Pulmonary disorders

Introduction
The course of Sjögren’s syndrome may be complicated by various lung disorders. In this context, primary Sjögren’s syndrome (pSS) must be distinguished from secondary Sjögren’s syndrome (sSS) as patients with sSS by definition have a second systemic autoimmune disease. These are usually systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) or systemic sclerosis, diseases in which lung involvement is common.

The lungs are composed of several tissues (figure 11.1). The alveoli (air sacs), connective tissue, bronchi and smaller airways, blood vessels, nerves and pleura. Each of these tissues can become inflamed. In addition, the lungs may become infiltrated with cells or substances that do not belong there.

In interstitial lung disease (ILD), the tissue between the alveoli becomes inflamed hampering the gas exchange between the alveolar air and the blood.

Several ILDs have been shown to occur more common in patients with Sjögren’s syndrome than in the general population. Lung biopsy is often required to establish a pulmonary diagnosis. Shi et al compared the results of transbronchial lung biopsies (TBLB) with surgical lung biopsies.23 None of 7 TBLB cases showed changes considered to be the correct diagnosis based on the surgical biopsy. Small airway involvement was found in none of the TBLB specimens of the 6 patients who had definitive small airway involvement established via surgical lung biopsy.23

Overall involvement of the respiratory tract is more common in sSS but ILD is more common in pSS.13

In Sjögren’s syndrome, general dryness and lack of airways secretion cause the major problems of hoarseness, cough, and bronchitis.

Ramos-Casals et al found lung involvement in 112 out of 1010 (11%) patients.4 In his study, lung involvement was defined as persistent cough and/or dyspnea, with chronic diffuse interstitial infiltrates on x-ray, altered pattern on pulmonary function studies, and/or evidence of pulmonary alveolitis/fibrosis in computed tomography scans. No further details on the pulmonary diagnosis were given.

Table 11.1 Interstitial lung diseases in 18 patients with primary Sjögren’s syndrome and pulmonary disease

<table>
<thead>
<tr>
<th>diagnosis</th>
<th>patients (n,%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>nonspecific interstitial pneumonia</td>
<td>5 (28)</td>
</tr>
<tr>
<td>organizing pneumonia</td>
<td>4 (22)</td>
</tr>
<tr>
<td>usual interstitial pneumonia</td>
<td>3 (17)</td>
</tr>
<tr>
<td>lymphocytic interstitial pneumonia</td>
<td>3 (17)</td>
</tr>
<tr>
<td>primary pulmonary lymphoma</td>
<td>2 (11)</td>
</tr>
<tr>
<td>diffuse interstitial amyloidosis</td>
<td>1 (6)</td>
</tr>
</tbody>
</table>

Transbronchial versus surgical lung biopsy

Transbronchial lung biopsies (TBLB) tend to contain more nonspecific findings and none of 7 TBLB cases showed changes considered to be the correct diagnosis based on the surgical lung biopsy.

Shi et al. 200923
Interstitial lung diseases

Interstitial lung diseases (ILDs) are nonmalignant disorders and not caused by identified infectious agents. In ILD, the tissue between the alveoli becomes inflamed making it difficult to breathe. ILD includes more than 200 individual diseases.

Many approaches to classification exist. For each ILD there may be an acute phase, and there is usually a chronic one as well. The chronic stage is called by a variety of names, including interstitial pulmonary fibrosis, pulmonary alveolar fibrosis, and idiopathic pulmonary fibrosis.

The American Thoracic Society and the European Respiratory Society have outlined a joint classification system and terminology that will be used in this chapter.11,12

Causes

ILDs are associated with occupational and environmental exposures, radiation, drugs and autoimmune diseases or have no known cause (“idiopathic”). Several idiopathic pneumonias are recognized. These are:

- nonspecific interstitial pneumonia (NSIP)
- usual interstitial pneumonia (UIP) / idiopathic pulmonary fibrosis (IPF)
- idiopathic pulmonary fibrosis (IPF) / cryptogenic fibrosing alveolitis (CFA)
- desquamative interstitial pneumonia (DIP)
- respiratory bronchiolitis associated interstitial lung disease (RB-ILD)
- acute interstitial pneumonia (AIP)
- lymphocytic interstitial pneumonia (LIP)
- cryptogenic organizing pneumonia (COP) / organizing pneumonia (old name: BOOP)

In general, UIP is the most prevalent of the idiopathic interstitial lung diseases. Less common types of idiopathic interstitial lung diseases include NSIP and LIP.

Among the ILDs of known cause, the largest group comprises occupational and environmental exposures. Examples are silica dust, chemical fumes and chlorine gases or organic substances such as grain dust, dust from bird and animal droppings. Radiation therapy for lung or breast cancer may cause lung damage after many years. Some drugs can damage the interstitium of the lungs such as methotrexate and nitrofurantoin.

Sarcoidosis and idiopathic pulmonary fibrosis are the most common ILDs of unknown etiology.

General aspects of ILD

General features of ILD are presented below. Organizing pneumonia (old name: bronchiolitis obliterans organizing pneumonia, BOOP) has a course and prognosis that differ from the other ILD. See separate paragraph on next page.

Symptoms and physical findings

Dyspnea is a common and prominent complaint in patients with ILD. Findings at physical examination are usually not specific. Most commonly, physical examination reveals tachypnea and bibasilar end-inspiratory dry crackles.

Radiology

ILD may be first suspected based on an abnormal chest radiograph, which most commonly reveals a bibasilar reticular pattern. A nodular or mixed pattern of alveolar filling and increased reticular markings may also be present. In most cases, the chest radiograph is nonspecific and usually does not allow a specific diagnosis. High-resolution CT (HRCT) is superior to the plain chest x-ray for early detection and confirmation of suspected ILD.1

Treatment

Since therapy does not reverse fibrosis, the major goals of treatment are permanent removal of the offending agent, when known, and early identification and aggressive suppression of the acute and chronic inflammatory process, thereby reducing further lung damage. Corticosteroids are the mainstay of therapy for suppression of the alveolitis present in ILD, but the success rate is low and there is no direct evidence that steroids improve survival. Many cases of ILD are chronic and irreversible despite the therapy and lung transplantation may then be considered.

Pneumonitis versus pneumonia

Pneumonia is a term that was used in the past for lung inflammation that resulted from infection. Pneumonitis is lung inflammation in general but was mainly used if the inflammation was not caused by infection. The terms pneumonia and pneumonitis are often used interchangeably. In recent publications on interstitial lung diseases, the term pneumonia is used, such as in lymphocytic interstitial pneumonia (LIP).
Parambil et al. analyzed 18 patients with pSS and interstitial lung disease. Most patients presented with dyspnea and cough. The most common lung diseases were nonspecific interstitial pneumonia and organizing pneumonia (table 11.1).

Patients with Sjögren’s syndrome without respiratory symptoms and a normal chest x-ray, may have pulmonary abnormalities on high-resolution CT.

**Lung diseases in Sjögren’s syndrome**

The following pulmonary disorders will be discussed in relation with Sjögren’s syndrome:

1. **Tracheitis and bronchitis**
2. **Pleuritis**
3. **Interstitial lung diseases**
   a. nonspecific interstitial pneumonia
   b. lymphocytic interstitial pneumonia
   c. usual interstitial pneumonia
4. **Organizing pneumonia**
5. **Amyloidosis**
6. **Blood vessel mediated disorders**
   a. pulmonary embolism
   b. pulmonary arterial hypertension
   c. pulmonary vasculitis

1. **Tracheitis and bronchitis**
   Tracheitis sicca and bronchitis sicca are inflammations of the trachea and bronchi due to dryness. Mild forms are probably very common but no data are available in the medical literature.

2. **Pleuritis**
   Pleuritis, inflammation of the pleura, may be seen in patients with sSS and SLE or RA. It is almost nonexistent in pSS.

3. **Interstitial lung disease**
   The most common forms of interstitial lung diseases (ILDs) in pSS patients are nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), and lymphocytic interstitial pneumonia (LIP). Pulmonary manifestations may occasionally precede the more typical systemic manifestations of autoimmune diseases by months or years.

   Uffman et al. studied 37 consecutive patients with pSS and normal chest radiographs. Abnormal HRCT findings were seen in 24 patients (65%), seven of whom had normal pulmonary function tests (PFTs). The overall correlation between HRCT and PFTs was poor. HRCT and PFTs appear to be sensitive for both the early detection of parenchymal abnormalities and a decrease in lung function in asymptomatic patients with pSS. However, abnormal HRCT findings do not necessarily indicate a substantial alteration in PFTs. ILDs in patients with pSS are associated with a variety of histopathologic patterns that appear to have therapeutic and prognostic implications. Diffuse ILD is the most serious form of lung involvement due to its potentially progressive nature and the concomitant risk of respiratory failure.

   Parambil et al. performed a follow-up of 18 patients with pSS. Seven patients (39%) died during the follow-up after a median interval of 67 months following the diagnosis of ILD.

3a. **Nonspecific interstitial pneumonia**
   Nonspecific interstitial pneumonia (NSIP) is nonspecific in that it presents similarly to the other ILDs, but lacks the histopathologic features that characterize the individual disorders. On the basis of the histopathology of the alveolar wall, three groups of NSIP are distinguished. Group I shows primarily interstitial inflammation; II: inflammation and fibrosis; III: primarily fibrosis. Some patients also show areas with the histopathology of UIP (see further).

   Treatment consists of corticosteroids. Azathioprine may be added as a steroid-sparing agent or in patients with no or incomplete response. Cyclophosphamide is used in patients with severe initial disease and in those who have progressed on therapy with corticosteroids and azathioprine.

   The prognosis in idiopathic cases is better than in patients with a systemic autoimmune disease. Specific therapies for those diseases may guide treatment of the NSIP.

   The prognosis of NSIP is better than UIP (see below).

3b. **Lymphocytic interstitial pneumonia**
   Lymphocytic interstitial pneumonia (LIP) occurs in a wide variety of settings such as autoimmune disease (usually Sjögren’s syndrome), AIDS and as an adverse reaction to medications.

   The incidence of LIP is about twofold greater in women than men. Symptoms of progressive cough and dyspnea predominate. LIP is an inflammation around the small bronchial tubes in the lungs that resembles the inflammation found in the lacrimal and salivary glands.

   Recognition of LIP is important as it is potentially treatable. It is frequently misdiagnosed and treated as infectious pneumonia multiple times before the correct diagnosis is made. HRCT shows extensive areas of ground-glass attenuation and interlobular septal
thickening with scattered thin-walled cysts. An open-lung biopsy is the best method of diagnosing this condition, as less invasive techniques do not provide an adequate tissue specimen.

LIP is characterized by diffuse hyperplasia of bronchus-associated lymphoid tissue. The dominant microscopic feature of LIP is a diffuse, polyclonal lymphoid cell infiltrate surrounding airways and expanding the lung interstitium. LIP belongs within a spectrum of pulmonary lymphoproliferative disorders that range in severity from benign, small, airway centered cellular aggregates to malignant lymphomas.9

There is great variability in the clinical course of LIP, from resolution without treatment to progressive respiratory failure and death. LIP is often regarded as a steroid-responsive condition, and oral corticosteroids continue to be the mainstay of therapy, but the response is unpredictable. There have been no controlled trials to date. About 33-50% of patients die within 5 years of diagnosis, and about 5% of cases of LIP transform to lymphoma.9

3c. Usual interstitial pneumonia
In usual interstitial pneumonia (UIP), pulmonary function tests show a restrictive pattern and chest radiographs diffuse interstitial opacities associated with reduced lung volumes. HRCT shows a characteristic pattern of subpleural and bibasilar reticulonodular opacities with architectural distortion including honeycomb changes and traction bronchiectasis.

The histologic hallmark of UIP is a heterogeneous appearance with alternating areas of normal lung, interstitial inflammation, fibroblast foci and honeycomb change.14 Most patients with UIP die of respiratory failure within 5-10 years.14

3d. Organizing pneumonia
The name BOOP (Bronchiolitis Obliterans with Organizing Pneumonia) has been replaced by "organizing pneumonia" (OP) to avoid confusion with airway diseases such as constrictive bronchiolitis obliterans.11,15 If the cause of OP is not known, it is called cryptogenic organizing pneumonia. The word organizing reflects the so-called organisation of the inflammatory exudates. The sequence of events is:

1. initial alveolar epithelial injury and infiltration of the alveolar interstitium with lymphocytes and neutrophils; the organisation is characterised by intraalveolar formation of fibrinoid inflammatory cell clusters
2. the formation of fibroinflammatory buds; fibroblasts become myofibroblasts and re-epithelialisation occurs by progressive proliferation of alveolar cells
3. the inflammatory cells disappear almost completely from most buds.

The organisation has many similarities with the process of normal wound healing.16 The end result may be resolution of the inflammation or fibrosis.

Disease presentation
Patients typically present with an illness of short duration, usually less than 3 months, with variable degrees of cough and dyspnea. The cough may be productive of clear or discolored sputum. Symptoms usually follow a suspected but unconfirmed lower respiratory tract infection, and patients have often received at least one and frequently several courses of antibiotics.

Diagnosis
The diagnosis depends on finding the characteristic pathological features of the disease in the proper clinical setting.17 In one-half of the cases, the onset is heralded by a flu-like illness with fever, malaise, fatigue, and cough. The most common features at presentation are persistent nonproductive cough, dyspnea with exertion and weight loss.

Lung function tests confirm a restrictive ventilatory pattern (usually mild to moderate) with a moderately reduced diffusion capacity in most. Localized or more widespread crackles are frequently present. A markedly raised ESR, elevated CRP, and increased blood neutrophils are common findings.11

The chest x-ray is quite distinctive, with bilateral diffuse alveolar opacities in the presence of normal lung volumes.

Examples of diseases that should be excluded are bacterial pneumonia, hypersensitivity pneumonitis, chronic eosinophilic pneumonia and pulmonary drug reactions.

Treatment and prognosis
The majority of patients recover completely on administration of oral corticosteroids, but a significant number relapse within 1-3 months when the corticosteroids are reduced (usually to below 15 mg/d) or stopped. Prolonged treatment for 6 months or longer is advised. A small proportion of patients recovers spontaneously. Rare cases progress to respiratory failure and death.11 Organizing pneumonia in systemic
autoimmune diseases usually runs a more severe course and need immunosuppressive treatment in addition to corticosteroids.

4. Pulmonary lymphoma

Pulmonary lymphoma in Sjögren’s syndrome usually is a MALT-lymphoma, a lymphoma of mucosa-associated lymphoid tissue. Pulmonary lymphoma may occur within the spectrum of lymphocytic interstitial pneumonia (see back), a spectrum of pulmonary lymphoproliferative disorders that range in severity from benign, small, airway-centered polyclonal cellular aggregates to monoclonal malignant lymphomas.9

5. Pulmonary amyloidosis

Amyloidosis is a term that refers to the tissue deposition of fibrils of a variety of proteins. Amyloid deposition can be isolated to a single organ (e.g. Alzheimer’s disease) or occur in many organs, the major sites being kidneys, heart and liver. Several types of amyloidosis are hereditary or secondary to chronic inflammatory diseases.19

In secondary amyloidosis, the fibrils are composed of fragments of serum amyloid A (SAA), an acute phase reactant. Underlying disorders are rheumatoid arthritis in one-half of the cases and further ankylosing spondylitis, familial Mediterranean fever, psoriatic arthritis and Crohn’s disease.18 Secondary amyloidosis can be expected to occur mainly in sSS patients with longstanding active rheumatoid arthritis. Very few case reports have been published on secondary amyloidosis in pSS. The best documented paper is from Ooms et al.20 She described the case of a 53-year-old man with pSS according to the American-European criteria complicated by longstanding chronic interstitial nephritis.

The patient was negative for ANA, antibodies to SSA/Ro and SSB/La and rheumatoid factor. Other laboratory tests revealed strongly elevated ESR and CRP as well as a mild polyclonal hypergammaglobulinemia. The amyloid deposition in the kidneys caused renal failure and nephrotic syndrome.

Wong et al described a 29-year-old woman who presented with diffuse pulmonary nodular amyloidosis and was subsequently diagnosed as having Sjögren’s syndrome.21

It may be concluded that secondary amyloidosis can occur in patients with Sjögren’s syndrome and another disease with severe inflammation. However, the finding of secondary amyloidosis in a pSS patient warrants a very careful search for an underlying inflammatory disease as the cause of secondary amyloidosis other than pSS.

6. Blood vessel mediated disorders

6a. Pulmonary embolism

Pulmonary embolism (PE) is a major cause of death and may occur without or with a relationship with Sjögren’s syndrome. A related cause mainly concerns the antiphospholipid syndrome (APS). APS is caused by autoanti bodies against phospholipid-associated molecules and may cause thrombosis in both veins and arteries. When venous thrombi dislodge from their site of formation, they embolize to the pulmonary arterial circulation or, paradoxically, to the arterial circulation through a patent foramen ovale or atrial septal defect. About half of patients with pelvic vein thrombosis or proximal leg deep venous thrombosis (DVT) develop PE, which is usually asymptomatic. Isolated calf vein thrombi pose a much lower risk of PE, but they are the most common source of paradoxical embolism.

Acquired predispositions for thromboembolism are much more relevant than genetic factors and include long air travel, obesity, cigarette smoking, oral contraceptives, pregnancy, postmenopausal hormone replacement, surgery, trauma, and medical conditions such as antiphospholipid syndrome, cancer, systemic arterial hypertension, and chronic obstructive pulmonary disease.

PE results in gas exchange abnormalities such as hypoxemia and other pathophysiological abnormalities including increased pulmonary vascular resistance. Progressive right heart failure is the usual cause of death from PE.

6b. Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a disease of the small pulmonary arteries with vascular proliferation and remodeling, resulting in a progressive increase in pulmonary vascular resistance and right ventricular heart failure. Right-heart catheterization is the gold standard for the diagnosis.

PSS patients with PAH had Raynaud phenomenon, cutaneous vasculitis, and interstitial lung disease significantly more frequently than pSS without PAH. They also more frequently had ANA, a positive rheumatoid factor, autoantibodies to SSA/Ro and RNP, as well as hypergammaglobulinemia. These data suggest that systemic vasculopathy, B cell activation, and autoimmunity could play a role in the pathophysiology of Sjögren-associated PAH.

Launay et al6 discussed whether PAH is truly a complication of primary Sjögren’s syndrome or if the association could be fortuitous in patients displaying idiopathic PAH or other causes of pulmonary hypertension. Many data favor a true link between PAH and
pSS. First, PAH occurred most often in Sjögren patients with laboratory markers of intense B-cell activation, such as a high frequency of antinuclear antibodies and hypergammaglobulinemia. Second, immunofluorescence studies revealed deposits immunoglobulins and complement in the pulmonary arteriolar walls of patients with Sjögren-associated PAH. Third, PAH in these Sjögren patients sometimes responds favorably to immunosuppressive therapy alone, which is not the case in idiopathic PAH.

Although rare, PAH should be searched for promptly in patients with pSS with unexplained dyspnea, in order to establish the diagnosis sooner, with presumably a better prognosis. PAH has a poor prognosis but treatment options have progressed strikingly in recent years. As B-cells activation and antibodies formation are thought to play a role in the pathophysiology of Sjögren-associated PAH, anti-CD 20 (e.g. rituximab) could be a therapeutic option in the future.  

6c. Pulmonary vasculitis

Pulmonary vasculitis (PV) is a common finding in a number of uncommon disease entities and may be a part of a systemic vasculitis or the sole site of involvement.

PV is characterized pathologically by cellular inflammation, destruction of the blood vessel wall, and tissue necrosis.

Clinically, PV is characterized by the size, type, and location of the affected vessels in association with the degree of inflammation, vessel destruction, and tissue necrosis.

PV is a common feature of Wegener’s granulomatosis and Churg-Strauss syndrome. It may also occur in systemic autoimmune diseases such as RA, SLE, dermatomyositis, and systemic sclerosis. It may, therefore, also be seen in patients with these diseases in combination with secondary SS.

Publications on clinically relevant cases of PV in pSS could not be found.

References