Pulmonary Involvement in Sjögren Syndrome

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Abstract

Sjögren syndrome (SS) is a chronic autoimmune disease characterized by lymphocytic inflammation of exocrine glands and a variety of extraglandular sites. Lung involvement as defined by symptoms and either pulmonary function testing or radiographic abnormalities occurs in approximately 10 to 20% of patients. Subclinical lung disease is even more frequent and often includes evidence of small airways disease and airway inflammation. In general, patients will have evidence of both airway and interstitial lung disease by radiographs and pathology. Bronchiolitis and bronchiectasis are the most common airway manifestations while the interstitial pathologies associated with SS include nonspecific interstitial pneumonitis, usual interstitial pneumonitis, and lymphocytic interstitial pneumonitis. Patients with SS are also at an increased risk of lymphoma. A protean of other lung abnormalities including amyloidosis, granulomatous lung disease, pseudolymphoma, pulmonary hypertension, and pleural disease have been described.

Keywords

► Sjögren syndrome
► airways disease
► interstitial lung disease
► lymphoma
► prevalence
► treatment

Sjögren Syndrome

Sjögren syndrome (SS) is a chronic, autoimmune disease characterized by lymphocytic infiltration and progressive injury to and dysfunction of the exocrine glands. The hallmark of SS is termed the "Sicca syndrome" as a result of hypofunction of the salivary and lacrimal glands manifesting as dry eyes (xerophthalmia) and dry mouth (xerostomia). However, it is also a multiorgan autoimmune disease that has a progressive course.1 This syndrome may present as a primary disease (primary Sjögren syndrome [pSS]) or in association with other autoimmune rheumatic diseases such as rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis defining a secondary SS. Like other autoimmune conditions, the pathogenesis includes genetic, environmental, and hormonal factors.

There is no single gold standard test for diagnosing SS and there have been numerous proposed criteria. The most recent expert consensus by the American College of Rheumatology1 requires at least two of the following three criteria: (1) Positive serum anti-SSA/Ro and/or anti-SSB/La or positive rheumatoid factor and antinuclear antibody (ANA) titer $\geq 1:320$; (2) labial salivary gland biopsy exhibiting focal lymphocytic sialadenitis with a focus score $\geq 1$ focus/4 mm$^2$; (3) keratoconjunctivitis sicca with ocular staining score $\geq 3$ (assuming that the individual is not currently using daily eye drops for glaucoma and has not had corneal or cosmetic eyelid surgery in the past 5 years). A history of head and neck radiation treatment, hepatitis C infection, acquired immunodeficiency syndrome, sarcoidosis, amyloidosis, graft versus host, and immunoglobulin G4 (IgG4)-related disease would exclude participation in SS studies or therapeutic trials because of overlapping clinical features or interference with criteria tests.

SS is one of the most common autoimmune diseases, affecting between 1 and 3% of the general population.2 Moreover, it has been estimated that up to 50% of pSS patients are currently under diagnosed, whereas up to 30% of patients with other autoimmune diseases can be diagnosed with secondary SS.3 It is most often diagnosed during the fourth and fifth decades of life with a female-to-male ratio of 9:1.4

The focus of this review will be on the pulmonary manifestations of pSS. Risk factors for lung disease in SS include...
hypergammaglobulinemia, lymphopenia, positive rheumatoid factor, presence of anti-Ro and anti-La antibodies, decreased forced vital capacity and forced expiratory volume in 1 second, history of smoking, male gender, and increased age.\(^5,6\) A restrictive ventilatory defect has also been associated with baseline laboratory signs of immunologic activity such as increased levels of serum protein, IgG, erythrocyte sedimentation rate, and \(\beta_2\)-microglobulin.\(^6\)

### Prevalence of Lung Disease in Sjögren Syndrome

Over the years, multiple studies have attempted to determine the frequency of lung disease in patients with both pSS and secondary SS. The estimates have varied widely from 9 to 75%.\(^5,7-13\) The variations are due to differences in patient populations and definitions of disease involvement. In general, studies defining lung involvement as requiring the presence of respiratory symptoms and either an abnormal pulmonary function test or radiograph quote estimates of 9 to 22%.\(^5,7,10-12\) – Table 1 provides a summary of studies examining the frequency of respiratory disease in SS.

Abnormalities in respiratory function or structure may be even more common than distinct pathologic diseases. Symptoms of cough and dyspnea appear to be very common in unselected series of patients with SS. For example, in a study from 1985, Constantopoulos et al screened 36 consecutive patients with pSS with symptom questionnaires, X-rays, and PFTs and found that 50% had a cough and 28% complained of dyspnea.\(^9\) In a larger series of 100 consecutive patients with pSS in the United Kingdom, 43% had respiratory symptoms when evaluated within 6 months of their diagnosis of SS.\(^14\) Interestingly, when followed up 4 year later, 57% of the cohort had symptoms. This suggests that respiratory-related symptoms are common in SS and likely increase over the duration of the illness. Recent studies continue to support the frequency of respiratory-related complaints in patients with pSS. Bellido-Casado et al reported in 2011 that of 36 consecutive patients with pSS in Spain, 42% had cough and 42% had dyspnea.\(^15\)

### Table 1 Prevalence of lung involvement in Sjögren disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>N/characteristics</th>
<th>Study design</th>
<th>Prevalence of lung disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strimlan et al(^7)</td>
<td>1976</td>
<td>United States</td>
<td>343/81% women, mean age 57</td>
<td>Retrospective review of patients seen at Mayo with “classic” SS</td>
<td>9% had abnormal imaging and/or symptoms</td>
</tr>
<tr>
<td>Constantopoulos et al(^9)</td>
<td>1985</td>
<td>Greece</td>
<td>36/92% women, mean age 53</td>
<td>Prospective screened patients with primary SS with symptom questionnaires, X-rays, and PFTs</td>
<td>75% had some abnormality (symptom or testing)</td>
</tr>
<tr>
<td>Gardiner et al(^13)</td>
<td>1993</td>
<td>UK</td>
<td>16/93% women, mean age 58</td>
<td>Consecutive patients with primary SS complaining of dyspnea underwent HRCT, PFTs, BAL, and transbronchial biopsies</td>
<td>69% had some abnormality on testing</td>
</tr>
<tr>
<td>Uffmann et al(^8)</td>
<td>2001</td>
<td>Austria</td>
<td>37/100% women, mean age 52</td>
<td>Consecutive patients with primary SS without symptoms and with a normal CXR were screened with PFTs and HRCT</td>
<td>73% had abnormal PFTs and/or HRCT</td>
</tr>
<tr>
<td>García-Carrasco et al(^10)</td>
<td>2002</td>
<td>Spain</td>
<td>400/93% women, mean age 53</td>
<td>Registry of consecutive patients with primary SS seen at four hospitals</td>
<td>9% had cough and/or dyspnea with interstitial changes on X-ray, abnormal PFTs and/or evidence of alveolitis/fibrosis on HRCT</td>
</tr>
<tr>
<td>Yazisiz et al(^2)</td>
<td>2010</td>
<td>Turkey</td>
<td>123/88% women, mean age 52</td>
<td>Patients with primary SS seen over a 5-year period without pre-existing lung disease</td>
<td>11.4% had signs/symptoms of lung disease with an abnormal PFT and/or HRCT</td>
</tr>
<tr>
<td>Palm et al(^12)</td>
<td>2013</td>
<td>Norway</td>
<td>117/92% women, mean age 62</td>
<td>Norwegian CTD and vasculitis registry patients identified as having primary SS</td>
<td>22% had symptoms and an abnormal PFT and/or HRCT</td>
</tr>
</tbody>
</table>

Abbreviations: CTD, connective tissue disease; HRCT, high-resolution computed tomography; PFT, pulmonary function testing; SS, Sjögren syndrome.
Unfortunately, there have been relatively few risk factors for lung involvement consistently identified. Strimlan et al found that those with lung involvement were more likely to have hypergammaglobulinemia and a positive ANA or rheumatoid factor.7 The association with a positive ANA was supported by one additional study.10 Yazisiz et al demonstrated that in their cohort, hypergammaglobulinemia and a positive SSA and SSB were highly specific though not sensitive for lung involvement.5 Davidson et al found that those with anti-Ro (SSA) were more likely to have lung involvement.16 On the contrary, the study of Ramos-Casals et al did not find any relationship to serologic status.11 Three studies have suggested that older age at disease onset and/or longer duration of disease was associated with a higher risk of lung involvement.11,12,17

**Pulmonary Function Testing Abnormalities**

The frequency and nature of pulmonary function testing (PFT) abnormalities described in patients with SS have varied widely in studies though the most common abnormality described appears to be a reduced diffusing capacity for carbon monoxide (DLCO).9,12,13,16,18 In addition, some studies demonstrate restriction19 while other suggest that obstruction may be more common.8,9,13,20 In particular, small airway dysfunction is likely fairly prevalent. For instance, in one study, the frequency of a reduced maximal expiratory flow (MEF) at 25% of FVC (MEF25) was 44%,9 while in another, it was 23%19 and in a third it was 41%.8 Almost all studies agree that while abnormalities may be common, the degree of impairment is typically mild. The evolution of PFT changes over time has been inconsistent from study to study. In Linstow et al, 27 patients with pSS who had baseline PFTs had follow-up studies at 7 years.21 In their study, they found that the DLCO and MEF75 actually improved over time. On the contrary, in a cohort of 30 patients with pSS in the United Kingdom, the DLCO actually worsened over the first 4 years of diagnosis and then remained at that level for years 4 through 10.16

**Radiographic Abnormalities**

Changes by plain chest radiograph appear frequent7-9 but fairly nonspecific. In addition, these changes appear to often not be very predictive of the underlying physiology by PFT or lung pathology. For instance, in one study published in 1986, 66 patients with pSS and secondary SS underwent routine chest X-ray screening.19 In 43% of the primary patients and 62% of the secondary patients, a diffuse reticulonodular pattern was seen predominantly in the lower lobes. However, these changes often did not correlate with the PFT or symptoms.

High-resolution computed tomography (HRCT) provides improved sensitivity but again may detect frequent changes of uncertain clinical significance. A wide variety of abnormalities have been demonstrated on patients with SS ranging from interstitial changes with reticulation and/or ground glass, to cysts, to airway-related changes. Often changes appear to coexist. The relative frequency of these changes vary from study to study likely reflecting the relative proportions of lung pathologies that can been seen in SS. –Table 2 summarizes many of the CT studies and their findings. In general, these studies document changes consistent with either an airway process or an interstitial process with no clear dominance of one category of lung disease over the other. In fact, in many studies found evidence of concomitant airways disease and interstitial changes in the same subject.

**Bronchoalveolar Lavage and Lung Pathology**

The presence of lymphocytosis on bronchoalveolar lavage (BAL) in patients with SS has been a relatively consistent finding from study to study. For example, Gardiner et al performed BAL on 16 patients with pSS who complained of dyspnea and found that 44% had significant lymphocytosis.13 In another study, a Japanese group performed BAL on 28 patients with SS and lung disease and found that 64% had lymphocytosis.22 Interestingly, a Greek group reported that not only was lymphocytosis common on BAL but when these patients were followed forward over time that these patients had a poorer prognosis overall both in terms of mortality but also with an increase need for therapy.23 On note, however, the increased mortality was not from respiratory failure so the mechanism of this increased risk was not apparent in their study.

Reports of biopsy findings in patients with SS mirror the array of abnormalities seen on chest imaging with both interstitial changes and airway disease being described with some patients having both simultaneously.17,28

**Quality of Life and Mortality**

Given the mild nature of the changes described and the poor correlation between PFTs and chest imaging, it would be tempting to dismiss lung involvement in Sjögren disease as relatively minor or clinically insignificant. However, there is evidence that having lung involvement significantly impacts both quality of life and mortality for patients with SS.

In 2005, Belenguer et al published a study of 110 patients with pSS.24 They found that those with lung involvement had a lower health-related quality of life as measured by role physical and role emotional subscales. In addition, they reported more pain and had a lower summary health summary score than those without lung involvement. Similarly, in the Norwegian connective tissue disease and vasculitis registry, those pSS patients with lung involvement reported a lower physical functioning score and had an increased risk of death compared with those without lung disease (17 vs. 5%).12

**Airway Disease in Sjögren Syndrome**

Even in patients without clear airway obstruction or airway changes by CT, airway inflammation is often detected. Papiris et al examined lobar bronchial biopsies for 10 patients with SS and compared them to biopsies from 10 healthy volunteers.25 They found that all the Sjögren patients had more CD4
positive lymphocytes in their bronchial mucosa. This was despite the fact that 4 of their subjects had no symptoms and 7 of the 10 had normal chest X-rays. Similarly, Gardiner et al found lymphocytic bronchial changes by transbronchial biopsies in 5 of 16 patients with SS complaining of dyspnea. A Japanese study of morphometric analysis of six autopsy specimens from Sjögren patients (two of which had pulmonary fibrosis) found that there was hyperplasia of airway secretory cells (airway epithelial goblet cells and submucosal gland cells) in patients with SS compared with normals. When taken together these studies suggest that the airway in SS may be a common site of extraglandular lymphocytic infiltration even without clinically apparent disease.

Clinically detectable and even significant airways disease does occur in SS (Fig. 1). In one Japanese study, bronchiolitis was detected in 12% of Sjögren patients undergoing lung biopsy. Various different types of bronchiolitis have been observed in patients with SS. For instance, in one Chinese series of 14 Sjögren patients with lung biopsy, 29% of the patients demonstrated changes consistent with follicular bronchiolitis, 21% with chronic bronchiolitis, and 7% with obliterative bronchiolitis. Interestingly, there was one

**Table 2 HRCT studies of Sjögren syndrome**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N</th>
<th>Normal</th>
<th>Airway findings</th>
<th>Interstitial findings</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gardiner et al</td>
<td>1993</td>
<td>16</td>
<td>47%</td>
<td>7% bronchiectasis</td>
<td>20% fibrosis</td>
<td>20% pleural changes 14% cysts</td>
</tr>
<tr>
<td>Franquet et al</td>
<td>1997</td>
<td>50</td>
<td>66%</td>
<td>22% bronchiolar abnormalities</td>
<td>22% reticulation</td>
<td>Air space consolidation 2% 64% of those with bronchiolar changes also had parenchymal changes</td>
</tr>
<tr>
<td>Papiris et al</td>
<td>1999</td>
<td>61</td>
<td>69%</td>
<td>22% airway thickening</td>
<td>6% had interstitial changes</td>
<td>9% cysts</td>
</tr>
<tr>
<td>Franquet et al</td>
<td>1999</td>
<td>34</td>
<td>32%</td>
<td>had bronchiolar abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uffmann et al</td>
<td>2001</td>
<td>37</td>
<td>35%</td>
<td></td>
<td>24% interlobular septal thickening 10% ground glass</td>
<td>24% micronodules 14% cysts</td>
</tr>
<tr>
<td>Taouli et al</td>
<td>2002</td>
<td>35</td>
<td>6%</td>
<td>54% airways disease</td>
<td>20% pulmonary fibrosis 14% had LIP by HRCT pattern</td>
<td></td>
</tr>
<tr>
<td>Matsuyama et al</td>
<td>2003</td>
<td>107</td>
<td>42%</td>
<td>pSS: 33% sSS: 16%</td>
<td>pSS: 50% sSS: 74%</td>
<td>pSS: 13% had lymphoproliferative pattern sSS: 5% had BOOP pattern (no lymphoproliferative)</td>
</tr>
<tr>
<td>Lohrmann et al</td>
<td>2004</td>
<td>24</td>
<td>22%</td>
<td>46% bronchiectasis</td>
<td>38% ground glass 29% interlobular septal thickening 25% honeycombing</td>
<td>46% cysts 46% small nodules</td>
</tr>
<tr>
<td>Watanabe et al</td>
<td>2010</td>
<td>80</td>
<td>10%</td>
<td>23% bronchiectasis</td>
<td>70% interlobular septal thickening 14% honeycombing</td>
<td>38% cysts</td>
</tr>
<tr>
<td>Yazisiz et al</td>
<td>2010</td>
<td>213</td>
<td>NR</td>
<td>Bronchiectasis 50%</td>
<td>Ground glass 64% Reticulation 50% Honeycombing 43%</td>
<td>Lymphadenopathy 50% Cysts 7%</td>
</tr>
<tr>
<td>Mandl et al</td>
<td>2012</td>
<td>41</td>
<td></td>
<td>Bronchiectasis 44%</td>
<td>Interstitial changes 54% Ground 7%</td>
<td>Emphysema 7%</td>
</tr>
<tr>
<td>Palm et al</td>
<td>2013</td>
<td>117</td>
<td></td>
<td>50% Air trapping 22% Reticulation 44%</td>
<td>Cysts 42%</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BOOP, bronchiolitis obliterans organizing pneumonia; HRCT, high-resolution computed tomography; LIP, lymphocytic interstitial pneumonitis; NR, not reported; pSS, primary Sjögren syndrome; sSS, secondary Sjögren syndrome.
patient with a peribronchial granulomatous process that was morphologically identical to sarcoidosis. In half of their patients’ biopsies changes of bronchiolitis coexisted with interstitial inflammation in various patterns. The study by Nakanishi et al.\(^{28}\) found chronic bronchiolitis to be more common than follicular bronchiolitis.

Follicular bronchiolitis is an uncommon bronchial disorder characterized by the presence of hyperplastic lymphoid follicles with reactive germinal centers distributed along bronchovascular bundles.\(^{29,30}\) A review of patients with follicular bronchiolitis on lung biopsy seen over a 9-year period at the Mayo Clinic found that 1 out of their 12 cases had SS as their likely underlying etiology;\(^{17}\) 8 of the 12 were idiopathic. Of the 12, three quarters had follicular bronchiolitis as the major finding of their lung pathology while in the other three, it was a minor finding. The patients with follicular bronchiolitis demonstrated either restriction (40%) or a low DLCO (30%) or normal findings (30%) on PFTs. Despite this being an airway centered process obstruction was not seen. CTs demonstrated reticular opacities, small nodules, and/or ground glass. The course was generally fairly benign with 75% of those receiving treatment improving by symptoms and 100% improving by PFTs and/or radiograph in that series.\(^{17}\)

While the bronchiolitis described in SS is typically described as being fairly mild, there are cases of more severe disease reported in the literature. For instance, Borie et al described five cases of severe bronchiolitis in patients with SS.\(^{31}\) There is minimal data on the therapy for bronchiolitis in SS. In the Mayo series on follicular bronchiolitis, one patient with SS was treated with steroids and was reported to have inactive disease at 103 months of follow-up.\(^{17}\) Rituximab has been used successfully at least once in bronchiolitis associated with SS.\(^{32}\)

Finally, bronchiectasis has been described as present in 23 to 54% of CTs of patients with SS.\(^{33–35}\) One study examined the patterns and clinical importance of bronchiectasis in a cohort of 41 patients with pSS.\(^{36}\) They found that all the patients had cylindrical bronchiectasis on CT. These patients tended to be older at the time of diagnosis of SS and had a higher frequency of hiatal hernias. On serologies those with bronchiectasis were less likely to have an anti-Ro (SSA) antibody and more likely to be antismooth muscle antibody positive. These changes had clinical implications with a higher frequency of respiratory infections (82 vs. 60%) and pneumonia (56 vs. 3%) in those with bronchiectasis compared with pSS patients without over a period of follow-up.

### Interstitial Lung Disease in Sjögren Syndrome

As noted previously, the finding of interstitial lung disease in SS is not infrequent (6–70%).\(^{5,8,12,13,33–35,37–40}\) Lymphocytic interstitial pneumonitis (LIP) has a classic association with SS\(^{41}\) but may not be the most common pathologic subtype identified in SS (\(\sim\) Fig. 2). For instance, in a Japanese series of Sjögren’s patients who underwent lung biopsy, 61% of their cohort had nonspecific interstitial pneumonitis (NSIP), 12% had bronchiolitis, 12% had lymphoma, 6% had amyloidosis, and 3% had honeycomb changes.\(^{22}\) In that series, no patients had LIP. In a Chinese series by Shi et al.,\(^{27}\) they also found that NSIP was the most common pathology on biopsy with organizing pneumonia being next most common. They also noted that concomitant airways disease was common. A third series of pSS patients from the Mayo Clinic again found NSIP to be the most common pathology (28%), followed by organizing pneumonia (22%), usual interstitial pneumonia (17%), lymphocytic pneumonitis (17%), lymphoma (11%), and amyloidosis (6%).\(^{42}\)

Data on the natural history and treatment of interstitial lung disease in SS are limited. In the Mayo series, they reported that during a median follow-up of approximately 3 years, 39% of their cohort died including three deaths from acute exacerbations of interstitial pneumonias.\(^{42}\) Similarly, in a recent review of 83 patients with collagen vascular disease-associated ILD (CV-ILD), Suda et al included 17 patients with SS and among those 17, 1 had an acute exacerbation (6%).\(^{43}\) This was similar to their overall incidence of acute exacerbations in all CV-ILD of 7.3%. In the Ito et al series, they found a more benign clinical course with a 5-year survival overall of 83% that did not differ for those with NSIP versus other lung pathologies.\(^{22}\)

A report from Brazil treated a group of 11 patents with ILD in the setting of SS with an azathioprine-based regimen and found a significant improvement overall in the forced vital capacity (FVC) in their patients (7/11 had a 10% or more increased in FVC).\(^{37}\) However, the study was nonrandomized and the exact nature of the underlying pathology was not provided, so our ability to make confident conclusions about the efficacy of azathioprine is limited. In the Mayo series, 15 of the 18 ILD patients were treated with corticosteroids and often another agent including hydroxychloroquine.

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**Fig. 1** A 68-year-old woman with primary Sjögren syndrome and a productive cough. The HRCT demonstrates lower lobe predominant bronchiectasis. HRCT, high-resolution computed tomography.
changes are common (e.g., see \textit{Fig. 2}). In some longitudinal studies of LIP, it appears that the nodules may progress to cystic changes over time.\textsuperscript{47} Honeycombing can occur but is not common. Although cystic changes may suggest the presence of underlying LIP, there are cases of lymphoma and amyloidosis presenting with a radiographic pattern similar to LIP\textsuperscript{22,42,48} and caution should be used in making the diagnosis of LIP on radiographic grounds alone.

Corticosteroids are most commonly used to treat LIP. In the National Jewish study, they treated nine of their patients with steroids among whom one progressed, four improved, and another four remained stable.\textsuperscript{43} The mean survival in their cohort was 11.5 years. Seven of the 15 died and of those 3 were respiratory related. No patients converted to lymphoma over their period of follow-up. In the series by Liebow and Carrington, 5 of the 10 patients treated with steroids improved radiographically.\textsuperscript{41} There are also reports of rituximab improving more refractory cases of LIP.\textsuperscript{49,50}

\textbf{Pulmonary Embolism}

Patients with immune-mediated diseases such as SS are at increased risk for venous thromboembolism. This may be related to the increased prevalence (\textgreater{} 30\%) of positive antiphospholipid antibodies (anticardiolipin, anti-\(\beta_2\)GP1, or lupus anticoagulant) seen in patients with pSS\textsuperscript{51} versus a consequence of chronic inflammation. In a large English national dataset containing 12,680 patients with SS, an increased observed versus expected admissions for deep venous thrombosis or pulmonary embolism were demonstrated with a relative risk ratio of 2.02.\textsuperscript{52}

\textbf{Pulmonary Amyloidosis}

Pulmonary amyloidosis is a rare complication of pSS. It occurs almost exclusively in women who typically complain of cough and dyspnea. Patients may also frequently complain of fatigue, weakness, hemoptysis, and pleuritic chest pain.\textsuperscript{53} Other associated abnormalities reported include immune thrombocytopenia,\textsuperscript{54} cryoglobulinemia,\textsuperscript{55,56} Raynaud phenomenon,\textsuperscript{57} antiphospholipid antibody syndrome,\textsuperscript{58} and lymphoma.\textsuperscript{54,58,59} The median onset of pulmonary amyloidosis is 7 years after diagnosis of pSS, but it may be diagnosed concurrently with pSS.\textsuperscript{53} The prognosis is unknown and there are no data to support any definitive therapeutic intervention for pSS-related pulmonary amyloidosis.

Large, calcified, randomly distributed, irregular, smooth-bordered nodules may be the sole radiological abnormality. Nodules may also occur in association with multiple cysts, septal thickening, and smaller nodules as seen with lymphoid interstitial pneumonia.\textsuperscript{53,59} Surgical lung biopsy is usually required to establish the diagnosis and rule out lymphoma, particularly in patients with marked constitutional symptoms. Nodular AL amyloidosis (both \(\lambda\) and \(\kappa\)) is the most common pathologic finding seen in isolated pSS-associated pulmonary amyloidosis. Although isolated pulmonary cases have been reported in pSS, the diffuse septal type (AA and AL) is generally associated with systemic amyloidosis.\textsuperscript{53,60}
Pulmonary Involvement in Sjögren Syndrome

Kreider, Highland

Pulmonary Hypertension

Pulmonary hypertension in the setting of SS can be the result of an arteriopathy, pulmonary veno-occlusive disease, valvular heart disease, or interstitial lung disease. The prevalence and incidence of pSS-pulmonary arterial hypertension (PAH) are unknown although 24 patients had evidence of pulmonary hypertension in an echocardiographic study of 107 consecutive patients with pSS. The rarity of pSS-PAH often results in a delay to diagnosis with most patients presenting with an advanced functional class and evidence of right heart failure. Therefore, survival estimates are low at 73 and 66% at 1 and 3 years, respectively.

The cases described in the literature are typically women in their third and fourth decades of life and more often of Japanese descent. Typically, pSS precedes the diagnosis of pulmonary hypertension, but the two can occur concurrently. Patients with pSS-associated PAH were more likely to have Raynaud phenomenon, cutaneous vasculitis, and interstitial lung disease. There does not appear to be any correlation between the severity of the sicca symptoms and the degree of pulmonary hypertension or with gas transfer.

Patients with pSS-PAH also more frequently had antinuclear, anti-Ro/SSA, and anti-RNP autoantibodies, as well as positive rheumatoid factor and hypergammaglobulinemia. Hypocomplementemia and cryoglobulinemia have also been shown to be strong predictors of pulmonary artery systolic pressure.

Microscopically, small arteries and arterioles show concentric fibrocellular intimal proliferation, medial hypertrophy, and plexiform lesions with deposits of IgG, C1q, C3c, C4, and C5. Eccentric intimal proliferation indicating organized thrombi has also been observed. Together, these data suggest that systemic vasculopathy, B cell activation, and autoimmunity could play a role in the pathology of pSS-associated PAH.

The best treatment strategy remains to be defined. In the largest case series reported in the literature (n = 28), standard PAH therapy (endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, or prostanoids) was initially effective in some patients but had short-term and long-term failures. Some patients were treated with first-line immunosuppressants alone leading to improvement in some, but second-line standard PAH therapy was added in all cases thereafter. No pSS-PAH patients seem to respond to acute vasodilator testing suggesting that calcium channel blockers would be ineffective.

Pleural Disease

Lymphocytic pleuritis with or without effusion and/or pleural thickening has rarely been described in pSS. The pleural fluid is a lymphocytic predominant exudate with a normal glucose and pH. The pleural fluid analysis may also have an increased pleural/serum levels of rheumatoid factor, SSA/rho, SSA/la, and immune complexes and decreased pleural/serum levels of complement. The presence of a coexisting autoimmune disease such as SLE or rheumatoid arthritis needs to be excluded.

Diaphragmatic Dysfunction

Shrinking lung syndrome is a rare complication of systemic autoimmune diseases, although mainly seen in systemic lupus erythematosus, it has also been described in SS. It is characterized by small lung volumes, elevation of the diaphragm and restrictive physiology without parenchymal involvement. Its pathogenesis remains controversial: diaphragm dysfunction, phrenic neuropathy, or pleural inflammation. No treatment has been validated.

Respiratory muscle weakness with or without failure can be a consequence of hypokalemic periodic paralysis associated with a distal renal tubular acidosis or rarely as a consequence of proximal skeletal myopathy.

Pulmonary Vasculitis/Alveolar Hemorrhage

Acute pulmonary hemorrhage has rarely been described in pSS. Only two cases have been reported, the first was secondary to pulmonary vasculitis in the context of immune thrombocytopenia and cryoglobulinemia. The second was a bland pulmonary hemorrhage that was followed by the rapid development of fibrotic NSIP.

Granulomatous Disease/Sarcoidosis

Sarcoidosis and SS share pathogenic, immunogenic, and several clinical features, making it difficult to differentiate between the two diseases. In 2002, the American-European study group revising the classification criteria for SS included sarcoidosis as an exclusion criterion for the diagnosis of pSS. However, multiple authors have supported a true coexistence of sarcoidosis and more than 70 cases of overlap have been reported. The prevalence of sarcoidosis in large series of patients with pSS ranges from 1 to 2%, a frequency of sarcoidosis that is higher than in the general population suggesting a true association. In a case series of 59 patients by pSS patients ranges from 1 to 2%, a frequency of sarcoidosis that is higher than in the general population suggesting a true association. In a case series of 59 patients by pSS patients ranges from 1 to 2%, a frequency of sarcoidosis that is higher than in the general population suggesting a true association.

Lymphoma

Patients with SS are at increased risk of developing non-Hodgkin lymphoma. In the largest cohort study of pSS (n = 676), the risk of lymphoma was 8.7. However, this...
increases to 16-fold in patients who strictly fit the American-European Consensus Criteria for pSS. The risk was more pronounced with longer follow-up time (> 10 years) although lymphoma can happen at any time. Markers of severe SS such as parotid enlargement, hypocoomplementemia, cryoglobulinemia, and palpable purpura are associated with a more pronounced risk of NHL and the greatest risk is associated with CD4+ cytopenia and a low CD4+ /CD8+ ratio. Clinically, primary pulmonary lymphoma presents with cough, dyspnea, weight loss, and fatigue. Radiographically, it can present as solitary or multifocal nodules, bilateral alveolar infiltrates, or interstitial markings randomly distributed with a mild predilection for the lower lobes. Mediastinal lymphadenopathy and pleural effusions may accompany the parenchymal abnormalities.

The most frequent location for lymphoma is in the lymph nodes, salivary glands, lacrimal glands, and the lungs. The prevalence of primary pulmonary lymphoma is estimated to be 1 to 2% in patients with pSS. A spectrum of lymphoproliferation occurs in the setting of pSS, from benign lymphoid infiltration confined to glandular tissue to widespread lymphoreticular malignancy and is believed to develop as a multistep process in which polyclonality is suppressed therapy; it rarely can progress to frank lymphoma. The prevalence of primary pulmonary lymphoma is estimated to be 1 to 2% in patients with pSS. A spectrum of lymphoproliferation occurs in the setting of pSS, from benign lymphoid infiltration confined to glandular tissue to widespread lymphoreticular malignancy and is believed to develop as a multistep process in which polyclonality is followed by monoclonality and eventually by a t(14;18) chromosomal translocation. Large B cell lymphoma is the most common subtype, although mucosa-associated lymphoid tissue (MALT) lymphoma is also well described.

Pseudolymphoma

Pseudolymphoma or pulmonary nodular lymphoid hyperplasia is a benign lesion characterized by infiltration of mature polyclonal lymphocytes and plasma cells. It is more common in patients with loan sicca syndrome. Patients are usually asymptomatic but can also present with cough and dyspnea. The typical CT finding is a solitary nodule or mass. Pseudolymphoma can also present as parenchymal consolidation with air bronchograms or even as multiple nodules. There is controversy whether pseudolymphoma is different from extranodal marginal Z cell lymphoma and differentiation of pseudolymphoma from other lymphoproliferative disorders can be only based on immunohistochemical and molecular studies. Pseudolymphoma usually regresses after treatment with corticosteroids of immuno-suppressive therapy; it rarely can progress to frank lymphoma.

References

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