Manifestations of scleroderma pulmonary disease. Clin Chest Med 1998; 19:713–731.
33. Arroliga AC, Podell DN, Matthay RA. Pulmonary manifestations of scleroderma. J Thorac Imaging 1992; 7:30–45.
34. Warrick JH, Bhalla M, Schabel SI, Silver RM. High-resolution computed tomography in early scleroderma lung disease. J Rheumatol 1991; 18: 1520–1528.
35. Remy-Jardin M, Remy J, Wallaert B, Bataille D, Hatron PY. Pulmonary involvement in progressive systemic sclerosis: sequential evaluation with CT, pulmonary function tests, and bronchoalveolar lavage. Radiology 1993; 188:499–506.
36. Kim EA, Johkoh T, Lee KS, et al. Interstitial pneumonia in progressive systemic sclerosis: serial high-resolution CT findings with functional correlation. J Comput Assist Tomogr 2001; 25:757–763.
37. Akira M, Sakatani M, Ueda E. Idiopathic pulmonary fibrosis: progression of honeycombing at thin-section CT. Radiology 1993; 189:687–691.
38. Tazelaar HD, Viggiano RW, Pickersgill J, et al. Interstitial lung disease in polymyositis and dermatomyositis: clinical features and prognosis as correlated with histologic findings. Am Rev Respir Dis 1990; 141:727–733.
39. Takizawa H, Hidaka N, Akiyama K. Clinicopathological studies on interstitial lung disease in polymyositis-dermatomyositis. Nihon Kyobu Shikkan Gakkai Zasshi 1985; 23:528–536. [Japanese]
40. Ikezoe J, Johkoh T, Kohno N, Takeuchi N, Ichikado K, Nakamura H. High-resolution CT findings of lung disease in patients with polymyositis and dermatomyositis. J Thorac Imaging 1996; 11:250–259.
41. Mino M, Noma S, Taguchi Y, et al. Pulmonary involvement in polymyositis and dermatomyositis: sequential evaluation with CT. AJR Am J Roentgenol 1997; 169:83–87.
42. Cain HC, Noble PW, Matthay RA. Pulmonary manifestations of Sjögren's syndrome. Clin Chest Med 1998; 19:687–699.
43. Silbiger ML, Peterson CC Jr. Sjögren's syndrome: its roentgenographic features. Am J Roentgenol Radium Ther Nucl Med 1967; 100:554–558.
44. Franquet T, Gimenez A, Monill JM, et al. Primary Sjögren's syndrome and associated lung disease: CT findings in 50 patients. AJR Am J Roentgenol 1997; 169:655–658.
45. Koyama M, Johkoh T, Honda O, et al. Pulmonary involvement in primary Sjögren's syndrome: spectrum of pulmonary abnormalities and computed tomography findings in 60 patients. J Thorac Imaging 2001: 16:94–98.
46. Meyer CA, Pina JS, Taillon D, et al. Inspiratory and expiratory high-resolution CT findings in a patient with Sjögren's syndrome and cystic lung disease. AJR Am J Roentgenol 1997; 168:101–103.
47. Prakash UBS. Lungs in mixed connective tissue disease. J Thorac Imaging 1992; 7:55–61.
48. Prakash UBS, Luthra HS, Divertie MB. Intrathoracic manifestations in mixed connective tissue disease. Mayo Clin Proc 1985; 60:813–821.
49. Sullivan WD, Hurst DJ, Harmon CE, et al. A prospective evaluation emphasizing pulmonary involvement in patients with mixed connective tissue disease. Medicine (Baltimore) 1984; 63:92–107.
50. Casserly IP, Fenlon HM, Breatnach E, Sant SM. Lung findings on high-resolution computed tomography in idiopathic ankylosing spondylitis: correlation with clinical findings, pulmonary function testing and plain radiography. Br J Rheumatol 1997; 36:677–682.
51. Fenlon HM, Casserly I, Sant SM, et al. Plain radiographs and thoracic high-resolution CT in patients who have ankylosing spondylitis. AJR Am J Roentgenol 1997; 168:1067–1072.

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