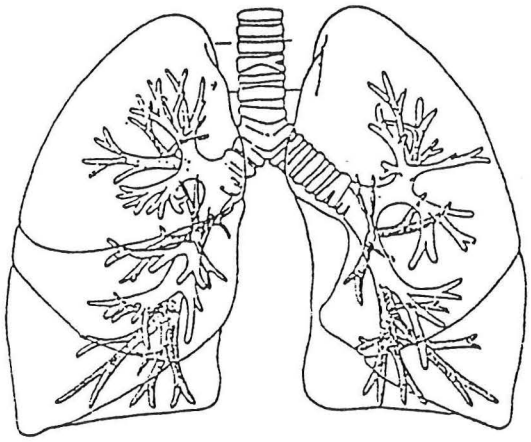
THE RESPIRATORY SYSTEM

IN COLLAGEN VASCULAR DISEASE



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I. Introduction

The collagen vascular diseases (CVD) are a heterogeneous group of chronic inflammatory and immunologically mediated disorders that share certain clinical characteristics including inflammation of joints, serosal membranes, connective tissue, muscle and blood vessels. The respiratory tract is particularly vulnerable in these conditions because of its abundant vasculature and large content of connective tissue. Potential targets of inflammation and injury include the lung parenchyma, tracheo-bronchial tree, pulmonary vasculature, pleura, upper airway and respiratory muscles.

This review was undertaken because many patients present with primarily pulmonary manifestations rather than musculoskeletal disease. Thus, in the age of enlightened health care reform, this group of patients will come under the direction of a primary care physician armed with the appropriate guidelines for diagnosis and treatment.

I have chosen to limit the discussion to the so called "Classic Collagen Vascular Diseases" as enumerated by Fauci (1). This classification includes Systemic Lupus Erythematosus, Rheumatoid Arthritis, Progressive Systemic Sclerosis, Dermatomyositis and Polymyositis, Mixed Connective Tissue Disease and Sjögren's Syndrome.

II. Systemic Lupus Erythematosus (SLE)

Involvement of the respiratory system by SLE was first recognized by Osler in the late 19th century (2). Since his original description it has become clear that SLE effects the respiratory system more than any other collagen vascular disease. From 50-70% of all patients have pulmonary dysfunction during the course of their illness (1, 3, 4). Although sepsis and renal disease are the common causes of death in SLE, pulmonary manifestations, particularly acute alveolar hemorrhage, may be lethal (5, 6).

A. Pleura in SLE

The pleura is the most common site of SLE involvement of the respiratory system. Pleural biopsy and autopsy specimens show infiltration of lymphocytes and plasma cells along with areas of fibrosis in 50 to 83% of patients (3, 4). This fibrinous pleuritis is frequently in various stages of organization in the same patient suggesting that there are chronic or multiple episodes of involvement which may be subclinical. Immunofluorescent studies have documented nuclear

staining of pleural mesothelial cells with either anti-IgM, anti-IgG or anti-C_3 (7). This observation lends support to the theory that a local immune response may play a part in the pathogenesis of both the pleuritis and pleural fluid formation seen in SLE. Vasculitis of the pleural vessels has also occasionally been reported; however, the importance remains unknown (8).

The clinical characteristics of patients with a confirmed diagnosis of lupus pleuritis are given in Table 1 (9).

TABLE 1

Clinical Characteristics of Lupus Pleuritis
n=14

Finding	Percent
Pleuritic Pain	86
Dyspnea	79
Tachycardia	71
Rub	71
Cough	64
Temperature >38°	57

As opposed to rheumatoid arthritis, patients with lupus pleuritis are usually quite symptomatic with pleuritic pain, dyspnea, tachycardia, pleural friction rub, cough and fever of >38°C. Pleuritic chest pain as the first presenting symptom of SLE has also been emphasized (10).

Radiographic features that are associated with lupus pleuritis are listed in Table 2 (9, 11).

TABLE 2

Radiographic Characteristics of Lupus Pleuritis
n=25

Finding	Percent
Abnormal CXR	100
Bilateral effusions	50
Right sided effusion	22
Left sided effusion	17
Alveolar infiltrates	22
Atelectasis	17

In one series all patients with symptomatic lupus pleuritis had an abnormal CXR when admitted to the hospital. One half had bilateral pleural effusions, while the other half involved the right and left sides equally. About 40% of effusions were associated with either alveolar infiltrates or basilar discoid atelectasis. Effusions are usually small and absorb completely leaving few residual radiographic changes. However, sporadic cases of massive effusions have been reported that require chest tube drainage and chemical poudrage for control.

Characteristics of pleural fluid have been extensively reported. The values of constituents which are routinely analyzed are given in Table 3 (10-13).

TABLE 3

Routine Pleural Fluid Characteristics
n=30

	pH Units	Glucose mg/DL	LDH PF/S	WBC Cells/μl	PMNS % Cells
Mean	7.35	92	>0.6	4900	72
Range	7.19-7.48	36-126		230-15000	21-100

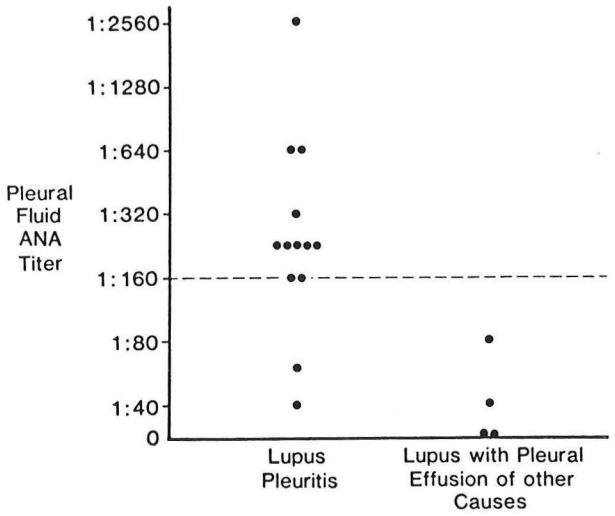
On thoracentesis the appearance of the pleural fluid has been described as clear, turbid, or serosanguinous; only rarely is it bloody (>100,000 RBC/mm^3). The pH is usually greater than 7.30 and the glucose usually >60 mg/dl. However there are occasional reports of low pH and glucose in native and drug induced SLE (9). The pleural fluid LDH to serum ratio universally exceeds 0.6 indicating an exudate. The nucleated cell count varies from a few hundred to approximately 15,000 cells/μl; these cells are predominantly PMN's if the injury is acute. Mononuclear cell predominance is more likely in effusions that have been present for over 2 weeks (9).

The presence of LE cells in pleural fluid is diagnostic of lupus (9). LE cells may be present in pleural effusions with a negative antinuclear antibody test and have been demonstrated in pleural fluid prior to their appearance in the blood (14, 15).

Low pleural fluid total hemolytic complement, low C_3 and C_4 values and C1q binding have occasionally been reported but are more typical in patients with rheumatoid arthritis (16-18). Double stranded DNA has been found in pleural fluid of patients with SLE, bronchogenic carcinoma and tuberculous pleurisy and is of unknown clinical significance (19).

FIGURE 1

Pleural Fluid ANA in Lupus Pleuritis

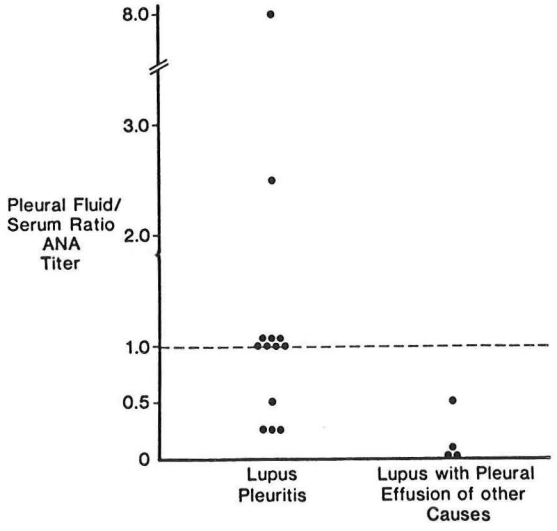


Good, Jr., J.T., et al: Chest 84:714-718, 1983.

The pleural fluid ANA also reflects activity of disease. As indicated in Figure 1, patients with lupus who had pleural effusions from other causes all had pleural ANA titers of <1:80. A pleural fluid ANA titer of >1:160 occurred only in patients with active lupus pleuritis and is considered diagnostic (9).

FIGURE 2

Pleural Fluid/Serum Ratio ANA Titer



Good, Jr., J.T., et al: Chest 84:714-718, 1983.

Similarly, as represented in Figure 2, a pleural fluid to serum ratio of the ANA titer over one >1 was observed only in patients with active lupus pleuritis and was <1 in all lupus patients with pleural effusions due to other causes (9).

However, the isolated presence of ANA positive pleural effusion is not diagnostic of SLE, since this phenomena has also been observed in malignancies, particularly lymphomas (16).

Symptoms of lupus pleuritis (pain, fever and dyspnea) usually respond rapidly to corticosteroid treatment, although the rate of reabsorption of the effusion may be variable. Other rare complications of lupus such as pneumothorax or hemothorax have been successfully managed with chest tube drainage.

B. Respiratory Muscles in SLE

One of the most interesting and controversial pulmonary manifestations of SLE is the "shrinking lung syndrome". This clinical syndrome presents with marked dyspnea on exertion or in the recumbent position associated with areas of linear atelectasis, elevated diaphragms and small but otherwise clear lungs on chest radiograph (20).

Pulmonary function testing reveals marked restriction (decrease in static lung volumes and vital capacity) and a decrease in lung compliance (21). Although these findings are compatible with interstitial lung disease the diffusing capacity of these patients has been reported as normal or only mildly reduced (21, 22). This pattern strongly suggests the extrapulmonary restriction which may be seen in other chest wall or neuromuscular disorders.

Two studies presented in Table 4 suggest diaphragmatic and intercostal muscle weakness as the etiology of this syndrome (22-24).

TABLE 4

Respiratory Muscle and Diaphragm Function in SLE

Parameter	Gibson n=7 Percent	Martens n=7 Predicted
Total lung capacity	51	67
Maximal inspiratory force	40	---
Maximal expiratory force	58	---
Pressure across the diaphragm	28	25
Compliance	75	55
Diffusion capacity	70	65

Gibson reported seven patients on very low dose or no steroid administration, without obvious systemic muscle weakness who had significant dyspnea unexplained by chest radiography. The total lung capacity (TLC), and the maximal inspiratory (P_{Imax}) and expiratory forces (P_{Emax}) were reduced approximately 50%, while the transdiaphragmatic pressure (P_{di}) was markedly reduced during inspiration. Lung compliance (C_L) was minimally reduced as was the diffusion capacity (D_{LCO}). Although an element of parenchymal lung disease could not be ruled out, the authors concluded that "diaphragmatic dysfunction more likely explained the shrinking lung syndrome" (23). Martens studied seven patients with similar clinical characteristics and confirmed a markedly decreased transdiaphragmatic pressure. He concluded a "restrictive defect existed due to respiratory muscle weakness" (22). Jacobelli (data not shown) extended these observations in 16 patients by correlating muscle function with a quantitative estimate of dyspnea. Significant correlations were found with maximal inspiratory pressure at the mouth, vital capacity, and with maximal transdiaphragmatic inspiratory pressure. He concluded that "inspiratory muscle dysfunction can be an important mechanism in the pathogenesis of the lung volume restriction and dyspnea in patients with SLE (24). Additional studies are required to confirm the apparent high incidence of diaphragmatic and respiratory muscle weakness in SLE patients. A recent study investigated phrenic nerve electrophysiology and found that phrenic neuropathy is an unlikely explanation for diaphragmatic dysfunction (25).

C. Lung Parenchyma in SLE

1. Acute Lupus Pneumonitis

Acute lupus pneumonitis (ALP) is a rare but serious manifestation of SLE. The best clinical description of ALP was by Matthay and associates who thoroughly studied twelve cases collected over a six year period (26). Patients present with the very abrupt onset of dyspnea, fever, cough, hypoxemia and diffuse infiltrates more prominent in the lower lung fields. Coexistent pleural effusions and pleuritic chest pain occur frequently and hemoptysis occasionally. Acute lupus pneumonitis may be the first recognized manifestation of SLE but almost always occurs only when multisystem disease is present (26). Mortality is about 50%. Several reports have found an increased incidence during pregnancy and immediately postpartum (27).

Bacterial infection is the most common cause of this constellation of symptoms in SLE patients; however, there is now ample evidence that this syndrome occurs in the absence of any infectious agents (4, 28).

The histologic appearance of acute lupus pneumonitis is non specific. No diagnostic or pathognomonic light microscopic

changes are present. Most often a non specific pattern of inflammation and injury to the alveolar epithelial cells, capillary endothelial cells and interstitium is described. Vasculitis of large pulmonary vessels also may occur but is an infrequent finding (26). There is, however, an increasing body of evidence demonstrating focally bound immunoglobulins within pleura and deposition of IgG, C_3 and DNA-anti-DNA antibodies along alveolar and alveolar capillary walls (7, 28). Thus, deposition of immune complexes in parenchymal vessels and tissues likely play a role in the pathogenesis of acute lupus pneumonitis.

No specific therapeutic regimens have been investigated, but if lupus pneumonitis is suspected it is reasonable to treat with a combination of broad spectrum antibiotics and high dose corticosteroids with or without cytotoxic agents (29, 30).

2. Alveolar Hemorrhage in SLE

The incidence, pathophysiology and clinical significance of alveolar hemorrhage in SLE has received increasing emphasis, but in two large series of patients followed for extended periods alveolar hemorrhage was uncommon occurring in only 0.6 to 2.0% of patients (3, 31). The clinical manifestations of this syndrome are present in Table 5.

TABLE 5

Clinical Manifestations of
Alveolar Hemorrhage in SLE

Incidence 0.6 - 2.0%
Acute onset dyspnea, fever, tachycardia, hypoxemia
Hemoptysis-none to massive
Decreasing hematocrit
Increased diffusion capacity

A mild subclinical chronic form of alveolar hemorrhage has been reported that pathologically resembles idiopathic hemosiderosis and may in fact precede the signs and symptoms of SLE (12). However, this syndrome is most frequently reported as the acute onset of dyspnea, fever, tachycardia and severe hypoxemia similar to lupus pneumonitis. It should be emphasized that hemoptysis may be entirely absent, occur as blood tinged sputa or be massive and life threatening (31-40). Chest radiographs show ill defined, patchy acinar infiltrates that are usually bilateral and located in the lower lung zones. In most cases coagulopathies are not present; however there is one report of a circulating lupus anticoagulant presenting with pulmonary hemorrhage, infarction and vasculitis as the first manifestations

of SLE (35). Even if hemoptysis is not present there is usually a marked drop in the hematocrit over the first 12 to 36 hours. An increase in diffusion capacity has also been reported secondary to a combination of extravascular hemoglobin with carbon monoxide similar to that reported in patients with Goodpasture's Syndrome (3).

The clinical presentation, radiographic findings, pathological appearance and natural history are almost identical in patients with lupus pneumonitis or with the lupus alveolar hemorrhage syndrome. Granular depositions of immunoglobulin IgG and C_3 as well as immune complex deposition have been detected in alveolar walls, interstitium and capillary endothelial cells even more frequently than in lupus pneumonitis (32, 39). More recent studies show the presence of both DNA and anti-DNA antibodies suggesting the immune complexes represent deposits of DNA-anti-DNA immune complexes (28).

The syndrome of alveolar hemorrhage in patients with SLE is apparently not distinct from that of acute lupus pneumonitis. Both conditions are likely a spectrum of lung damage resulting from immunologically mediated acute injury to the alveolar capillary unit (12). Why hemorrhage is a more prominent feature in some cases remains unclear. Moreover, the fluffy acinar opacities seen on chest radiograph on many patients with lupus pneumonitis are likely due in part to alveolar hemorrhage. Most experts treat them as a single clinical entity. Reasonable therapy of the alveolar hemorrhage syndrome of SLE is given in Table 6.

TABLE 6

Treatment of Alveolar Hemorrhage Syndrome in SLE

Broad spectrum antibiotics	
Prednisone	1.0 to 2.0 mgm/kg/d or 1.0 gm/d
Azathioprine	2.0 to 2.5 mgm/kg/d
Cyclophosphamide	1.5 to 2.0 mgm/kg/d
Plasmapheresis	

Since infection cannot be excluded in alveolar hemorrhage syndrome patients should be treated with broad spectrum antibiotics with sensitivities specific to the hospital and critical care units involved. Most patients who develop this syndrome are already receiving corticosteroids for other manifestation of their SLE. Occasional patients in this group have exhibited a marked clinical response to either a dose of 1.0 - 2.0 mgm/kg/d of Prednisone or to doses as high as 1.0 gm/d (26, 37). Others have expired in spite of the same treatment. Azathioprine at a dose of 2.0 to 2.5 mgm/kg/d or Cyclophosphamide

at a dose of 1.5 to 2.0 mgm/kg/d have each been added to patients who did not respond to corticosteroids alone. Results have been equivocal with the best survival (25%) data in those patients treated with Azathioprine (31). All reports however are small, uncontrolled and anecdotal. Isbister and others have reported individual patients who were deteriorating on high dose corticosteroids and improved clinically after plasmapheresis (30). As in the syndromes of vasculitis described at Grand Rounds by Dr. Alpern there are no data on the use of plasmapheresis although a sound theoretic rational exists for removal of the immune complexes that most likely mediate this disease complex (39).

3. Interstitial Lung Disease and Fibrosis in SLE

In contrast to scleroderma and rheumatoid arthritis chronic interstitial lung disease is not common in lupus. Several studies have estimated an incidence of 3.0 - 5.0% of patients with a long history of SLE (1, 3). The most detailed evaluation is from Eisenberg who reported on 18 patients identified over a one year period (41). All had chronic dyspnea, interstitial infiltrates on chest radiography and evidence of multiorgan disease. Half had pleuritic chest pain, rales and a pleural reaction on chest radiography, frequently associated with elevated diaphragms and poor diaphragmatic movement. Pulmonary function studies revealed approximately 50% restriction of lung volumes and a significant decrease in diffusion capacity that was often severe. The serum rheumatoid factor was less commonly positive (6% vs 57%) in fibrosis patients than in a large control group of SLE patients without interstitial disease. However, LE preparations were positive in all patients (41).

It has been postulated that interstitial inflammation and fibrosis may represent the chronic phase of acute pneumonitis. All survivors of ALP in the series of Matthay had persistent functional defects, and one-half had persistent radiographic abnormalities (26). Huang also reported on 3 of 28 patients who had parenchymal scarring and a history of lupus pneumonitis (42). All eighteen of Eisenberg's patients had a diagnosis of SLE for three years with pulmonary symptoms present for at least two years (41). Evidence that fibrosis is a chronic phase of acute pneumonitis is obviously indirect.

Corticosteroids are the treatment of choice for patients with SLE and interstitial fibrosis, although the response has been quite variable. It is likely that this form of interstitial fibrosis is similar to idiopathic pulmonary fibrosis in which the degree of acute cellular inflammation versus true fibrosis predicts response to corticosteroids (43). Since open lung biopsies are rarely available in these patients, a six week trial of these agents seems rational.

Azathioprine has been reported to benefit some patients with idiopathic pulmonary fibrosis who do not respond to

corticosteroids (43). Similar data are not available for interstitial fibrosis patients with SLE.

D. Pulmonary Vasculature in SLE

Pulmonary hypertension rarely develops in patients with SLE. When present it can usually be attributed to interstitial pneumonitis, small pulmonary artery vasculitis, thrombosis in situ, or pulmonary thromboembolism (44-46). The level of pulmonary hypertension in these secondary causes is usually mild (45).

There is, however, a growing body of evidence that "primary" pulmonary hypertension occurs in some patients with SLE (47, 48). Investigators are unable to determine whether these patients have had two coexistent diseases or if the pulmonary hypertension is caused by SLE. Biopsy specimens show concentric medial and intimal hypertrophy with plexiform lesions. These changes may be found in patients with severe pulmonary hypertension of any cause and do not help in ascribing an etiology. Interstitial lung disease, vasculitis, thrombosis and thromboembolism were minimal if found (47). Interestingly almost all patients with significant pulmonary hypertension and SLE had Raynaud's phenomena. This compares to an overall incidence of 20% in patients with SLE and 30% of patients with primary pulmonary hypertension (41, 44). Patients with Raynauds and SLE may be at extra risk to develop primary pulmonary hypertension (12).

There is no effective therapy for pulmonary hypertension secondary to parenchymal or vascular disease in patients with SLE. Vasodilators such as Nifedipine, Hydralazine and Captopril are apparently ineffective (49, 50). The response to corticosteroids therapy is variable (51). Aggressive combination of therapy with corticosteroids, anticoagulants, Cyclophosphamide or Azathioprine yielded definite improvement in three patients with pulmonary artery hypertension caused by a combination of vasculitis, interstitial pneumonitis and pulmonary thrombosis (52).

E. Other Rare Respiratory Tract Manifestations of SLE

Rarely reported respiratory tract manifestations of SLE are listed in Table 7.

TABLE 7

Unusual Respiratory Tract
Manifestations of SLE

Airway disease
Bronchiolitis
Laryngeal involvement
Pseudolymphoma
Lymphocytic interstitial pneumonitis
Amyloidosis

Focal asymptomatic bronchiolitis has been found histologically in occasional patients with SLE as has laryngeal involvement severe enough to cause stridor (53, 54). Two syndromes of lympho-histocytic lung invasion have also been reported. The lesions are called pseudolymphoma if focal and lymphocytic interstitial pneumonitis (LIP) if diffusely scattered in the interstitium. These abnormalities have not been clearly demonstrated to be due to lupus and may merely represent the incidental coexistence of two diseases (55, 56).

Additionally, there is one report of pulmonary amyloidosis associated with SLE (57).

III. Rheumatoid Arthritis (RA)

A. The Pleura in RA

Pleuritis was initially recognized as a complication of rheumatoid arthritis in 1943. The characteristics of pleural involvement have been studied in a large series of patients and are presented in Table 8 (58).

TABLE 8

Clinical Associations With
Rheumatoid Pleural Disease
n=516

Pleuritis	21%
Pleural effusion	3%
Subcutaneous nodules	80%
Age greater than	50
Male>Female	5:1

As in SLE, pleuritis with or without effusion is the most common respiratory manifestation of RA. Walker and Wright reported a series of 516 patients in which pleuritis with or without effusion occurred in 21%. The overall incidence of pleural effusion was 3% of which one-fourth preceded the onset of arthritis by six weeks to six months. Subcutaneous nodules indicating activity of disease were present in 80% and the mean age was over 50 years. Although RA is more likely to occur in females than in males, pleural effusions occur five times more frequently in males.

The clinical characteristics of patients with rheumatoid pleuritis and effusion differ from patients with SLE and are listed in Table 9 (59).

TABLE 9

Clinical Characteristics of Patients
With Rheumatoid Pleural Effusion
n=25

Finding	Percent
Asymptomatic	52
Pleuritic pain	32
Dyspnea	24
Temperature >38°C	8

Half of the patients with rheumatoid pleural effusions are asymptomatic. Only a third have pleuritic pain and only 25% shortness of breath. Fever indicated by a temperature over 38°C is distinctly uncommon. Rheumatoid pleuritis is, therefore, much less symptomatic than lupus pleuritis.

Radiographic features associated with rheumatoid pleuritis are listed in Table 10 (59, 60).

TABLE 10

Radiographic Characteristics of
Rheumatoid Pleuritis
n=43

Finding	Percent
Abnormal CXR	23
Right sided effusion	56
Left sided effusion	40
Bilateral effusions	5
Pneumonitis or nodules	19

Also in contrast to lupus only a quarter of patients with rheumatoid effusions have underlying pulmonary abnormalities on chest radiographs. There is a slight predominance of right sided effusion and the bilateral disease commonly seen in SLE is distinctly uncommon in RA (59, 60). Simultaneous nodules or areas of pneumonitis are likewise infrequent.

The pleural fluid characteristics in RA have been extensively investigated. The values of constituents that are routinely analyzed are presented in Table 11. Although it is not possible to be precise due to variable reporting, the values given are representative of their potential magnitude in patients with rheumatoid effusion.

TABLE 11

Pleural Fluid Characteristics in RA

Finding	Level
pH	<7.20
Protein	>3.5 to 5.5 gm/D_L
LDH	>1000 IU/L
Cell count	100-7000/mm^3
Mononuclear cells	↑ lymphocytes

On thoracentesis the pleural fluid has been described as serous, turbid, yellow-green, milky or very occasionally hemorrhagic (>100,000 RBC's). The pH of rheumatoid effusions has been systematically investigated by Taryle who found that it is usually acidic with a pH of <7.20, and the pH has been shown to decrease as glucose end products accumulate (61). The protein content is from 3.5 to 5.5 gm/D_L consistent with an exudate and correlating well with a pleural fluid LDH of >1000 IU/L. I was unable to find reports of the pleural fluid to serum LDH ratios.

Nucleated cell counts range from a few hundred to greater than 7000 cells/mm^3. There is a lymphocytic predominance. Occasional reports of uninfected effusions have noted a predominance of PMN's or even more rarely eosinophils (59-60).

A compilation of 76 reported cases supports the conventional teaching of a low concentration of glucose in rheumatoid effusions. These data are presented in Table 12 (58, 59, 62-80).

TABLE 12

Pleural Fluid Glucose in
Rheumatoid Pleural Effusions
n=76

Pleural Fluid Glucose mg/D_L	No. Cases	Percent
0-9	32	42
10-19	16	21
20-29	11	14
30-50	4	5
>50	13	17

A glucose of <50 mg/D_L was documented in 82% of cases, whereas a value over 50 mg/D_L was present in only 17%. Taryle and Sahn have extended this observation and demonstrated that the decreasing glucose and acidic pH occur after rheumatoid fluid formation because of 1) a selective block in glucose transfer from blood to pleural fluid, 2) an increased glucose utilization by rheumatoid pleural cells and 3) as the rheumatoid pleural membrane thickens there is a virtually complete bidirectional impairment of movement substances across the pleura. Thus, the decrease in pleural fluid glucose is highly associated with the duration of an effusion and may not be present in acute, transient effusions. This mechanism of decreased pleural glucose is not the same as that in empyema or carcinomatous effusions (61, 81).

Special characteristics of rheumatoid pleural effusions that are useful in confirming a diagnosis are listed in Table 13.

TABLE 13

Special Characteristics of
Rheumatoid Pleural Effusion

RA cells
Rheumatoid factor
Immunoglobulin synthesis
Total complement, C_3, C_4 decreased
Cytopathology
Pseudochylous
Thoracoscopy

Rheumatoid arthritis (RA) cells (granulocytes containing rheumatoid factor) may be found in rheumatoid effusions but are not diagnostic, since they are frequently reported in tuberculosis, malignancy and pneumonia (82). Rheumatoid factor is usually 1:320 or greater and tends to be higher than serum values. This finding is also not specific (83).

Halla and Pettersson have demonstrated an increased pleural fluid IgG, IgM, and immune complex formation in rheumatoid pleural effusion. Additionally, it has been shown that the pleural fluid mononuclear cells can synthesize IgG and IgM supporting the concept that local immune injury is responsible for the pleuritis and pleural effusion formation in RA as in other collagen vascular diseases (84, 85). Total complement, C_3 and especially C_4 are also decreased (85). Pleural fluid cytopathology is also helpful in substantiating the diagnosis of rheumatoid pleural effusions. The triad of giant multinucleated macrophages, elongated macrophages, and elongated macrophages with a background of granular debris may be unique to the rheumatoid effusion (78, 86, 87).

Rheumatoid effusions may rarely contain high levels of cholesterol and cholesterol crystals and thus be classified as pseudochylous effusions (76). In fact RA has replaced tuberculosis as the most common cause of a pseudochylous effusion. This finding is only present in long standing disease and is useful in ruling out malignancy or acute infection.

Thorascopy may also be useful in evaluating patients with rheumatoid pleurisy. The visceral pleural surface shows varying degrees of nonspecific inflammation. The parietal pleural surface has a characteristic "gritty" or frozen appearance (88). Histopathologic study demonstrates loss of the mesothelial cell layer and replacement with a pseudostratified layer of epitheloid cells that differ from Langerhans cells and foreign body giant cells (72, 89-92). Rarely the pariental pleural will show evidence of rheumatoid granuloma.

Rheumatoid effusions clear much more slowly than effusions in SLE, but a majority (75%) are cleared in six months. Residual pleural thickening is common (59). A small percentage have a protracted course that lasts years and may lead to symptomatic pleural fibrosis requiring decortication (93). Although most rheumatoid effusions are small, large and occasionally massive effusions have been documented (94). No treatment is usually necessary, but large effusions have been shown to respond to systemic but not to intrapleural steroid administration (95).

B. Lung Parenchyma in RA

1. Necrobiotic Nodules

Radiographically detectable intraparenchymal rheumatoid nodules, first described in 1954, are rare. Several large series have provided a probable incidence of two cases per 1000 patients with RA (96-99). The clinical and radiographic features of these nodules are listed in Table 14.

TABLE 14

Clinical and Radiographic Characteristics of Necrobiotic Nodules in RA

Male>Female	Single or multiple
Seropositive RA	0.5 - 7.0 cm
Subcutaneous nodules	Upper lobes/peripheral
Asymptomatic	Non-calcified
Bronchopleural fistula	50% cavitation

Like rheumatoid pleural effusions necrobiotic nodules are more common in males than females. They occur most often in patients with seropositive arthritis with subcutaneous nodules but have been reported prior to development of clinical arthritis. Changes in size may or may not parallel activity of disease. Patients are usually asymptomatic but cough, dyspnea or hemoptysis may occur as presenting symptoms. Since the nodules are frequently subpleural they may cause pleural effusion, pneumothorax or bronchopleural fistula. Radiographically they may be single or multiple and range in size from 0.5 - 7.0 cm in diameter. They may wax and wane in concert with subcutaneous nodules, completely disappear or continue to increase in size. There is a propensity for the periphery of the upper and mid lung fields; calcification has not been reported. Cavitation however occurs in approximately 50% (98-102). Lack of calcification, cavitation and increasing size make rheumatoid nodules difficult to distinguish from bronchogenic carcinoma. Fiberoptic bronchoscopy and FNA of the nodules are rarely useful as diagnostic tools. Nodules of increasing size in a smoker should

be pursued surgically with either thoracotomy or thoracoscopy (103).

2. Caplan's Syndrome

In 1953 Caplan described a characteristic radiographic pattern in coal miners with rheumatoid arthritis that was distinct from the typical progressive massive fibrosis pattern of coal miner's pneumoconiosis. The presentation was the sudden onset of rounded discrete nodules, 0.5 to 5 cm in diameter distributed throughout the lungs but primarily in the periphery (104). The course varied from regression to progression. The presence of "Caplan Syndrome" in European coal miners is more common than in the United States for unexplained reasons. The incidence of pulmonary nodules in patients with pneumoconiosis and rheumatoid arthritis is much greater than the incidence in patients with rheumatoid arthritis alone. Like necrobiotic nodules in general the nodules in Caplan's Syndrome may precede the development of clinical arthritis. The presence of dust within the nodule histologically differentiates them from the nodules of rheumatoid arthritis unassociated with pneumoconiosis (105). Since Caplan's original description these lesions have been described in the pneumoconioses associated with silica, foundry workers, roof tile manufacture, asbestosis-related workers, aluminum powder exposure and dolomite quarry workers (106).

3. Interstitial Lung Disease in RA

As with pleural and nodular forms of rheumatoid lung disease (RLD) the infiltrative form can occur before, after or with the onset of arthritis. Characteristics of interstitial involvement are presented in Table 15.

TABLE 15

Interstitial Involvement in RA

Radiographic changes (n=516)	4%
Abnormal D_{LCO} (n=40)	40%
Lung biopsy in RA (n=20)	60%
Male>Female	2:1
Age greater than	60
Subcutaneous nodules (n=30)	50%

Typical radiographic changes of basilar interstitial infiltrates are only found in approximately 4% of patients with rheumatoid arthritis (58). However, the diffusion capacities in unselected RA patients were decreased in 40%, and open lung biopsies performed on volunteers with RA showed histological evidence of interstitial inflammation and fibrosis in up to 60%

(107, 108). As in rheumatoid pleural effusion there is a 2:1 male predominance of interstitial disease which occurs most commonly after the age of 60. Subcutaneous nodules are present in half of the patients but do not seem to correlate with progression of fibrosis (109).

The clinical characteristics and variability of progression of rheumatoid interstitial lung disease do not differ from idiopathic pulmonary fibrosis and are listed in Table 16.

TABLE 16

Clinical Characteristics of Patients
With Rheumatoid Interstitial Fibrosis
n=31

Finding	Percent
Dyspnea	80
Fine rales	75
Clubbing	72
Pleuritic chest pain	25
Sjögren's Syndrome	13

The majority of patients present with dyspnea, tachypnea and the "Velcro" type rales characteristic of interstitial fibrosis. Clubbing, which is rare in RA without fibrosis, is described in 72%. Although pleuritic chest pain and Sjögren's Syndrome have been reported, they are uncommon (109).

The radiographic features of pulmonary fibrosis have been investigated and the pertinent findings are summarized in Table 17.

TABLE 17

Radiographic Characteristics of Interstitial
Fibrosis in RA

Early	- Bibasilar alveolar infiltrates
Late	- Basilar interstitial fibrosis bronchiolar ectasia-honeycomb
Concurrent	- Nodules, pleural thickening, effusions

Several retrospective studies have detailed a gamut of radiographic changes seen in patients with RA and fibrosis.

During the early stages, chest radiography usually reveals bilateral, soft alveolar type infiltrates located in the bases. The early stage is followed by incomplete clearing with residual fibrosis. As the fibrosis progresses there is bronchiolar ectasia producing the appearance of a honeycomb lung. These changes have been confirmed by CT exam (70, 97, 110, 111). Concurrent radiographic abnormalities may include pulmonary nodules (20%) and pleural fibrosis (17).

Although laboratory abnormalities are numerous, findings that may be clinically pertinent are summarized in Table 18.

TABLE 18

Laboratory Characteristics of Interstitial Fibrosis in RA

Rheumatoid factor	- high
C_4 complement	- low
Alpha 1 antitrypsin	- M_1 M_2 phenotype
BAL abnormalities	

RA patients with pulmonary fibrosis have significantly higher RF titers and lower C_4 levels than the general RA population. There is an inverse correlation between the RF titer and C_4 level suggesting RF immune complexes may promote RLD via activation of the classical complement pathway (109).

Recent evidence has shown an intriguing association between α 1 antitrypsin phenotypes and the susceptibility to rheumatoid interstitial lung disease. Patients with RA interstitial fibrosis have a 50% incidence of non MM (MZ or MS) phenotypes of α 1 antitrypsin when compared to controls and to RA patients without pulmonary involvement who have a 12-14% incidence (112). Recently Michalski has extended these observations to show that M_1 M_2 subtypes of the M phenotype are increased in RA patients as a whole and are highly associated with RA interstitial fibrosis (113). These observations may be important, because it is reasonable to postulate that protease release during lung inflammation may be partially responsible for pulmonary damage due to the lack of α 1 antitrypsin deactivation in rheumatoid lung disease.

The clinical course of RA interstitial fibrosis is extremely heterogeneous from indolent to rapidly progressive respiratory insufficiency and death within months. Early diagnosis in an active alveolitis phase has been suggested as a way to improve outcome by early initiation of treatment. Results of bronchoalveolar lavage (BAL) have demonstrated a myriad of abnormalities but none is currently considered a marker of rapidly progressive disease. Although there is incomplete

agreement, high levels of neutrophil elastase or a high percentage of BAL PMN's have correlated with diminished FVC and D_{LCO}. Patients with lymphocytosis on the other hand showed no evidence of interstitial lung disease despite high levels of neutrophilic chemotactic activity and neutrophilic products (114). Although these data may be extended in the future there is no current clinical role for BAL in staging and management of rheumatoid arthritis.

Therapeutic agents that have been investigated in the treatment of RA interstitial fibrosis are listed in Table 19.

TABLE 19

Therapy of Interstitial Fibrosis in RA

Corticosteroids	<40 mg/d or 40 mg/d or 1 mg/kg/d
Methotrexate	20 to 40 mg/wk
Azathioprine	100 mg/d

Results of treatment with corticosteroids have been equivocal. A dose of <40 mg/d was associated with progression of disease (115). Treatment with 40 mg/d for 3 months followed by a taper to 10 mg/d showed a 6 month improvement followed by deterioration (116). Non specific fibrosing alveolitis patients with a neutrophilic alveolitis by BAL treated with 1 mg/kg/d did not deteriorate over a 12 month period; however, the study was uncontrolled and there is evidence that similar patients will not deteriorate in this same time frame (117).

There is one report in which methotrexate was administered to two patients at a dose of 20 or 40 mg/wk. Both cases were associated with radiographic improvement but follow-up is unknown (118). One report of Azathioprine administered at a dose of 100 mg/d resulted in slow pulmonary function improvement over 5 years despite worsening of arthritis (119).

Since spontaneous remission of RA interstitial fibrosis is highly unusual, a trial of therapy may be justified, particularly in patients with rapidly deteriorating function. Since there are no proven treatment protocols a trial of high dose corticosteroids followed by immunosuppressive agents including methotrexate or azathioprine is not unreasonable. The use of cyclosporin has yet to be investigated.

C. The Airway in RA

The syndrome of bronchiolitis obliterans has been classically described as a small airway obstructing lesion following viral pneumonias and toxic fume inhalations. In 1977 Geddes was the first to describe a similar lesion in patients with RA. Similarly, bronchiolitis obliterans with organizing pneumonia (BOOP) was first classified as an unusual pathologic form of BO in patients with cryptogenic fibrosing alveolitis or usual interstitial pneumonitis. BOOP has only recently been shown to be a unique clinical entity which usually follows an episode of viral pneumonia. This lesion has only recently been reported in association with RA.

1. Bronchiolitis obliterans (BO)

Following Geddes observation of idiopathic bronchiolitis obliterans occurring in patients with RA there have been sufficient reports in the literature to confirm this syndrome. The characteristics of patients with BO and RA are presented in Table 20 (120-122).

TABLE 20

Clinical Characteristics of
Bronchiolitis Obliterans and RA

Female>Male	10:1
m age	>50 years
Seropositive	RF≃100%, ANA≃50%
RA (duration)	2-31 years
Sjögren's Syndrome	50%
Dyspnea	rapid onset
Rales	bilateral

Unlike most respiratory complications of RA, the syndrome of BO occurs almost exclusively in females. The mean age is greater than 50 years. Patients are virtually all rheumatoid factor seropositive, most often with high titers, and many are ANA positive. The articular disease is most often nodular and deforming with a duration which varies from 2 to 31 years. Half of the patients have an associated Sjögren's Syndrome, and half had received either penicillamine or gold therapy or both during the course of their RA. However, no causal association of BO with penicillamine or gold therapy has been found. Indeed, there are clearly documented cases unassociated with the use of these modalities. The onset of dyspnea is rapid and associated with bilateral rales which clearly distinguishes this type of airway obstruction from that usually seen in chronic obstructive pulmonary disease.

Laboratory findings of patients with BO and RA are listed in Table 21 (120-123).

TABLE 21

Laboratory Characteristics of
Bronchiolitis Obliterans in RA

CXR	Hyperinflation
CT of chest	Patchy infiltrates
Spirometry	Small and large airways obstruction
D_{LCO}	Normal
Pathology	Predominantly bronchioles Airway narrowing Fibrosis
Immunoglobulin deposition	IgM, IgG in bronchiolar and alveolar walls

The chest radiograph most often shows hyperinflation without parenchymal infiltration. However, chest CT has delineated irregular patchy infiltrates that can be either central or peripheral in location (124). Pulmonary function tests show airway obstruction that begins in the small airways and progresses to involve the large airways. The D_{LCO} is normal when corrected for alveolar volume. These changes are reflected in arterial blood gases which indicate mild hypoxemia, hypocapnia and respiratory alkalosis.

Lung biopsies have confirmed small airway involvement with early changes of mononuclear cell infiltration of peribronchiolar tissue. There is severe luminal narrowing and ulceration but sparing of alveolar ducts. Late in the disease there is complete luminal obliteration with replacement by collagenized fibrous tissue (122). Immunofluorescence studies show deposition of IgM and IgG along bronchiolar and alveolar walls again suggesting an immunologically mediated lung injury (125-127).

The course of BO and RA is most often fulminate with death in respiratory failure occurring on average 18 months after onset of symptoms (123). Patients with fulminant disease have not shown a response to corticosteroids or bronchodilators. Experience with cytoxic agents (cyclophosphamide, azathioprine) is limited, but the report of an occasional case in which these agents have appeared to halt progression make their use warranted in patients with rapidly progressive disease (125, 126).

2. Bronchiolitis Obliterans With Organizing Pneumonia

An idiopathic, corticosteroid responsive bronchiolitis distinct from BO was first described by Grinblat in 1981 (128). Unique features were further delineated by Davison and Epler who named the condition bronchiolitis obliterans with organizing pneumonia (BOOP) (129, 130). Yamamoto and others have described the clinical characteristics of this syndrome in patients with RA which are listed in Table 22 (123, 131).

TABLE 22

Clinical Characteristics of Bronchiolitis Obliterans With Organizing Pneumonia and RA
n=10

Female>Male	10>1
$\bar{m}$ age	58 years
Seropositive	$\simeq$ 80%
RA (duration)	6 weeks-30 years
Dyspnea, cough	rapid onset
Rales	not characteristic

Patients with RA and BOOP are also almost exclusively females. The mean age is 58 years. Patients have usually been RA seropositive, commonly with high titers; an insufficient number of patients with measurements of the ANA have been reported to reliably determine the prevalence of positivity. Articular disease is usually erosive, and nodules have not been reported. The duration of articular disease prior to onset of symptoms has been from 6 weeks to 30 years. The onset of dyspnea is rapid and the physical exam of the chest is most often normal, although rales have occasionally been described (123, 131).

Laboratory findings in BOOP are distinct from BO and are listed in Table 23.

TABLE 23

Laboratory Characteristics of Bronchiolitis Obliterans With Organizing Pneumonia and RA

CXR	Bilateral alveolar infiltrates
CT of chest	Peripheral and lower lobe
Spirometry	Restrictive
D_{LCO}	Decreased
Pathology	Alveolar ducts Airway narrowing-mild Fibrosis-mild
BAL	Lymphocytosis ↓ $\frac{CD_4}{CD_8}$

The chest radiograph most often shows normal to small lung volumes with patchy alveolar, ground glass infiltrates that become bilateral over time. There is a lower lobe predilection with a distinctly peripheral distribution. CT scans have confirmed the peripheral and lower lobe location and are useful in choosing an optimal biopsy site. Spirometry shows a predominantly restrictive pattern and D_{LCO} is uniformly decreased. Open lung biopsy is the procedure of choice for diagnosis although transbronchial biopsy has occasionally been successful (129, 130, 132, 133). The distinguishing histological feature of BOOP is the uniform presence of plugs of fibrin and granulation tissue filling alveolar ducts and alveoli with less involvement of the bronchioles. These plugs consist of collagen and elastin with chronic inflammatory cells. The underlying pulmonary architecture is preserved and fibrosis is initially minimal, and honeycomb changes are only rarely reported (128-130, 134). Bronchoalveolar lavage fluid contains an increased number of lymphocytes with a decreased CD_4/CD_8 ratio; this finding is non specific and therefore BAL is not useful as a diagnostic technique (135, 136). Immune complex deposition in the lung has not been investigated in BOOP.

Patients with RA and BOOP have been reported to have a better prognosis than patients with idiopathic BOOP. All cases have responded clinically and radiographically to treatment with 40-80 mg/d of prednisone (123). Clinical improvement is seen within several days and the usual outcome is complete physiologic and radiographic clearing. Relapse has recurred with discontinuance of steroids and the duration of treatment is unknown (130).

D. Other Rare Respiratory Tract Manifestations of RA

Rarely reported manifestations of RA are listed in Table 24 (12).

TABLE 24

Unusual Respiratory Tract Manifestations of RA

Upper airway
Idiopathic hemosiderosis
Chronic eosinophilic pneumonia
Decreased rib cage compliance
Upper lobe fibrosis

RA may involve the small joints of the larynx, specifically the cricoarytenoid joints. Lawry studied 44 RA patients with indirect laryngoscopy and CT scanning of the larynx. Sixty six percent had abnormalities on indirect laryngoscopy which included vocal cord edema, nodules and decreased mobility. Fifty five percent demonstrated CT abnormalities. Sore throat and difficulty during inspiration were the only symptoms predictive of abnormalities. The presence of interstitial fibrosis in 36% was the only lower respiratory manifestation that correlated with laryngeal involvement (137). In rare cases laryngeal involvement has led to severe upper airway obstruction with stridor and may require tracheostomy (138). Response to an increase in corticosteroids has been poor.

Four cases of idiopathic hemosiderosis and at least three cases of chronic eosinophilic pneumonia have been reported in association with RA (138-140). A reduction in rib cage compliance has also been reported. The resulting increase in diaphragmatic breathing may contribute to dyspnea (141).

Upper lobe fibrosis with apical cavities similar to that seen in ankylosing spondylitis have been reported. Autopsy confirmed necrobiotic nodules and excluded other causes (142, 143).

IV. Progressive Systemic Sclerosis (PSS)

Progressive systemic sclerosis (PSS) has been divided into two broad categories based on clinical findings: 1) a limited form and 2) a diffuse form (144, 145). Approximately 60% of patients with scleroderma have limited disease usually manifest by the CREST Syndrome of calcinosis, Raynaud's phenomenon, esophageal involvement, sclerodactyly, and telangiectasias. These patients tend to be older women with clinical findings

present for years or even decades before appearance of systemic involvement. Patients with diffuse disease tend to be young or middle aged women with a more abrupt onset of symptoms with prominent Raynaud's phenomenon, constitutional symptoms and wide spread skin involvement.

A. Interstitial Fibrosis in PSS

The most common respiratory manifestation of both forms of PSS is interstitial fibrosis. Although the exact prevalence is unknown an estimate based on the method of detection is listed in Table 25.

TABLE 25

Prevalence of Interstitial Lung Disease in PSS
n=195

Finding	Percent
Symptoms	54
Radiographic abnormalities	53
Abnormal PFT	92
Postmortem	74

A summary of eleven studies of 195 cases of PSS showed that 54% were symptomatic with dyspnea and 53% had radiographic abnormalities consistent with interstitial fibrosis. Ninety-two percent had abnormal pulmonary function tests commonly a reduction in DLCO, and 74% had postmortem changes of interstitial fibrosis (146, 147).

The clinical characteristics of patients with interstitial fibrosis are listed in Table 26.

TABLE 26

Clinical Characteristics of Patients with Interstitial Fibrosis in PSS

Symptom or Sign	First Evaluation	Later Development	Total n=1088
	Percent		
Dyspnea	49	21	69
Dyspnea at rest	5	10	15
Cough	11	18	29
Bibasilar rales	26	22	48

Respiratory signs and symptoms of PSS with interstitial fibrosis are similar to those seen in patients with idiopathic pulmonary fibrosis (IPF). Seventy percent have dyspnea during the course of the disease and 15% progress to dyspnea at rest. One-third have a non productive cough occasionally associated with wheezing. Characteristic "velcro" rales at the lung bases occur in 50%. In contrast to IPF clubbing is an unusual finding; a phenomenon that may be due to the presence of sclerodactyly (148, 149).

Thoracic imaging abnormalities in PSS have been extensively reported. Changes in the plain chest radiograph differ slightly in the two forms of disease and are listed in Table 27.

TABLE 27

Radiographic Characteristics of Patients with PSS

Finding	Diffuse n=77	Limited n=88
	Percent	
Pulmonary fibrosis	40	33
Pattern		
Reticulonodular	35	18
Reticular	0	10
Nodular	5	5
Pulmonary Artery ↑	0	6
Microcalcification	14	67
Rib notching	17	0

Plain chest radiographs may be normal even in symptomatic patients with pulmonary function abnormalities (150). Only 40% of patients with diffuse PSS and 33% with the CREST Syndrome had definite changes of pulmonary fibrosis. The pattern in diffuse PSS was more likely to be reticulonodular and in CREST to be reticular which is consistent with a longer duration of disease. Both of these patterns occur more frequently at the lung bases and may progress to a honeycombed pattern of fibrosis often with loss of lung volume (151, 152). Pulmonary artery enlargement did not occur in diffuse disease but was present in 6% of patients with the CREST Syndrome. As would be expected microcalcifications were common in the CREST Syndrome (67%) and relatively uncommon in diffuse disease (14%). Pulmonary calcification does not correlate with peripheral subcutaneous

tissue calcification (149). Although relatively uncommon, the finding of bone resorption (rib notching) on the superior aspect of the upper ribs may be somewhat specific to patients with interstitial fibrosis and diffuse PSS (150, 153).

Due to the poor correlation of plain chest radiographic abnormalities and the autopsy findings of interstitial fibrosis, high resolution computed tomography (HRCT) has been investigated as a tool for early diagnosis. Studies have shown that the technique is more sensitive in identifying minimal interstitial changes but is non specific with similar changes described in IPF, rheumatoid lung disease and mixed connective tissue disease (151, 154). In one report Harrison found abnormal cell profiles in bronchoalveolar lavage (BAL) fluid of patients with normal chest radiographs and abnormal HRCT, suggesting a role in early disease detection (154). These studies show that HRCT is more sensitive than plain chest radiography but the prognostic value and therapeutic implication have yet to be determined. Currently HRCT has no place in the clinical evaluation of patients with scleroderma.

Gallium -67 lung scans have also been investigated to determine the presence of acute alveolitis (inflammation) which is thought to be the precursor of all forms of interstitial fibrosis. Although an increased gallium uptake in the lung has been shown to correlate with an increased number of activated macrophages, it has not correlated with duration of disease, clinical symptoms, PFT's, or chest radiographs (155, 156). Like HRCT, Gallium -67 scanning currently has no place in the clinical evaluation of patients with scleroderma.

Pulmonary function abnormalities of patients with PSS and radiographic changes of interstitial fibrosis are listed in Table 28.

TABLE 28

Pulmonary Functional Characteristics
of Patients With PSS

Finding	Diffuse n=77	Limited n=88	Total n=165
		Percent	
Normal	37	28	32
Restrictive	34	23	28
Obstructive	11	23	17
Isolated D_{LCO} reduction	18	26	22

The study group comprised 165 nonsmokers who had diffuse or limited scleroderma but no other known lung disease. One third

of the 165 patients had normal lung function. Overall, a restrictive pattern was found in 28% and airflow obstruction in only 17%. Airflow obstruction was twice as common in patients with limited disease and most likely reflected chronicity and airway distortion similar to that reported in idiopathic interstitial fibrosis. The presence of airflow obstruction was also correlated with a poor prognosis. An isolated reduction of D_{LCO} without other abnormality was present in 22% of patients in the total study group (149, 150). In other studies the reduction in D_{LCO} parallels the severity of the restrictive ventilatory deficit and correlates with development of pulmonary artery hypertension (157, 158).

Patients with unspecified types of PSS have been evaluated by BAL in an attempt to establish early disease. The findings using this technique are extremely variable and are listed in Table 29.

TABLE 29

Bronchoalveolar Lavage Fluid
Findings in PSS

Granulocytes
Lymphocytes
Immune complexes
Activated macrophage products
Anticollagen
IgG

Overall 50 to 60% of patients with scleroderma have abnormal findings on BAL. Granulocytosis and lymphocytosis have both been associated with normal and with severely impaired lung function. The presence of immune complexes, activated macrophage products, anticollagen antibody and an increase in IgG only support the role of immunologically mediated inflammation in the pathogenesis of interstitial fibrosis in PSS. The clinical role and prognostic value of BAL in PSS has yet to be determined (157, 159-161).

Corticosteroids, immunosuppressive/cytotoxic agents, colchicine and plasmapheresis do not modify the course of progressive interstitial fibrosis in PSS (162-166). Two recent studies have found that treatment with D-penicillamine, an antifibrotic immunosuppressive agent, alleviated skin thickening and stabilized or improved D_{LCO} in patients with PSS (167, 168). Although these studies had several methodologic problems, the results suggest that chronic D-penicillamine therapy is a reasonable choice in patients with progressive interstitial lung disease and PSS.

B. Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is a well recognized complication of scleroderma. PAH has been reported in 33% of patients with diffuse disease and 50% of patients with limited disease (169). PAH can occur secondary to severe interstitial fibrosis and restrictive lung disease, but it has also been reported with limited scleroderma independent of the degree of interstitial fibrosis (158). Isolated PAH is more common in patients with longstanding Raynaud's phenomenon and is most often associated with rapid progression and death (150). Histologic lesions are the same as reported in primary pulmonary hypertension. Vasodilator treatment has reduced pulmonary artery pressures but has been ineffective in retarding progression (170).

C. Unusual Manifestations

Rarely reported respiratory tract abnormalities in PSS are listed in Table 30.

TABLE 30

Unusual Respiratory Tract Abnormalities in PSS

Pleural disease
Carcinoma
Muscle weakness
Hemoptysis

Although pleural abnormalities such as fibrosis and subpleural cystic changes are frequently found at postmortem examination, clinically significant pleural disease is uncommon in PSS. Spontaneous pneumothorax has been reported but is uncommon given the degree of cystic changes (171, 172).

The incidence of bronchogenic carcinoma is increased in patients with interstitial fibrosis and PSS. Initially a propensity for bronchoalveolar carcinoma was reported, but recent publications have documented both small cell and non small cell carcinoma. The magnitude of the risk is apparently similar to idiopathic pulmonary fibrosis (173).

Respiratory muscle weakness including diaphragmatic dysfunction and respiratory failure have been reported in PSS but the clinical significance of the defect is apparently minimal (174).

Hemoptysis is also a rare complication of PSS. Case reports include hemoptysis secondary to alveolar hemorrhage and as a

result of airway telangiectasias, both occurring during rapidly progressive PSS (175, 176).

V. Polymyositis - Dermatomyositis (PM-DM)

Polymyositis-dermatomyositis (PM-DM) is a diffuse inflammatory myopathy of striated muscles that causes symmetric proximal muscle weakness principally of the limb girdles, neck and pharynx. When the characteristic heliotrope rash is present the disorder is termed dermatomyositis (177). Although there are subtle histologic differences, the systemic manifestations are similar and for the purpose of this review they will be considered a single entity.

A. Aspiration Pneumonia

Recurrent aspiration pneumonia is the most frequent pulmonary complication of PM-DM. The clinical characteristics of patients with a propensity to develop an aspiration pneumonia syndrome are listed in Table 31.

TABLE 31

Clinical Characteristics of PM-DM
Patients Prone to Aspiration
n=42

Finding	Percent
Dysphagia	43
Weight loss	38
Dysphonia	13

The pathophysiology of the pharyngeal dysfunction involves inflammatory infiltrates and weakness of the striated muscles of the soft palate, pharynx and upper esophagus. During the course of PM-DM 43% of patients develop dysphagia, 38% experience weight loss and 13% have dysphonia. When dysphagia is present it is frequently associated with nasal regurgitation and weakness of the muscle of deglutition. Weight loss is secondary to the dysphagia and dysphonia portends severe pharyngeal muscle involvement. With either dysphagia or dysphonia there is vallecular pooling, pharyngeal reflux and disorganized pharyngeal emptying with occasional tracheal aspiration (178-180). In severe diffuse myopathy with muscle bundle atrophy cricopharyngeal achalasia occurs which predisposes to massive aspiration (181).

The syndromes of aspiration pneumonia can be classified by the nature of the aspirated material. These include non toxic

substances such as food and buffered gastric contents, toxic material such as unbuffered gastric acid and most commonly oropharyngeal secretions with pathogenic organisms. Patients with PM-DM are susceptible to each of these syndromes.

The treatment of aspiration pneumonia in PM-DM is specific to the material aspirated. Pharyngeal achalasia has been successfully treated surgically with cricopharyngeal myotomy (181).

B. Respiratory Muscle Dysfunction

Histopathologic studies of patients with long standing PM-DM have shown typical inflammatory and degenerative changes in the intercostal muscles, the accessory muscles of respiration and in the diaphragm (182). Clinically these changes are manifest by symptoms of dyspnea secondary to respiratory muscle weakness which may progress to respiratory failure. Clinical findings indicative of muscle disease in patients with PM-DM are listed in Table 32.

TABLE 32

Clinical Manifestations of
Respiratory Muscle Dysfunction in PM-DM
n=50

Finding	Percent
Weakness of proximal muscles	100
Dyspnea	10
Weakness of respiratory muscles	10
Respiratory failure	7

Fifty patients were followed from initial diagnosis of PM-DM for 17-25 years; among this typical patient population, 70% presented with proximal muscle weakness, and there was universal involvement at long term follow-up. Ten percent presented with dyspnea and 10% were thought to have respiratory muscle weakness on extended follow-up. True hypercapnic respiratory failure unassociated with interstitial lung disease occurred in this population in only 7% (183).

Rochester studied a highly selected referral population of patients with severe muscle involvement in PM-DM. Respiratory muscle and pulmonary function abnormalities are listed in Table 33.

TABLE 33
Respiratory Muscle and Pulmonary
Function in PM-DM
n=38

Finding	Percent Predicted
Maximal inspiratory force (P_{imax})	50
Maximal expiratory force (P_{emax})	50
Respiratory muscle strength (RMS)	46
Vital capacity (VC)	62

Both maximal static inspiratory pressures (P_{imax}) and maximal static expiratory pressures (P_{emax}) were reduced to 50% of predicted. These findings indicated that muscle weakness was evenly distributed between inspiratory and expiratory muscles of respiration. This finding is unique to PM-DM neuromuscular weakness. Respiratory muscle strength was calculated as the average of P_{imax} percent of predicted and P_{emax} percent of predicted and found to be reduced to 46%. This reduction in muscle function resulted in hypercapnic respiratory failure in 38% with severe involvement.

Mean vital capacity (VC) was on average 60 percent predicted. These authors concluded that respiratory muscle weakness alone was sufficient to account for hypercapnia when RMS is less than 30% of normal. Vital capacity is a useful test to predict hypercapnia; a reduction below 55% of predicted is associated with hypercapnia in PM-DM patients with isolated muscle disease (184).

C. Interstitial Lung Disease

Interstitial lung disease (ILD) in association with PM-DM was first reported in 1956 (185). This complication is now well recognized with an overall incidence of 3 to 10% (12, 186). Patients have been divided into three groups based on onset, symptomatology and radiographic abnormalities (Table 34).

TABLE 34

Clinical Characteristics of Patients
With ILD in PM-DM
n=42

Finding	Percent
Insidious onset with infiltrates	60
Acute onset with infiltrates	30
Asymptomatic with infiltrates	10

Although the reported incidence varies between series, approximately 60% present with slowly progressive dyspnea on exertion. Chest radiographs show diffuse reticulonodular disease more prominent in the lung bases. The lung disease may precede the muscle weakness or be superimposed on well established muscle disease. Thirty percent develop a Hamman-Rich type syndrome with the acute onset of fever, dyspnea and non productive cough. Chest radiographs frequently show a granular or "ground glass" appearance superimposed on the usual reticulonodular infiltrate. With this pattern the muscle disease may be overlooked due to the limitation of activity by dyspnea. A minority will present without pulmonary symptomatology but with characteristic radiographic and pulmonary functional evidence of ILD (187-189). Circulating antibody to the enzyme histidyl-t RNA-synthetase (anti-JO-1) has been demonstrated in 50-70% of patients with ILD complicating PM-DM. Anti-JO-1 antibody is found in less than 20 percent of PM-DM patients without ILD (190, 191).

The onset of ILD in patients with PM-DM has generally been associated with a poor prognosis with a high mortality. However there have been several reports of a corticosteroid responsive form associated with long term survival. Acute or insidious onset of symptoms, muscle involvement or radiographic changes do not predict outcome of patients with ILD in PM-DM. A recent study and review of the available literature indicates that histologic patterns obtained from open lung biopsy may be the best predictor of patient outcome (192) (Table 35).

TABLE 35

Histologic Patterns and Outcome
in Patients With ILD and PM-DM
n=42

Histologic Pattern	Percent Survival
Bronchiolitis obliterans with organizing pneumonia (BOOP)	67
Cellular interstitial pneumonitis (CIP)	50
Usual interstitial pneumonitis (UIP)	37
Diffuse alveolar damage (DAD)	25

Patients with bronchiolitis obliterans with organizing pneumonia (BOOP) had the best prognosis, with a 67% survival rate. This response is similar to that in patients with BOOP and RA and to patients with BOOP without collagen vascular disease (130, 193). Patients classified as cellular interstitial pneumonitis (CIP) had a 50% survival rate. This pattern of cellularity is similar to desquamative interstitial pneumonitis

(DIP) as originally described by Liebow and Carrington. Patients with usual interstitial pneumonitis (UIP) had only a 37% survival rate with most following a slowly progressive respiratory failure course in spite of corticosteroid and immunosuppressive therapy. Patients with the pattern of diffuse alveolar damage (DAD) had only a 25% survival and confirmed the clinical observations that patients with PM-DM may develop an acute Hamman-Rich type syndrome. This prognosis is similar to patients with DAD unassociated with collagen vascular disease (193). Results of these studies have led some to an aggressive diagnostic approach to include open lung biopsy to more accurately delineate the inflammatory process (194). Enthusiasm for this approach should be tempered by the fact that 3 of 15 patients developed ARDS with rapid demise following open lung biopsy (192). The role of BAL in patients with IF and PM-DM remains unclear. All patients with PM-DM have increased numbers of inflammatory cells unassociated with pulmonary function or radiographic changes of ILD. The etiology of the inflammatory alveolitis in PM-DM is less clear than in SLE or RA. In a limited number of patients with PM-DM and ILD neither circulating immune complexes, immunoglobulin, or complement deposition in lung tissue have been detected (195, 196). An empiric clinical trial of corticosteroids followed by immunosuppressive/cytotoxic agents in unresponsive patients has been recommended (194).

VI. Mixed Connective Tissue Disease (MCTD)

The term mixed connective tissue disease (MCTD) was first used by Sharp in 1972 to identify patients with clinical features of SLE, PSS and PM-DM who had high titer of circulating antiribonucleoprotein antibody (RNP) (197). Although anti-RNP is uncommon in SLE, PSS, PM-DM, RA and other rheumatologic diseases its specificity has been questioned. Patients originally diagnosed as MCTD may become antibody negative or progressed to classical manifestations of either PSS or SLE (198). Nevertheless MCTD is generally considered a unique clinical entity with pleuropulmonary manifestations that overlap with the classic collagen vascular diseases (199).

The major pleuropulmonary manifestation of MCTD are listed in Table 36.

TABLE 36

Pulmonary Manifestations of MCTD

Thromboembolism
Pulmonary hemorrhage
Pleural effusion
Pulmonary artery hypertension
Pulmonary vasculitis
Aspiration
Respiratory failure
Interstitial fibrosis

Respiratory tract manifestations have been described in 20-80% of patients with MCTD (200-203). Frequency of respiratory abnormality is related to the predominant clinical expression of the collagen vascular disease and have no unique features of MCTD. Thromboembolism, pulmonary hemorrhage and pleural effusions have been reported in patients with predominant SLE-like clinical features. Pulmonary artery hypertension and vasculitis are commonly seen in patients with PSS-like clinical features. Aspiration and respiratory failure occur in the PM-DM-like group. Interstitial fibrosis however is common to all clinical presentations but is indistinguishable clinically, radiographically and histologically from that seen in PSS and idiopathic pulmonary fibrosis (199).

Specific treatment regimens of pulmonary complications have not been studied. Pleural disease has responded to corticosteroids and treatment with non steroidal drugs. pulmonary fibrosis has been unresponsive to corticosteroids, immunosuppressives and cytotoxic agents. The overall prognosis is estimated to be similar to SLE but better than PSS (204).

VII. Sjögren's Syndrome (SS)

Sjögren's Syndrome (SS) is defined by the clinical features of keratoconjunctivitis sicca and xerostomia. Histologically there is destruction of exocrine glands with wide spread lymphocytic infiltration. Involved organs show activated T-helper cells as well as activated B cells producing monoclonal immunoglobulins. Natural killer cells are either defective or absent (205, 206). Primary SS occurs in postmenopausal women without an associated collagen vascular disease. Secondary SS occurs in a more heterogeneous population and is associated with a collagen vascular disease. Although secondary SS is highly associated with RA it has also been described in SLE, PM-DM, PSS, primary biliary cirrhosis and psoriasis (207).

Clinical characteristics of SS are listed in Table 37.

TABLE 37

Clinical Characteristics of Sjögren's Syndrome

Finding	Primary n=40	Secondary n=26	Control n=100
		Percent	
Asymptomatic	58	81	100
Dry cough	18	3	0
Dyspnea	25	4	0
Xerotrachea	13	0	0
Bibasilar rales	25	35	12
Pleurisy	0	8	0
Positive radiograph	43	62	10

In the past the clinical characteristics of SS were difficult to evaluate since primary and secondary disease were not separated. Recently Papathanasiou has shown that primary SS is a disease of women. Of 66 patients studied 64 were females and 2 were males both of whom had secondary disease. The control group was 100 age and sex matched, life long non-smokers. A majority of patients were asymptomatic. When symptoms occurred, they were generally in patients with primary disease. Bibasilar rales and basilar reticulonodular infiltrates did not separate primary from secondary disease. However, dyspnea on exertion and clinically significant xerotrachea manifest by a dry, hacking, exhaustive cough occurred significantly more commonly in primary SS. Pleurisy and pleural effusions apparently are limited to patients with secondary SS and RA (208, 209). Thus, xerotrachea with a dry hacking cough is the most characteristic finding of primary SS. There are no clinically significant respiratory manifestations of secondary SS except those of the primary collagen vascular disorder.

A. Airway Disease in SS

Pulmonary function findings in patient with primary SS are presented in Table 38.

TABLE 38

Pulmonary Function Abnormalities in SS

Finding	Primary SS n=40	Control n=100
	Percent Predicted	
TLC	95	98
$FEV1.0/_{FVC}$	83	83
$MMEF_{25-75}$ reduced	62	64
D_{LCO}	91	94

Airflow obstruction in primary SS has been controversial. Earlier studies of small numbers of patients revealed significant airways obstruction and restriction of lung volume (210). Recently PFT's have been re-evaluated and, when compared with normal non-smoking controls there was no significant difference in TLC, $FEV1.0/_{FVC}$, $MMEF_{25-75}$ or D_{LCO} (208). The authors concluded that airflow obstruction is not clinically significant in primary SS (211). The reported increased incidence of atelectasis, bronchitis and bronchiectasis may be manifestations of secondary SS (203, 212). Upper airway obstruction with a tracheal mass or tracheal compression with nodes has been reported but is distinctly uncommon (213, 214).

B. Lymphocytic Infiltration of Lung Parenchyma in SS.

1. Lymphocytic alveolitis in primary SS.

Results of bronchoalveolar lavage (BAL) have been reported in patients with primary SS with normal chest radiographs and without signs and symptoms of pulmonary disease. Results of these investigations are presented in Table 39 (215).

TABLE 39

Bronchoalveolar Lavage in
Patients With Primary SS
n=29

Finding	Percent
Normal	45
Lymphocytic predominance	38
Neutrophilic predominance	17

Over one half of patients had abnormal bronchoalveolar lavage. Lymphocytosis was most common occurring in 38%; however,

a neutrophilic predominance was present in 17%. When a lymphocytosis was present the predominant cell was the T helper cell (CD_4) and the CD_4:CD_8 ratio was normal. Patients with neutrophilia had an increase in CD_8 lymphocytes and a decrease in the CD_4:CD_8 ratio. Patients with either lymphocytosis or neutrophilia were asymptomatic, but patients with neutrophilia and increased T_8 cells had a lower TLC and D_{LCO} than those with lymphocytosis (216). The clinical relevance of these observations have yet to be determined.

2. Lymphocytic Interstitial Pneumonitis and Fibrosis in SS.

Lymphocytic interstitial pneumonitis (LIP) and overt interstitial fibrosis have both been reported in SS. LIP is most often associated with primary SS and is a clinically benign disease. Chest radiographs show delicate bibasilar infiltrates and there is a mild reduction of the diffusing capacity. Patients are either asymptomatic or have mild dyspnea. Hilar and mediastinal lymph nodes are not involved. Histology shows pleomorphic mononuclear infiltrates with lymphocytes, plasma cells and histocytes in the interstitium without significant fibrosis (215). The process was first described by Liebow and Carrington, and they postulated that LIP represented primary SS in the lung (217). LIP associated with SS accounts for 25% of all cases of LIP in the literature. The natural history of LIP in primary SS has not been adequately described, but it is likely that most patients have a stable or only mildly progressive course (209). A rare patient with LIP and primary SS will progress to a rapidly progressive syndrome typical of idiopathic pulmonary fibrosis. The rapidly progressive patients typically have extraglandular involvement, autoantibodies, hyperglobulinemia, and circulating immune complexes (218).

Since the course is usually mild but unpredictable, frequent observation has been recommended with corticosteroid or immunosuppressive intervention only if there is deterioration.

The typical syndrome of progressive interstitial fibrosis is more common in secondary SS associated with RA. Clinically these patients develop progressive dyspnea associated with reticulonodular infiltrates on chest radiography and a progressive decrease in the diffusing capacity. Histology shows lymphocytic infiltration of the lung parenchyma associated with frank pulmonary fibrosis (209, 219). These patients have a prognosis similar to idiopathic pulmonary fibrosis, and treatment can only be inferred from patients with IPF.

3. Lymphocytic Masses in SS

The spectrum of lymphocytic involvement in the lung in SS includes pseudolymphoma, malignant lymphoma, lymphomatoid granulomatosis and reticulum cell sarcoma.

Approximately 25% of patients with SS develop tumor-like lymphoproliferation in extraglandular sites; most commonly the lungs, kidneys, salivary glands and reticuloendothelial system. Without histologic proof of malignancy these disorders are termed "pseudolymphoma". Histologic examination shows aggregates of mature large and small lymphocytes, plasma cells, and reticulum cells with preservation of lymphoid architecture (209, 220, 221). Chest radiographs show single or multiple parenchymal masses often with hilar or mediastinal adenopathy (222). Several authors have suggested that pseudolymphoma is a premalignant condition; however, progression to malignancy has not been universal and the theory remains untested (209, 217, 223). Pseudolymphoma associated with hypogammaglobulinemia, negative rheumatoid factor, and monoclonal gammopathy is thought to be more likely to evolve into malignancy (224, 225).

An estimated 5% of patients with SS develop a lymphoreticular malignancy (226). This increase in the incidence of lymphoma related malignancies is present in both primary and secondary SS. The risk of lymphoma is thought to be 44 times greater in persons with SS than in the normal population (227). Histologic findings include malignant lymphoid infiltrates, with immature lymphocytes and loss of nodal architecture (227-229). Chest radiographic findings include diffuse opacities, bilateral masses or unilateral nodules. Malignancy occurs more frequently in patients with severe SS associated with extraglandular complications such as neuropathy, spenomegaly and generalized adenopathy (230, 231). Most lymphomas in SS are of B-cell origin, but T cell malignancies have also been reported (232, 233).

TABLE 40

Comparative Spectrum of Respiratory Tract Involvement in CVD

Site	SLE	RA	PSS	PM-DM	SS
Pleura	+++	++	0	0	+
Lung parenchyma					
Acute pneumonitis	++	0	0	++	0
Chronic fibrosis	+	++	+++	++	++
LIP	+	0	0	0	+++
Pulmonary hemorrhage	+	0	+	0	0
Nodules	0	++	0	0	0
Bronchiolitis	+	+++	0	+	+
Muscles					
Diaphragm	+++	0	+	++	0
Pharyngeal	0	0	0	++	0
Vessels					
PPH	+	+	0	0	0
Larynx	+	++	0	0	++
Esophagus	0	0	+++	0	0
Aspiration	0	0	++	+++	0

Summary

This review has broadly covered respiratory tract involvement in the classic collagen vascular diseases. Table 40 in the protocol summarizes the comparative spectrum of involvement encountered in this group of diseases.

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