Pulmonary Manifestations of Collagen Vascular Diseases

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Disclosure

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Introduction

Collagen vascular diseases form a heterogeneous group of immune mediated disorders. In the thorax, they can involve the lung parenchyma, pleura and mediastinum. The spectrum of thoracic findings is broad, with considerable variation in extent and frequency of disease, which may be further compounded by association with infections or reaction to treatment.

Learning Objectives

1) Provide an approach to the most common thoracic manifestations of collagen vascular diseases.

2) Review patterns of interstitial lung diseases and other thoracic manifestations related to collagen vascular diseases that commonly involve the thorax.

3) Understand potential treatment complications.
Summary of most common chest imaging findings associated with collagen vascular diseases.

**Disease specific findings:**
- Necrobiotic nodules (RA)
- Pleural/pericardial disease (RA, SLE)
- Lupus pneumonitis (SLE)
- Diffuse alveolar hemorrhage (SLE)

**Rheumatoid arthritis (RA)**
- Scleroderma (Scl)
- Sjögren (Sj)
- Systemic lupus erythematosus (SLE)
- Dermatomyositis (DM)
- Polymyositis (PM)

**Diffuse alveolar damage (DAD)**

**Pulmonary hypertension**
- Pulmonary edema

**Treatment Complications:**
- Opportunistic infections
- Drug toxicity

**Interstitial pneumonias:**
- Non-specific interstitial pneumonia (NSIP)
- Usual interstitial pneumonia (UIP)
- Lymphocytic interstitial pneumonia (LIP)
- Cryptogenic organizing pneumonia (COP)
# Interstitial Pneumonias

Table 1. Frequency of interstitial pneumonias associated with collagen vascular diseases\(^1\)

<table>
<thead>
<tr>
<th>Disease</th>
<th>NSIP</th>
<th>UIP</th>
<th>LIP</th>
<th>COP</th>
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<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>++</td>
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<tr>
<td>Scleroderma</td>
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<td>Sjögren</td>
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<td>++</td>
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<tr>
<td>Dermatomyositis/Polymyositis</td>
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</table>

*Key fact*

NSIP is the most common pattern of interstitial lung disease associated with collagen vascular diseases.
Fig 1. NSIP in a patient with scleroderma.

Axial (a) and coronal (b) computed tomography of the thorax demonstrating **peripheral ground glass opacities** (arrow) and **inter/intralobular septal thickening** (arrowhead) with **basal predominance**. There is also areas of **subpleural sparing**. The findings are typical of NSIP pattern. Note that honeycombing is not a prominent feature, as opposed to UIP.
Fig 2. Pathological correlation for NSIP

Low magnification demonstrating a uniform appearing, diffuse interstitial pneumonitis involving multiple lobules of lung (a).

Higher magnification showing chronic inflammatory cells in alveoli septae (arrows) (b).
Fig 3. UIP in a patient with scleroderma.

Axial computed tomography of the thorax showing bilateral irregular interlobular septal thickening, traction bronchiectasis, honeycombing and architectural distortion alternating with normal lung (a). The findings are typical of a UIP pattern.

Luminal dilatation of the oesophagus is also noted, a feature seen with scleroderma. The main pulmonary artery is enlarged, which is suggestive of pulmonary arterial hypertension (b).
**Fig 4. Pathological correlation for UIP**

Micropictograph showing a focus of fibroblastic tissue (arrow) surrounded by areas of more mature, dense collagen (a). Low power magnification shows variably severe disease characteristic of UIP, with less affected lobule at lower center and marked interstitial fibrosis of the adjacent lobules (b). Note the variegated appearance of UIP, with spacial and temporal heterogeneity.
Fig 5. LIP pattern in a patient with Sjögren.

Axial (a) and coronal (b) computed tomographies of the chest showing scattered thin walled cysts (arrows) in a perivascular and subpleural distribution, typical of LIP. Also noted are poorly defined centrilobular nodules (arrowhead).

Another case of pathology proven LIP shows bilateral ground glass opacities and minimal interlobular septal thickening (c).
Fig 6. DM and PM patients with COP

Axial CT of a patient with dermatomyositis demonstrating **patchy subpleural consolidative changes** and a **reverse halo sign** (arrow) in the right lower lobe (a).

Coronal CT of another patient with polymyositis and biopsy proven COP showing extensive subpleural consolidations in the right lung (b).
Diffuse Alveolar Damage

Causes in collagen vascular diseases (CVD)²,³

1) CVD without underlying interstitial pneumonia
2) Underlying interstitial pneumonia (occasionally)
3) Drug toxicity (cyclophosphamide, gold salts)
4) Others*

*Other causes of DAD:
Idiopathic (acute interstitial pneumonia), uremia, infection, sepsis, transfusion-related acute lung injury, shock, toxic inhalation, trauma.

Histopathologic Findings⁴

Acute exudative phase:
• Protein rich alveolar edema
• Hyaline membranes
Late reparative phase:
• Fibroblastic proliferation
• Collagenisation
• Pneumocyte hyperplasia

CT Findings⁵

• Diffuse pattern / geographic appearance
• Consolidations/ground glass attenuation
• Lobular sparing
• Late/organizing phase: traction bronchiectasis

Table 2. Frequency of DAD associated with CVD³

<table>
<thead>
<tr>
<th>RA</th>
<th>Scl</th>
<th>Sj</th>
<th>SLE</th>
<th>DM/PM</th>
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<td>+</td>
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Fig 7. DAD in a patient with SLE.

Coronal (a) and axial (b) computed tomographies of the chest demonstrating bilateral **diffuse ground glass attenuation** and **consolidation**. There are associated pleural effusions and bilateral atelectatic changes.

Biopsy in this patient confirmed hyaline membranes, pulmonary edema and pleural adhesions.
Fig 8. Pathological correlation for DAD

Diffuse airspace filling by lightly staining proteinaceous fluid, with focal hyaline membranes (arrow) and chronic interstitial inflammation.
Disease Specific Findings: Necrobiotic Nodules (RA)

Fig 9. Rheumatoid nodules

RA patient with **cavitary subpleural lung nodules** (arrows) and secondary bilateral pneumothoraces.

**Necrobiotic nodules**:¹
- <5% of patients with RA
- More common in men & smokers
- Solitary or multiple
- Peripheral (subpleural)
- Thick walled cavitation (50%)

**Disease specific findings:**
- Necrobiotic nodules (RA)
- Pleural/pericardial disease (RA, SLE)
- Lupus pneumonitis (SLE)
- Diffuse alveolar hemorrhage (SLE)
Disease Specific Findings: Pleural/pericardial disease (RA, SLE)

**Rheumatoid Pleurisy**\(^1,6\)
- Most common pulmonary finding
- Pleural effusion in 5%
- Men > women
- Often recurrent
- Small, unilateral
- Complications: diffusely thickened pleura, fibrothorax
- Fluid characteristics:
  - Exudate
  - Low pH
  - Low glucose
  - Positive rheumatoid factor

**Lupus Pleuritis / Effusion**\(^1,6,7\)
- Most common pulmonary finding
- Early finding with exacerbations
- Pleural and pericardial effusions
- Small, bilateral (50%)
- Fluid characteristics:
  - Exudate
  - High protein content
  - Normal glucose
Disease Specific Findings: Lupus Pneumonitis* (SLE)

Fig 10. Acute lupus pneumonitis in a patient with SLE

Axial CT of the thorax in a patient with pathology proven acute pneumonitis shows bilateral ground glass attenuation.

Disease specific findings:
- Necrobiotic nodules (RA)
- Pleural/pericardial disease (RA, SLE)
- Lupus pneumonitis (SLE)
- Diffuse alveolar hemorrhage (SLE)

Acute lupus pneumonitis¹:
- Vasculitis & hemorrhage
- Widespread consolidations
- Associated with increased mortality

* There has been some argument about the existence of acute lupus pneumonitis. In one large series, every case could be explained by other factors.

Disease Specific Findings: Diffuse Alveolar Hemorrhage (SLE)

**Fig 11. Diffuse alveolar hemorrhage**

Axial and coronal CTs show bilateral dependent consolidations secondary to alveolar filling with blood.

Another less severe case shows bilateral lobular ground glass opacities (c).
Pulmonary Hypertension

- Resting pulmonary artery pressure ≥ 25mmHg
- Most commonly seen in scleroderma (10-33%)
- Histologic features similar to primary pulmonary hypertension

**Imaging features:**

- Enlarged pulmonary trunk
- Enlarged pulmonary arteries
- Enlarged right heart chambers
- Reflux in hepatic veins / SVC

**Fig 12. Pulmonary hypertension**

Selected axial images show enlarged pulmonary trunk (3.2cm) and right ventricle (arrow) (a,b). Incidental note of a hiatal hernia.
Table 3. Commonly used drugs in collagen vascular diseases and associated pulmonary infections\textsuperscript{10,11}

- **Steroids**
  - Bacterial
  - Fungal
  - Viral
  - Mycobacterial

- **Methotrexate**
  - Dose related (neutropenia)
  - Bacterial
  - Opportunistic - viral, fungal

- **Cyclophosphamide**
  - Bacterial
  - Opportunistic - viral, fungal

- **TNFα inhibitors**
  - Mycobacterial - TB, MAI
  - Fungal - Histoplasmosis, Aspergillosis, PCP, Candida, Cryptococcus
  - Bacterial - Streptococcus pneumoniae, Listeria
Fig 13. Immunocompromised woman with pulmonary reactivation TB.

Axial (a) and coronal (b) CTs of the chest show right apical cavitation (arrow) and consolidative changes. Those features are highly suggestive of reactivation TB, which was confirmed with biopsy in this patient.

*Key facts*

- Risk of reactivation TB is greater with TNF α inhibitors, which are commonly used in the treatment of collagen vascular diseases.

- A UK study demonstrated 36-144/100,000 patients depending on the agent\textsuperscript{12}. 
Fig x. PCP
Coronal CT of the chest in an immunocompromised patient with shortness of breath. Bilateral faint **diffuse ground glass opacities** and **reticulations** are seen.

Fig 14. Pathological correlation for PCP

Pneumocystis pneumonia is characterized by eosinophilic, foamy alveolar exudate and interstitial pneumonitis. P. Jiroveci organisms lie within the alveolar exudate, although they are not easily seen on Hematoxylin-Eosin staining.
**Viral Infection: CMV**

**Fig x. CMV superinfection**

Axial (a) and coronal (b) CTs of the chest in a patient with SLE. Wedge biopsy was performed and showed pneumonitis and superimposed CMV infection. **Ground glass opacities** and **interstitial reticulations** are seen.
Table 4. Most common pulmonary toxicities associated with treatments for collagen vascular diseases\textsuperscript{13}.

<table>
<thead>
<tr>
<th>Pulmonary reaction</th>
<th>Associated drugs</th>
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<tbody>
<tr>
<td>Diffuse alveolar damage (DAD)</td>
<td>Cyclophosphamide, gold salts</td>
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<td>Non-specific interstitial pneumonia (NSIP)</td>
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<td>Cryptogenic organizing pneumonia (COP)</td>
<td>Gold salts, methotrexate, cyclophosphamide</td>
</tr>
<tr>
<td>Eosinophilic pneumonia</td>
<td>Nonsteroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>Pulmonary hemorrhage</td>
<td>Anticoagulants, cyclophosphamide</td>
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Conclusions

- Knowledge of the most common thoracic imaging findings of collagen vascular diseases and the complications related to their treatment is crucial for adequate patient management.

- Correct diagnosis of the different thoracic manifestations of collagen vascular diseases is often challenging, as many present with similar radiological and clinical findings. Imaging abnormalities related to drug-related toxicities and infections may be superimposed on the primary pathology, making the diagnosis even more challenging.

- A multidisciplinary approach, including the clinician, the radiologist and the pathologist is key in the evaluation of the pulmonary manifestations of collagen vascular diseases.
References

6. www.statdx.com