Respiratory Medicine

Connective Tissue Diseases Associated With Restrictive Lung Disease: Nonspecific Interstitial Pneumonia (NSIP), Scleroderma, Dermatomyositis and Polymyositis

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Introduction

Chronic lung diseases are broadly classified as:

- **Obstructive lung diseases**, for example, asthma and chronic obstructive pulmonary disease.
- **Restrictive lung diseases**, for example, pneumoconiosis, interstitial lung diseases, and sarcoidosis.
These two groups present with overlapping clinical features of dyspnea and other pulmonary manifestations, but they are easily differentiated based on pulmonary function testing. **Restrictive lung diseases** have a hallmark of:

1. Reduced lung volumes (reduced total lung capacity TLC);
2. Decreased forced expiratory volume at 1 minute (FEV1) and forced vital capacity (FVC);
3. Increased or near normal FEV1/FVC ratio.

These conditions could arise from pathologies of the lung parenchyma or outside the lung parenchyma (for instance, pleura, chest wall, neuromuscular components of respiration). Thus, they are classified into:

**Intrinsic/interstitial lung disease** which affects the lung parenchyma, leading to inflammation, scarring, and fibrosis of the lung or accumulation of air spaces with debris, leading to pneumonitis. They include:

- Connective tissue diseases associated with interstitial lung diseases (CT-ILD);
- Fibrotic lung diseases
- Primary interstitial lung diseases, such as sarcoidosis
- Idiopathic interstitial lung diseases

**Extrinsic/extrapulmonary lung disease that affects the**

- Chest wall
- Pleura
- Respiratory muscles and nerves

**Connective tissue diseases associated with interstitial lung diseases (CT-ILD)**

Lungs are frequently involved in multiple connective tissue disorders. These include:

- Scleroderma/systemic sclerosis
- Dermatomyositis and polymyositis
- Nonspecific interstitial pneumonia (NSIP)
- Rheumatoid arthritis
- Sjogren syndrome
- Systemic lupus erythematosus (SLE)
- Mixed connective tissue disease (MCTD)

**Scleroderma/systemic sclerosis (SSc)** is an autoimmune connective tissue disorder with a heterogeneous presentation. It induces connective tissue deposition and leads to hardening of the tissues. They commonly affect the skin, blood vessels, muscles, internal organs, and lungs.

**Nonspecific interstitial pneumonia (NSIP)** is a form of idiopathic interstitial pneumonia that follows an autoimmune reaction of the body towards the lung parenchyma. It is classified based on histological findings into:

- **Cellular type**, which runs a chronic inflammation pathogenic pathway with minimal fibrosis, thus, marked with inflammatory infiltrate and type II pneumocyte hyperplasia.
- **Fibrosing type**, which has interstitial fibrosis with minimal chronic
**Polyomyositis** is an idiopathic inflammatory myopathy that is characterized by the triad of:

1. proximal muscle weakness,
2. elevated skeletal muscle enzymes
3. electromyographic and muscle biopsy abnormalities.

**Dermatomyositis** is similar to polymyositis but additionally, these patients have characteristic skin rashes involving sun-exposed areas such as face, neck, upper chest, and hands.

In polymyositis and dermatomyositis, the lung involvement is more common with antisynthetase antibodies.

**Epidemiology**

**NSIP** is the second most common form of interstitial lung disease. It mainly affects adults aged 40-50 years, with a slight female predilection.

**Systemic sclerosis**, on the other hand, affects three people per 100,000 in the general population. The disease has a slight predilection for women ranging 40-50 years in age. Lung involvement is one of the most common complications of scleroderma, being evident in 53 % of patients with systemic sclerosis and 35% of patients with cutaneous sclerosis.

**Dermatomyositis and polymyositis** are rare diseases with a prevalence of 0.5-8.4 cases per million people of the population. They are associated with people of all ages. Two peaks are observed: the first peak is around 5-10 years of age and the second peak is around 50 years.

They have a female to male ratio of 2:1, with black women being affected more. Lung involvement precedes other system involvement in up to 30–40 % of dermatomyositis and polymyositis.

**Etiology**

The connective tissue disorders are mostly autoimmune disorders that have a genetic and environmental influence. Certain risk factors have been linked to these disorders:

1. **Family history and genetic predisposition** is more pronounced in dermatomyositis and polymyositis where there is an association with HLA-DR3/5/7 mutations.
2. **Environmental toxins**, such as exposure to silica, chlorinated toxins, and welding fumes, induce and maintain the autoimmune process.
3. **Malignancy** is also a trigger for autoimmune processes.
4. **Infection processes** that trigger an autoimmune process include HTLV-1, coxsackie viruses, and parvoviruses.
5. **Drugs**, such as statins, have been incriminated in the development of polymyositis and dermatomyositis. Drug-induced lupus is another well-recognized entity.
6. **Immunologic predisposition** to an autoimmune reaction is evident in polymyositis and dermatomyositis where TNF-α-308A allele is associated with an increase in photosensitivity.
7. **Advanced age**
8. **Smoking** predisposes to an autoimmune process and worsens existing interstitial lung disease.

## Pathophysiology

When a genetically predisposed individual is exposed to environmental triggers, such as infections, drugs, or malignancies, an autoimmune process is triggered that affects multiple tissues including the lungs. This leads to progressive destruction of lung parenchyma due to persistent **inflammation**, **fibrosis**, and **vascular injury**.

Further, alveolar epithelial injury leads to cytokine release (IL-1, LPA) and growth factors release (TGF-β and IGF-1) which activates the fibroblasts. Fibroblast activation leads to collagen deposition in the lung parenchyma which induces solidification and fibrosis.

Besides the lung parenchyma inflammation and fibrosis, the airway, pulmonary vasculature, and chest wall may also be involved, leading to:

- airflow limitation
- pulmonary hypertension
- vasculitis
- extrapulmonary restriction.

## Clinical features

These patients have clinical features affecting the respiratory system as well as the systemic involvement.

### Respiratory system involvement

1. Cough
2. Shortness of breath
3. Fatigue
4. Chest pain
5. Pulmonary hypertension

The systemic features depend upon the underlying connective tissue disorder.

## Polymyositis and dermatomyositis

1. Bilateral symmetrical **proximal muscle weakness**.
2. **Skin rashes** (in dermatomyositis). It commonly consists of heliotrope rash in the periorbital region, shawl sign due to clavicular and shoulder skin involvement, gottron papules and plaques.
3. **Esophageal and pharyngeal involvement**. It leads to weakness and dilatation that causes aspiration pneumonia and worsens existing interstitial pneumonia.

## Scleroderma/Systemic Sclerosis

It affects almost every system, causing:

1. Tightened skin especially around the fingers (sclerodactyly)
2. Raynaud’s phenomenon
3. Telangiectasias
4. Dizziness, palpitations, hypertension and congestive cardiac failure
5. Dysphagia, GERD

**Systemic lupus erythematosus (SLE)**

1. Photosensitivity and skin rash, characteristically the butterfly rash around the cheeks.
2. Oral ulcers
3. Joint pain
4. Muscle weakness
5. Neuropsychiatric symptoms
6. Thrombotic state (Abortions or deep vein thromboses)

**Investigations**

The diagnostic investigations include:

**Laboratory tests**

- Systemic sclerosis patients have a **positive ANA test** and anti-topoisomerase antibodies in serum, among other markers.
- In dermatomyositis and polymyositis, there is leukocytosis and thrombocytosis on complete blood count as well as **elevated muscle enzymes** such as CK and aldolase. They also exhibit positive ANA and other serum markers.
- SLE patients may have positive ANA, anti-dsDNA, along with autoimmune related pancytopenia.

**Imaging**

- A chest x-ray may be normal in most cases but may also exhibit nodular opacities in NSIP.
- High-resolution CT-scan (HRCT) of the chest may show the characteristic ground glass opacities appearance in most of the disease with associated:
  1. pruning (loss of pulmonary vasculature)
  2. loss of pulmonary volume
  3. enlarged right pulmonary artery >1.1cm
  4. honeycomb pattern.

**Pulmonary Function Tests / Spirometry**

Pulmonary function tests (PFTs) are important in diagnosing the restrictive lung diseases. They show:

1. Reduced lung volumes (reduced total lung capacity TLC, tidal volume, residual volume);
2. Decreased forced expiratory volume at 1 minute (FEV1) and forced vital capacity (FVC)
3. **Increased or near normal** FEV1/FVC ratio.
Bronchoscopy

Lung biopsy and histology show a mixed pattern of inflammation and fibrosis.

Echocardiogram

An echocardiogram may be considered in cases of severe cardiovascular compromise. It helps in diagnosing the associated pulmonary hypertension. Cardiac catheterization can be done to confirm the pressures.

Differential diagnosis of Restrictive Lung Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
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<tr>
<td>Usual interstitial pneumonia (UIP)</td>
<td>• Has similar imaging findings of opacification as in NSIP but lacks the restrictive and fibrotic lung injury pattern.</td>
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<tr>
<td>Eosinophilic fasciitis</td>
<td>• An autoimmune disease with eosinophilia and connective tissue involvement like scleroderma.</td>
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<tr>
<td>Mycosis fungoides</td>
<td>• A cutaneous form of cancer that is marked by skin rashes like those seen in scleroderma.</td>
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<td>Fibromyalgia</td>
<td>• Presents with muscle pain and stiffness and sometimes mimic polymyositis and dermatomyositis.</td>
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<tr>
<td>Discoid lupus erythematosus</td>
<td>• Has skin involvement with a shawl sign as seen with scleroderma.</td>
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Treatment

The treatment is mainly symptomatic, as the pulmonary changes are largely irreversible. Effective therapies for connective tissue disease-associated interstitial lung disease (CTD-ILD) are still lacking but multiple clinical trials have been carried out with varying degrees of success.

Supportive management

- Long-term continuous oxygen therapy;
- Analgesics for muscle and chest pains;
- Muscle relaxants for spasticity and rigidity;
- Treatment of skin ulcers that develop in systemic sclerosis;
- Pharmacological agents to reduce pulmonary hypertension.

Definitive management

**Corticosteroid therapy** with high dose prednisone, especially in situations of lung involvement. In the treatment of dermatomyositis and polymyositis, the drug is administered for 4-8 weeks, and in that time muscle enzymes must have returned to normal levels.

**Immunosuppressive** therapy with methotrexate, azathioprine, and cyclophosphamide that decrease the autoimmune activity within the body. These drugs are considered when the disease is refractory to high dose steroids. The need is based on:

- Disease progression at a faster rate;
- Severe lung disease;
- Likelihood of the response, based on prior experience of a similar patient;
- Age of the patient with a better response anticipated in young patients;
- Ability to comply with the medication schedule.

**Lung transplant** has been tried with success, especially in complications of restrictive lung disease.

**Complications**

Complications associated with restrictive lung disease can arise from the disease progression or problems associated with treatment:

1. **Pulmonary hypertension** is the most common and dangerous complication that arises from prolonged fibrosis and vessel damage; it may cause ischemia-induced revascularization.
2. **Cor pulmonale** is the final pathway for pulmonary hypertension that leads to right heart strain and ultimately, right heart failure.
3. **Respiratory failure** arises from the restriction of exhalation and compromised volume that may be worsened by medications such as methotrexate. Serial pulmonary function tests are done to assess for this complication.
4. **Renal failure**.
5. **Infections** arise due to prolonged use of immunosuppressive therapy. Close monitoring of the patient’s immunity alongside a broad spectrum antimycobacterial coverage is recommended.
6. **Malignancy** may arise from the prolonged fibrotic states.
7. **Skin sores and ulcers** that mainly arise due to peripheral vessel damage by autoimmune processes.

**Prognosis**

The five-year survival rate for NSIP ranges from 86–92% for the fibrosing type and up to 100% for the cellular intervention due to its good response to treatment. The median survival of systemic sclerosis with lung involvement is 6–8 years.

**References**


Mayo clinic staff. (2017, July 21). “Interstitial Lung disease.” Available at:

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