The lung in systemic autoimmune disorders

SA Papiris
Review article

The respiratory system in connective tissue disorders

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Thoracic Manifestations of Systemic Autoimmune Diseases: Radiographic and High-Resolution CT Findings

Jennifer P. Mayberry, MD • Steven L. Primack, MD • Nestor L. Müller, MD, PhD


Allergy 2003; 60: 715–734
The majority of patients with SLE develop pleural or pulmonary disease in the course of their illness. Respiratory involvement is more common in men than in women.

<table>
<thead>
<tr>
<th>Table 1. Pleuropulmonary manifestations of systemic lupus erythematosus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
</tr>
<tr>
<td>Pleuritis with or without effusion</td>
</tr>
<tr>
<td>Upper and lower airways disease</td>
</tr>
<tr>
<td>Acute lupus pneumonitis</td>
</tr>
<tr>
<td>Alveolar hemorrhage</td>
</tr>
<tr>
<td>Organizing pneumonia</td>
</tr>
<tr>
<td>Chronic interstitial lung disease</td>
</tr>
<tr>
<td>Lymphocytic interstitial pneumonia</td>
</tr>
<tr>
<td>Nonspecific interstitial pneumonia</td>
</tr>
<tr>
<td>Usual interstitial pneumonia</td>
</tr>
<tr>
<td>Desquamative interstitial pneumonia</td>
</tr>
<tr>
<td>Respiratory muscle weakness (shrinking lung syndrome)</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Mediastinal lymphadenopathy</td>
</tr>
<tr>
<td>Lung involvement has been associated with increased mortality</td>
</tr>
</tbody>
</table>
SLE
Infectious Pneumonia
CMV - Aspergillosis
### Systemic lupus erythematosus

#### Presence and frequency of pulmonary manifestations in SLE and APS

<table>
<thead>
<tr>
<th>Pulmonary manifestations</th>
<th>SLE</th>
<th>APS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleuritis</td>
<td>40–60%</td>
<td>–</td>
</tr>
<tr>
<td>Infectious pneumonia</td>
<td>common</td>
<td>–</td>
</tr>
<tr>
<td>Acute pneumonitis</td>
<td>1.4–4%</td>
<td>–</td>
</tr>
<tr>
<td>Diffuse interstitial lung disease</td>
<td>3–8%</td>
<td>–</td>
</tr>
<tr>
<td>‘Shrinking lung syndrome’</td>
<td>Rare</td>
<td>–</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>30%</td>
<td>30%</td>
</tr>
<tr>
<td>Pulmonary hemorrhage</td>
<td>2%</td>
<td>May occur</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>5–14%</td>
<td>1.8–3.5%</td>
</tr>
</tbody>
</table>
Lupus Pleuritis

- The pleura is the most common thoracic localization of SLE. Pleural involvement may be asymptomatic although pleuritic pain is very common, affecting 45–60% of patients, and may occur without radiographically detectable chest effusion.
- Pleural involvement may be the first manifestation of SLE. Pleuritis is commonly associated with pericarditis.

Figure 1. Systemic lupus erythematosus with pleural involvement. CT scan shows pleural effusion of the left lung, as well as pericardial effusion.
The pleural effusion is uni- or bilateral, small to moderate in size (but may be massive).
Chest pain, dyspnea, cough and fever.
Serous or serosanguineous sterile exudate. The leukocyte differential count may show a predominance of neutrophils or mononuclear cells.
Spontaneous resolution of SLE effusions may occur.
Lupus pleuritis is very sensitive to small doses of systemic corticosteroids, usually providing a rapid relief of symptoms within days.
Antiphospholipid Antibody Syndrome

Antiphospholipid antibodies constitute a diverse family of antibodies that are associated with a hypercoagulable state.

Between 27% and 42% of SLE patients have aPL-ab syndrome, which is characterized by arterial and veno-occlusive disease, thrombocytopenia, and recurrent vascular thromboses and miscarriages.

Figure 5. Acute pulmonary embolism in a 66-year-old man with SLE and aPL-ab syndrome. Pulmonary CT angiogram shows a large clot in the central right lung (arrow).
CLINICAL MANIFESTATIONS OF THE ANTIPHOSPHOLIPID ANTIBODY SYNDROME

Venous thrombosis

Deep venous thrombosis, with or without pulmonary embolism
Superficial venous thrombosis
Cerebral
Retinal
Renal
Hepatic
Arterial Thrombosis
Cerebral
Peripheral
Coronary
Renal
Retinal

Obstetric: pregnancy loss, intrauterine growth retardation
Hematologic: thrombocytopenia, hemolytic anemia
Cutaneous: livedo reticularis, leg ulcers
Cardiac: valvular vegetations, intracardiac thrombus, cardiomyopathy
Neurologic: chorea, transverse myelopathy, complicated migraine, encephalopathy
Pulmonary: pulmonary hypertension, adult respiratory distress syndrome,* alveolar hemorrhage*
Renal: hypertension,* renal failure*
Gastrointestinal: abdominal pain, visceral ischemia/gangrene
Endocrine: adrenal infarction*
Antiphospholipid Antibody Syndrome

Clinical criteria for Antiphospholipid Antibody Syndrome (APS) include:
- Vascular thrombosis
- One or more episodes of arterial, venous, or small vessel thrombosis
- Confirm by imaging or histopathology (except for superficial venous thrombosis)
- Pregnancy morbidity
- One or more unexplained fetal death at 10 or more weeks of gestation, or premature birth before 34 weeks of gestation, or because of pre eclampsia, eclampsia, or placental insufficiency, or three or more unexplained consecutive spontaneous abortions at less than 10 weeks of gestation.
Antiphospholipid Antibody Syndrome

Laboratory criteria
Anticardiolipin antibody
  IgG or IgM isotype
  Medium or high titer
  On two occasions 6 weeks or more apart
Lupus anticoagulant
  Prolonged phospholipid-dependent coagulation test*
  Failure to correct by mixing with normal plasma
  Correction with addition of excess phospholipid
  Exclusion of other coagulopathies
Antiphospholipid Antibody Syndrome Treatment

- Low molecular weight heparin
- These patients may be more susceptible to the syndrome of warfarin-induced skin necrosis because of acquired functional deficiencies of protein C and/or protein S. To avoid this potential complication, we recommend delaying initiation of warfarin by at least 1 or 2 days after full heparinization, omitting a loading dose of warfarin and letting the patient become therapeutic over approximately 1 week while maintaining full heparinization.
- “High-intensity” therapy, with an international normalized ratio of more than 3.0, is associated with fewer recurrent thromboses but greater incidence of hemorrhagic complications
- Thrombocytopenic patients with the APS remain at risk for thrombosis.
- The treatment of thrombotic events in patients with antiphospholipid antibodies and thrombocytopenia is particularly challenging. Corticosteroids to achieve a platelet count of more than 50x10^9 per L concurrent with anticoagulation.
Catastrophic Antiphospholipid Antibody Syndrome

Fulminant presentation of antiphospholipid antibody-associated disease characterized by multiorgan system failure that evolves over days to weeks. 50% mortality

Renal insufficiency 80% of patients, often accompanied by hypertension occasionally malignant. The lung (70%). The most frequent type of lung injury was adult respiratory distress syndrome, presumably induced by tissue injury/ischemia and sometimes accompanied by diffuse alveolar hemorrhage; Pulmonary embolism or interstitial infiltrates were also seen. Other common organ system involvement included neurologic (56%), cardiac (50%), cutaneous (50%), gastrointestinal (38%), hepatic, and adrenal (26%).

Treatment
Combined use of anticoagulation, high doses of corticosteroids, and early plasmapheresis to remove antiphospholipid antibodies rapidly was associated with the best survival
Lupus Pneumonitis

The treatment of acute lupus pneumonitis is based upon high doses intravenous steroids (predn, 1-2 mg/kg/day). Most patients will improve with this treatment despite 50% mortality has been reported in older series. Pulse methylpredn (250-1000 mg/day for several days) have been used in patients with a severe initial presentation. Cyclophosphamide in nonresponders.

Figure 3. Systemic lupus erythematosus with lupus pneumonitis. Posteroanterior radiograph shows patchy bilateral areas of air-space consolidation.
“The shrinking lung syndrome”

- The term ‘shrinking lung syndrome’ has been applied to SLE patients presenting with progressive dyspnea, the characteristic chest radiographic findings of small lung volumes, elevated hemidiaphragms and bibasilar atelectasis, with a restrictive ventilatory defect and a preserved carbon monoxide transfer coefficient.
- Diaphragmatic myositis? NO?
- Phrenic nerve paralysis? YES?

Some improvement of dyspnea and restriction has been observed with corticosteroids. Many patients seem to stabilize and have no worsening of lung function with time.
Diffuse alveolar hemorrhage
“Crazy-paving” Appearance in Systemic Lupus Erythematosus
Rheumatoid arthritis (RA) is the most common ARD. Pleural abnormalities and interstitial lung disease being the more common. Although RA affects women preferentially, men are more affected by pleuropulmonary manifestations of the disease.

<table>
<thead>
<tr>
<th>Table 2. Pleuropulmonary manifestations of rheumatoid arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airways disease</td>
</tr>
<tr>
<td>- Upper airways disease: cricoarytenoid arthritis</td>
</tr>
<tr>
<td>- Airway obstruction</td>
</tr>
<tr>
<td>- Constrictive bronchiolitis (bronchiolitis obliterans)</td>
</tr>
<tr>
<td>- Bronchiectasis</td>
</tr>
<tr>
<td>Interstitial lung disease</td>
</tr>
<tr>
<td>- Organizing pneumonia</td>
</tr>
<tr>
<td>Rheumatoid nodules</td>
</tr>
<tr>
<td>- Caplan’s syndrome</td>
</tr>
<tr>
<td>Pleural disease</td>
</tr>
<tr>
<td>- Pleuritis</td>
</tr>
<tr>
<td>- Pleural effusion</td>
</tr>
<tr>
<td>- Pneumothorax</td>
</tr>
<tr>
<td>- Bronchopleural fistula</td>
</tr>
<tr>
<td>- Empyema</td>
</tr>
<tr>
<td>Vascular disease</td>
</tr>
<tr>
<td>- Pulmonary hypertension</td>
</tr>
<tr>
<td>- Pulmonary vasculitis</td>
</tr>
<tr>
<td>Bullous lung disease</td>
</tr>
<tr>
<td>Amyloidosis</td>
</tr>
<tr>
<td>Obstructive apnea syndrome</td>
</tr>
</tbody>
</table>
Pleural involvement may be clinically silent. Symptomatic pleural involvement manifests with pain and/or dyspnea. Pleural chest pain occurs in 25% of RA patients; 5% of RA patients develop pleural effusions, usually small to moderate in volume, unilateral more often than bilateral. Effusions are usually spontaneously resolving within weeks, however chronic effusions are possible.
The patient, a 33-year-old woman with rheumatoid arthritis (RA), had a right pleural effusion. Cytologic examination of the pleural fluid with Papanicolaou staining revealed amorphous, granular background material and elongated cells, with oval nuclei and a long, tadpole-like, cytoplasmic tail, called “comet cells” (1). These cytologic features are specific to and pathognomonic of RA (2–5). Pleural disease is common in patients with RA; cytologic findings of elongated, often multinucleated, fusiform, comet-like macrophages are typical, but rarely encountered. Recognition of this distinctive cytopathologic picture may be useful in selected difficult cases (2,3).
Rheumatoid Pleural Effusion in the Absence of Arthritic Disease
James S. Allan, MD, Dean M. Donahue, MD, and Julie M. Garrity, RN

Frequent (26% of RA patients in one study) and overlooked manifestation of RA that may present with poorly defined symptoms: sensation of foreign body in the throat, sore throat, hoarseness, fullness in the throat, dyspnea, difficulty with inspiration, pain radiating to the ears, stridor, dysphagia, odynophagia, and pain with speech.

The diagnosis is clinically evident with direct or indirect laryngoscopy showing inflammatory changes of the arytenoids (erythema, swelling, thickening of mucosa) with reduced motility.

CT scan confirms the diagnosis. In some cases, ankylosis of the cricoarytenoid joint may induce an upper airway obstruction with a characteristic pattern on the flow-volume curve.

Cricoarytenoid arthritis is treated with anti-inflammatory medications. In patients with dyspnea, surgery may be needed.
Because the cricothyroid and cricoarytenoid joints are the two synovial joints of the larynx, they can be affected by a number of rheumatologic processes.

Because the vocal ligament and the vocal folds are attached to the arytenoids posteriorly, any involvement of the cricoarytenoid joint could lead to impaired vocal fold movement.
Relapsing polychondritis is a rare disorder characterized by recurrent episodes of inflammation of the cartilaginous and connective tissue. The association of relapsing polychondritis with other connective tissue diseases and the occasional finding of antibodies to type II collagen suggest an autoimmune origin.

- Bilateral auricular chondritis
- Nonerosive seronegative inflammatory polyarthritis
- Nasal chondritis with saddle nose deformity
- Ocular inflammation
- Respiratory tract chondritis
- Vestibular damage
<table>
<thead>
<tr>
<th>Rheumatologic disease</th>
<th>Mucosal or chondral disease</th>
<th>Cricoarytenoid arthritis</th>
<th>Neurologic or muscular vocal fold paralysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>+</td>
<td>++ + +</td>
<td>+</td>
</tr>
<tr>
<td>Juvenile rheumatoid arthritis</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>++ +</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Relapsing polychondritis</td>
<td>++ + +</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Wegener’s granulomatosis</td>
<td>++ + +</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Angioedema</td>
<td>++ + +</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Abbreviations: 0, nonexistent to very rare; +, isolated case reports; ++, frequency 5% to 20%; ++++, frequency greater than 20%*
Rheumatoid nodules

RN are the only specific lesion observed in the lung of RA patients. RN are histologically similar to that observed in the subcutaneous tissue. Occasionally, giant cells and well-formed granulomas may be observed in the peripheral region of the RN. Very frequent at microscopic examination of the lung (30%), or on HRCT lung slices (20%), RN are seldom seen on standard chest X-ray (<1%). RN usually predominate in the upper- and mid-lung regions, in the peripheral sub-pleural zone, although endobronchial RN do exist. The RN are more prevalent in males, and in patients with extra-articular manifestations or with subcutaneous RN. Multiple widespread RN have been described as rheumatoid nodulosis. RN are usually asymptomatic and do not evolve over time, but cavitation and infection may occur.
Computed Tomography Findings of Caplan Syndrome

Hiroaki Arakawa, MD, Koichi Honma, MD, Hisao Shida, MD, Yoshiaki Saito, MD, and Hiroshi Morikubo, MD
RA and bronchiolitis
Constrictive Bronchiolitis
clinical features

- Patients with bronchiolitis present with persistent cough and worsening dyspnea
- Basilar inspiratory crackles and or squeaks may be heard on auscultation of the lungs in some patients
- Progressive airway obstruction, often associated with air trapping, is seen by pulmonary function testing in the majority of affected patients
- Diffusing capacity is commonly reduced, and there is no significant response to bronchodilators during pulmonary function testing
Constrictive Bronchiolitis
prognosis and response to treatment

• In most clinical settings, constrictive bronchiolitis tends to be progressive and is poorly responsive to corticosteroid therapy
• Progressive airflow limitation may result in respiratory failure and death
RA and bronchiectasis
“patients with suppurative phlegm”
Renè Théophile Hyacinthe Laënnec
19th century

“Uncommon” disease...
architectural derangement...
permanent dilatation of small and larger bronchi...
Drug induced lung disease in RA

Figure 5. Methotrexate pneumonitis in a patient with rheumatoid arthritis. Progressive respiratory failure with high fever developed within 2 weeks (panel A: initial radiograph) and required an admission in intensive care unit (panel B). Computed tomography of the lung showed bilateral alveolar opacities (panel C). Methotrexate was stopped, methylprednisolone was given because of profound hypoxemia and chest radiograph normalized within 1 week (panel D).
Reducing the risk of methotrexate pneumonitis in rheumatoid arthritis

V. Saravanan¹ and C. A. Kelly²

Rheumatology 2004;43:143–147

| Table 2. Criteria of Searles and McKendry [25] for diagnosis of MTX pneumonitis |
|---------------------------------|--------------------------------------------------------------------------------|
| 1                               | Acute onset dyspnoea                                                           |
| 2                               | Fever > 38.0°C                                                                  |
| 3                               | Tachypnoea ≥28/min and dry cough                                               |
| 4                               | Radiological evidence of pulmonary interstitial or alveolar infiltrates         |
| 5                               | White blood cell count ≤15.0 × 10⁹ with or without eosinophilia                |
| 6                               | Negative blood and sputum cultures (mandatory)                                 |
| 7                               | Restrictive defect and decreased diffusion capacity on pulmonary function tests |
| 8                               | PO₂ < 7.5 kPa on air                                                            |
| 9                               | Histopathology consistent with bronchiolitis or interstitial pneumonitis with giant cells and without evidence of infection |

Definite: >6 criteria present
Probable: 5 of 9 criteria present
Possible: 4 of 9 criteria present
Algorithm for screening for lung disease in RA prior to MTX and managing suspected pneumonitis.
## Systemic sclerosis (scleroderma)

<table>
<thead>
<tr>
<th>Table 4. Pleuropulmonary manifestations of systemic sclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Interstitial lung disease</td>
</tr>
<tr>
<td>Non specific interstitial pneumonia</td>
</tr>
<tr>
<td>Usual interstitial pneumonia</td>
</tr>
<tr>
<td>Lymphocytic interstitial pneumonia</td>
</tr>
<tr>
<td>Organizing pneumonia</td>
</tr>
<tr>
<td>Pneumoconiosis (silicosis)</td>
</tr>
<tr>
<td>Alveolar hemorrhage</td>
</tr>
<tr>
<td>Pleural involvement</td>
</tr>
<tr>
<td>Bronchogenic carcinoma</td>
</tr>
<tr>
<td>Respiratory muscle weakness</td>
</tr>
<tr>
<td>Aspiration pneumonia</td>
</tr>
<tr>
<td>Small airways disease</td>
</tr>
</tbody>
</table>
Pulmonary Fibrosis

Risk Factors
- Early disease, diffuse scleroderma
- Anti-Scl-70 or nucleolar antibody
- FVC < 75% early in disease (< 18 months)
- FVC decreasing by > 10%/year
- Isolated decrease in DLCO is NOT predictor for fibrosis
- New SOB with prior FVC < 65% not necessarily alveolitis

Diagnosis of Alveolitis
- A combination of the following:
  - ↓↓ FVC in early disease (FVC 60% with < 1 year)
  - A decreasing FVC (not DLCO) (> 10% FVC/year)
  - “Ground glass” pattern on HRCT
  - BAL with ↑ poly’s or eos on BAL
- Does not need to have much shortness of breath
# Table 1. Histopathologic Diagnosis, According to Type of Scleroderma and Duration of External Dyspnea

<table>
<thead>
<tr>
<th>Histologic Subset</th>
<th>No. of Subjects</th>
<th>Type of Scleroderma (Limited/Diffuse)</th>
<th>Mean Duration of Dyspnea at Biopsy (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSIP</td>
<td>62 (77.5%)</td>
<td>43/19</td>
<td>11</td>
</tr>
<tr>
<td>UIP</td>
<td>6 (7.5%)</td>
<td>4/2</td>
<td>28</td>
</tr>
<tr>
<td>ESL</td>
<td>6 (7.5%)</td>
<td>5/1</td>
<td>24</td>
</tr>
<tr>
<td>Miscellaneous*</td>
<td>6 (7.5%)</td>
<td>4/2</td>
<td>12</td>
</tr>
</tbody>
</table>
Figure 3. Survival compared between NSIP and UIP/ESL. No significant difference was disclosed.
In conclusion, we have found that the great majority of patients with fibrosing alveolitis associated with systemic sclerosis have a histologic pattern of NSIP rather than UIP, in contrast to patients with idiopathic interstitial pneumonia. However, although a number of markers of lung disease were linked to survival, the histopathologic distinction between cellular and fibrotic NSIP had no prognostic significance.
Pulmonary hypertension in collagen vascular disease
M.M. Hoeper

Pulmonary hypertension in autoimmune rheumatic diseases
Patricia E. Carreiro

Autoimmunity Reviews

Cross Section of the Ascending Aorta (on the Left) and the Pulmonary Trunk (on the Right)

Risk Factors and Diagnostic Clues for Pulmonary Hypertension

Pulmonary Hypertension
Risk Factors
- Longstanding (> 10 year), limited SSc
- Anticentromere or antinuclear antibodies
- DLCO < 65% predicted, FVC/DLCO ratio > 1.6
- Mild to moderate fibrosis on CXR or HRCT

SOB develops slowly. Patients not always aware

Diagnosis of Pulmonary Hypertension
- Suspect PHT:
  - Late limited, ACA, antinuclear AB, low DLCO, FVC/DLCO > 1.8
  - Echo PASP > 30 mm Hg
  - Right heart changes
- Exclude:
  - Left heart failure
  - Pulmonary emboli
  - Severe pulmonary fibrosis
  - Right heart catheterization
Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach

D Mukerjee, D St George, B Coleiro, C Knight, C P Denton, J Davar, C M Black and J G Coghlan

The Prevalence of Undiagnosed Pulmonary Arterial Hypertension in Subjects With Connective Tissue Disease at the Secondary Health Care Level of Community-Based Rheumatologists (the UNCOVER Study)

Fredrick M. Wigley,¹ Joao A. C. Lima,¹ Maureen Mayes,² David McLain,³ J. Lincoln Chapin,⁴ and Clive Ward-Able⁴

Conclusion. A significant number of patients with SSc or MCTD (13.3%) followed up in a community rheumatology practice setting have undiagnosed elevated ERVSP consistent with PAH.
SSc patients with no severe pulmonary function abnormalities

Doppler echocardiography

VTR < 2.5 m/s

VTR 2.5–3 m/s

VTR > 3 m/s

NO DYSPNEA
(or dyspnea explained by another cause)

DYSPNEA
(not explained by another cause)

No PAH

Suspected PAH

Figure 1. Screening algorithm for diagnosis of pulmonary arterial hypertension (PAH) in patients with systemic sclerosis (SSc). VTR = peak velocity of tricuspid regurgitation; mPAP = mean pulmonary artery pressure; PAWP = pulmonary artery wedge pressure. Right heart catheterization was performed except when Doppler echocardiography provided evidence of left heart disease.
Figure 1. Screening algorithm for diagnosis of pulmonary arterial hypertension (PAH) in patients with systemic sclerosis (SSc). VTR = peak velocity of tricuspid regurgitation; mPAP = mean pulmonary artery pressure; PAWP = pulmonary artery wedge pressure. Right heart catheterization was performed except when Doppler echocardiography provided evidence of left heart disease.
Pulmonary involvement may precede by many years, or occur simultaneously or follow the muscular manifestations of PM–DM.

<table>
<thead>
<tr>
<th>Table 5. Pleuropulmonary manifestations of polymyositis and dermatomyositis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interstitial lung disease</td>
</tr>
<tr>
<td>Non specific interstitial pneumonia</td>
</tr>
<tr>
<td>Usual interstitial pneumonia</td>
</tr>
<tr>
<td>Lymphocytic interstitial pneumonia</td>
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<tr>
<td>Diffuse alveolar damage</td>
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<tr>
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</tr>
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</tr>
<tr>
<td>Aspiration pneumonia</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
</tr>
</tbody>
</table>
Antisynthetase syndrome

This syndrome includes PM or DM (63-100%), ild (40-100%), Raynaud’s phenomenon (25-100%), (mechanics hands), and the presence of one of the seven identified antisynthetase antibodies. Severe constitutional symptoms are common, with fever in 80% of the patients, asthenia and weight loss. ILD with CD8+ lymphocytic alveolitis without muscle involvement may be observed. Five to 8% of cases in the antisynthetase syndrome manifest as overlap with other CTD including RA, lupus, scleroderma, and SS. The antisynthetase syndrome carries a poor prognosis that seems related to the severity and frequent steroid resistance of interstitial lung disease.

About 15% of patients with PM-DM have a diagnosis of cancer in their medical history

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Cellular target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Jo1</td>
<td>Anti-histidyl-tRNA synthetase</td>
</tr>
<tr>
<td>Anti-PL7</td>
<td>Anti-threonyl-tRNA synthetase</td>
</tr>
<tr>
<td>Anti-PL12</td>
<td>Anti-alanyl-tRNA synthetase</td>
</tr>
<tr>
<td>Anti-OJ</td>
<td>Anti-isoleucyl-tRNA synthetase</td>
</tr>
<tr>
<td>Anti-EJ</td>
<td>Anti-glycyl-tRNA synthetase</td>
</tr>
<tr>
<td>Anti-KS</td>
<td>Anti-asparaginyl-tRNA synthetase</td>
</tr>
<tr>
<td>Anti-Wa</td>
<td>48 kDa protein bound to acetylated tRNA</td>
</tr>
</tbody>
</table>
Anti-histidyl tRNA synthetase antibody (anti-Jo1) is the most frequently found, in approximately 20% of patients with PM. The reported frequency of ILD in patients with anti-Jo1 antibodies is more than 70%. Elevated levels of Krebs von den lungen-6 (KL-6), a glycoprotein expressed on type II alveolar pneumocytes and bronchiolar epithelial cells, is a sensitive marker of ILD presence in PM.
In PM/DM patients, NSIP is reported to be the predominant type seen in as many as 80%, and other observed types include DAD, UIP, and BOOP. FK506 (Tacrolimus, Prografe) is a macrolide immunosuppressive drug originally discovered in 1984 in the fermentation broth of the filamentous bacterium, Streptomyces tsukubaensis.

Polymyositis/dermatomyositis and interstitial lung disease: A new therapeutic approach with T-cell-specific immunosuppressants


KAZUKI TAKADA¹, KENJI NAGASAKA², & NOBUYUKI MIYASAKA¹

T-cell targeted therapies have a potential to be the cornerstone of the treatment for ILD in PM/DM patients. The combination therapy with CsA and corticosteroids may be efficacious especially when used early. FK506 may be advantageous even in refractory cases to CsA.
**Figure 1.** A 57-year-old man with NSIP and PM in group II. *Top:* the initial high-resolution CT scan shows diffuse bilateral ground-glass and reticular opacities. The abnormalities involve both central and peripheral lung zones. *Bottom:* a follow-up high-resolution CT scan obtained 22 months later shows significant improvement of the ground-glass and reticular opacities. Traction bronchiectasis developed in this patient during follow-up (not shown).

**Figure 4.** Change of CT scores for increased lung opacity before and after treatment in each patient. The difference was significant (*p* < .05) by Wilcoxon signed rank test.
Organizing pneumonia in a patient with the antisynthetase syndrome (anti-Jo1 antibody).
High titers of antibodies against uridine-rich RNA-small nuclear ribonucleoprotein (anti-RNP).
Major respiratory manifestations include interstitial lung disease and pulmonary fibrosis (20–65%), pleural effusion (50%), and PHT (10–45%).
Pulmonary Vascular Manifestations of Mixed Connective Tissue Disease

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Pulmonary Involvement in Mixed Connective Tissue Disease: Comparison With Other Collagen Vascular Diseases Using High Resolution CT

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Sjögren’s Syndrome and the Lung
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\textit{Handbook of Systemic Autoimmune Diseases, Volume 2}
Pulmonary Involvement in Systemic Autoimmune Diseases
A.U. Wells and C.P. Denton, editors

Sjögren’s syndrome, an autoimmune epithelitis, is characterized by: (a) a T lymphocytic infiltration of the exocrine glands and epithelia in multiple sites, including those of the upper and lower airways, leading to diminished or absent glandular secretions and to a more or less generalized, mucosal dryness, and (b) a marked B lymphocytic cell hyperreactivity manifested by various serum autoantibodies, such as those directed against the Ro(SSA) and La(SSB) ribonucleoproteins, or immunoglobulins (rheumatoid factor).
Pulmonary involvement in primary Sjögren’s syndrome includes: (a) upper and lower, large and small airways disease (common, but mild in severity), (b) different patterns of diffuse interstitial pneumonia, such as chronic organizing pneumonia (COP), non-specific interstitial pneumonia (NSIP), and usual interstitial pneumonia (UIP) (uncommon, but of variable severity), and (c) a spectrum of lymphoproliferative diseases, extending from follicular bronchiolitis to lymphocytic interstitial pneumonia (LIP) and, finally, to malignant B-cell non-Hodgkin’s lymphoma (in a small but significant number of patients and of variable severity).
Respiratory manifestations in Sjögren’s syndrome

Upper airways disease
  - Nasal mucosa infiltration and dryness (‘rhina sicca’)
  - Epistaxis
  - Sinusitis
  - Oral cavity major and minor salivary glands involvement (xerostomia)
Lymphocytic infiltration of the tracheobronchial submucosal glands (xerotrachea)
Subepithelial bronchial and bronchiolar lymphocytic infiltration (lymphocytic bronchitis/bronchiolitis)
Bronchial hyperresponsiveness
Lymphoproliferative disorders
  - Diffuse lymphoid hyperplasia of the lungs
    - Peribronchiolar (reactive lymphoid hyperplasia/follicular bronchiolitis)
    - Diffuse alveolar interstitial, (lymphoid interstitial pneumonia, LIP)
Pseudolymphoma
  - Lymphomatoid granulomatosis.
  - Malignant B-cell non-Hodgkin’s lymphoma
Other diffuse interstitial pneumonias
  - Pulmonary fibrosis, usual interstitial pneumonia (UIP) type
  - Non-specific interstitial pneumonia (NSIP)
  - Cryptogenic organizing pneumonia (COP)
Diffuse panbronchiolitis
Multiple lung cysts or bullae
Vasculitis and primary pulmonary hypertension
Pulmonary amyloidosis
Pleural disease (mainly in the secondary Sjögren’s syndrome)
F. Follicular bronchiolitis

Figure 10. Follicular bronchiolitis. Intermediate-magnification photomicrograph showing follicular bronchiolitis characterized by prominent peribronchiolar lymphoid aggregates with secondary germinal centers.
FIG. 14. Cellular distribution in hyperplastic bronchus-associated lymphoid tissue. LE, lymphoepithelium; DA, dome area; FA, follicular area (B cell zone); PFA, parafollicular area (T cell zone); open circles, IgG; crosses, IgA; closed circles, IgM; closed triangles, CD8; open triangles, CD4; double circles, CD57.
The presence of mucosa-associated lymphoid tissue (MALT) in the lung was first described by Bienenstock and colleagues in 1973, as bronchial and bronchiolar subepithelial aggregates of lymphoid tissue named bronchus-associated lymphoid tissue (BALT).

However, the presence of BALT in normal human lungs is still debatable and it is actually considered that the human lung has the capacity to form BALT under certain stimulatory conditions such as chronic lung infections, autoimmune disorders and especially Sjögren’s syndrome (SS), human immunodeficiency virus (HIV) or other viral infections.

BALT is thought to participate in immunologic reactions to airborne antigens, and can be the source of various pathologic lesions ranging from benign hyperplasia to lymphoid malignancy.
From BALT hyperplasia to LIP to MZCL of the lung of MALT type
Underlying systemic immune disorders were frequent, including Sjögren's, RA, SLE, PM, common variable immunodeficiency, and dysproteinemia. Only three patients were classified as idiopathic.
MZCL of MALT-type of the lung

- MALT-type lymphomas of the lung, also known as BALT lymphomas, are very rare malignancies.

- MALT lymphomas originate from the marginal zone B cells that surround the mantle zone and germinal centre and are currently classified as a distinct subgroup of non-Hodgkin’s lymphomas under the term extranodal marginal zone B-cell lymphoma (MZCL) of MALT-type.

- MALT-type lymphomas have also been associated with autoimmune disorders, as well as *Helicobacter pylori* infection, HIV infection, common variable immunodeficiency, chronic active hepatitis C, *Borrelia burgdoferi* infection, and other chronic inflammatory conditions but may also develop in patients with no pre-existing disease.
Currently, there is no consensus treatment for Sjögren’s syndrome which remains fundamentally an incurable disease. The treatment is generally aimed at alleviating the dryness symptoms and related morbidities. The pleomorphism of the respiratory manifestations and their variability in clinical severity that may range from mild to severe and occasionally life-threatening disease require special therapeutic measures.