Pulmonary manifestations of Sjögren’s syndrome

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Summary

Sjögren’s syndrome is a chronic inflammatory disorder characterized by lymphocytic infiltration of the exocrine glands, mainly the lacrimal and salivary glands. However, extraglandular organ systems may frequently be involved, including the lungs. Although subclinical pulmonary inflammation exists in more than 50% of patients, clinically significant pulmonary involvement affects approximately 10% of patients and may be the first manifestation of the disease. The entire respiratory tract may be involved, with a wide spectrum of manifestations including xerotrachea and bronchial sicca, obstructive small airway disease, various patterns of interstitial lung disease, lymphoinfiltrative or lymphoproliferative lung disease, such as lymphoma (usually of MALT type), pulmonary hypertension, pleural involvement, lung cysts, and pulmonary amyloidosis.
and pulmonary involvement. In addition, SS is associated with a 16- to 44-fold increased risk of lymphoma compared to the general population [3,4].

Despite SS being undoubtedly the most common connective tissue disease, recent epidemiological studies suggest that it has a lower prevalence that previously thought, affecting about 0.1 to 0.6% of the general population [5,6]. Prevalence is higher in females than in males, with a female-to-male ratio of 9:1. Although SS may occur at any age, including in childhood, first symptoms appear at a mean age of 50 years [1,2]. The disease has a variable onset: glandular involvement with a dry syndrome and/or parotid tumefaction, or extraglandular manifestations, complicating and often delaying the diagnosis. The new American-European criteria (Box 1) are now used internationally, but present a limitation in that they do not include the systemic manifestations on which the disease prognosis depends.

This chapter deals only with pSS; drug-induced pulmonary diseases and pulmonary infections are therefore not included.

**Prevalence of pulmonary manifestations in Sjögren’s syndrome**

Assessments of the prevalence of pulmonary involvement in SS vary considerably, depending on which diagnostic criteria are used. The new American-European criteria are considered to be more specific than previous sets of criteria. In addition, some studies include pSS and sSS, in which the pulmonary manifestations may have been related to coexisting connective tissue disease. The prevalence also depends on the criteria used to diagnose the respiratory involvement: clinical features, functional exploration, standard chest X-ray or chest computed tomography, or bronchoalveolar lavage findings.

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**Glossary**

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<tr>
<th>Abbreviation</th>
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<tr>
<td>BAL</td>
<td>bronchoalveolar lavage</td>
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<tr>
<td>FEV1</td>
<td>expiratory volume in one second</td>
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<td>LIP</td>
<td>lymphocytic interstitial pneumonitis</td>
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<td>MALT</td>
<td>mucosa-associated lymphoid tissue</td>
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<td>mPAP</td>
<td>mean pulmonary arterial pressure</td>
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<td>MZBCL</td>
<td>marginal zone B-cell lymphoma</td>
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<td>NSIP</td>
<td>non-specific interstitial pneumonitis</td>
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<td>NYHA</td>
<td>New York Heart Association</td>
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<td>OP</td>
<td>organizing pneumonitis</td>
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<td>PAH</td>
<td>pulmonary arterial hypertension</td>
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<td>sSS</td>
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<td>UIP</td>
<td>usual interstitial pneumonia</td>
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<td>VC</td>
<td>vital capacity</td>
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**Box 1**

**Revised international classification criteria for Sjögren’s syndrome [146].**

I. Ocular symptoms: a positive response to at least one of the following questions:
1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
2. Do you have a recurrent sensation of sand or gravel in the eyes?
3. Do you use tear substitutes more than 3 times a day?

II. Oral symptoms: a positive response to at least one of the following questions:
1. Have you had a daily feeling of dry mouth for more than 3 months?
2. Have you had recurrently or persistently swollen salivary glands as an adult?
3. Do you frequently drink liquids to aid in swallowing dry food?

III. Ocular signs – that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:
1. Schirmer’s I test, performed without anaesthesia (≤ 5 mm in 5 minutes)
2. Rose bengal score or other ocular dye score (≥ 4 according to van Bijsterveld’s scoring system)

IV. Histopathology: in minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score greater or equal to 1, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm² of glandular tissue

V. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:
1. Unstimulated whole salivary flow (≤ 1.5 ml in 15 minutes)
2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary or destructive pattern), without evidence of obstruction in the major ducts, 3. Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer

VI. Autoantibodies: presence in the serum of the following autoantibodies:
1. Antibodies to Ro(SSA) or La(SSB) antigens, or both

Revised rules for classification

*For primary SS*

In patients without any potentially associated disease, primary SS may be defined as follows:

a. The presence of any 4 of the 6 items is indicative of primary SS, as long as either item IV (Histopathology) or VI (Serology) is positive
b. The presence of any 3 of the 4 objective criteria items (that is, items III, IV, V, VI)
If only clinically significant pulmonary involvement is considered, most published studies remove homogeneous prevalence of around 9–12% of SS patients[2,7–10]. Most data come from Europe, USA, Turkey or Japan. However, when is systematically looked for, by clinical examination, functional studies, X-ray or CT scan, pulmonary involvement seems to be more frequent, change reaching for affecting 43 to 75% of patients[11,12]. For example cough was found in 41% of 61 patients observed by Papiris et al.,[13]. Systematic use of CT scan revealed abnormalities in 34 to 50% of patients[14,15]. Finally, when bronchoalveolar lavage (BAL) was used as a screening test in patients without any respiratory symptoms, pulmonary inflammation, mainly alveolar lymphocytosis, was found in 55% of the patients [16].

Clinical and biological profile of patients with pulmonary involvement

SS is a heterogeneous disease in terms of both clinical features and outcomes. Two forms of the disease exist:
- an “epithelial” form, limited to a dry syndrome, often associated with arthralgia, myalgia and fatigue;
- an “extra-epithelial” form, with systemic manifestations and recurrent parotid inflammation. This latter form is biologically characterized by the presence of hypergammaglobulinemia, a higher frequency of anti-SSA and SSB antibodies, and the presence of cryoglobulinemia with lower complement levels [2,7,10]. This extra-epithelial form carries a higher risk of lymphoma, particularly in patients with small vessel skin vasculitis, lower C3 and C4 levels, cryoglobulinemia, CD4 lymphopenia, and reduced CD4/CD8 ratio [4,17,2,18].

As well as other systemic manifestations, pulmonary involvement seems to be more frequent in patients with hypergammaglobulinemia and anti-SSA/Ro antibodies [8,9,11]. However, a higher prevalence of pulmonary manifestations in patients with immunologic abnormalities has not been observed in all studies [2]. This is likely due to the great diversity of pulmonary manifestations observed in SS: involvement of large and small airways resulting in dry tracheobronchitis, different types of interstitial involvement, and lymphoproliferative disorders (Box 2). Anti-SSA/Ro antibodies are almost always found in patients with interstitial pneumonia [19]. Male sex, advanced age at diagnosis, longer evolution, and also tobacco smoking probably increase the risk of interstitial pneumonia [2]. Rarely, interstitial lung disease or pleural involvement may be the first clinical manifestation of SS [20].

Airway involvement in Sjögren’s syndrome

Impairment and destruction of exocrine glands due to T-lymphocyte infiltration may involve the respiratory tract in SS.
patients. These lesions can be related either to sicca syndrome (glandular involvement) or to cell infiltrate (extraglandular involvement).

Depending on the detection methods used and the population studied, the frequency of clinical symptoms can vary from 9 to 75%. The populations in reported studies are heterogeneous, including pSS and sSS, as well as patients with or without auto-antibodies [9]. Airway involvement is the most frequent respiratory location described, although most studies have also reported interstitial pneumonitis [21].

Airway lesions may involve the trachea, bronchi and bronchioles (distal airways).

**Airway lesion pathology**

Very few studies have attempted to characterize the histopathological changes or the pattern of the glandular or extraglandular cell infiltrate in SS. SS lesions were described by Papiris et al. [22], following a review of bronchial and transbronchial biopsies. Thirteen non-smoker patients with radiological abnormalities were included. Ten out of 13 patients had extraglandular mononuclear cell infiltration of bronchial and bronchiolar submucosa. A CD4-positive T-lymphocytic phenotype was reported in six out 10 patients. Patients’ symptoms were not correlated with cell infiltration. Neutrophils and mast cells are also described in SS bronchial mucosa patients [23].

Bronchiolar disease may be isolated or associated with non-specific interstitial pneumonitis (NSIP), or with lymphocytic interstitial pneumonitis (LIP), such as follicular bronchiolitis. Ito et al. studied radiological and anatomical correlations in 33 SS patients. In four out of 33, bronchiolar lesions were dominant [24]. In four others, bronchiolar lesions were associated with other abnormalities. Therefore, bronchiolar pathological disease was present in 8/33 of the SS patients. Follicular bronchiolitis is the most frequently reported lesion in SS (figure 1). The development of hyperplastic lymphocytic follicles in bronchiolar walls can lead to bronchiolar lumen obstruction. SS is the systemic disease most frequently associated with follicular bronchiolitis [25]. Transbronchial biopsies are recommended as a first step if a pathological diagnosis is required [26]. Submucosal and peribronchiolar collagen fibrosis due to the active cellular inflammation induces bronchiolar lumen reduction. Other bronchiolitis types have also been described in SS patients, albeit less frequently:

- lymphocytic bronchiolitis, characterized by lymphocytic infiltration without follicles [27,28];
- constrictive bronchiolitis-associated bronchiolar destruction, most frequently associated with SS secondary to rheumatoid arthritis; it is exceptionally described in primary SS;
- organizing pneumonitis (OP), which is classified with interstitial pneumonitis.

**Clinical and functional patterns**

**Tracheobronchial disease**

Large airways involvement, as confirmed by pulmonary function testing, affects 8 to 12% of SS patients [29]. Exocrine glandular lesions are associated more frequently with tracheobronchial symptoms. Xerotrachea is a local sicca syndrome, responsible for a decrease in mucociliary clearance [30]. Tracheobronchial dryness was indirectly measured by mucociliary clearance. Measured by a ventilation scan, mucociliary clearance decrease is correlated with the severity of functional salivary disease [30]. Few studies have documented bronchial gland involvement in SS. Surprisingly, one study (six SS patients) reported an absence of bronchial gland atrophy compared to controls [31], a finding that argues in favor of a secretion functional defect rather than a glandular destruction. Further studies are required to confirm these data. In another study, a ventilation scan was used to document airway permeability function in 18 SS patients and 13 healthy volunteers. Technetium clearance was increased in the SS patients, indicating pulmonary permeability dysfunction [32]. Fifty percent of SS patients report having dry cough day and night, impairing their quality of life [33]. Recurrent respiratory infections (bronchitis, pneumonia) are associated with airway dysfunction in 20% of SS patients. Atelectasis related to mucus impaction may worsen bronchial obstruction. Wheezing can be observed. Proximal airway destruction may be responsible for bronchiectasis. Neither radiological nor respiratory functional abnormalities (vital capacity [VC] and forced expiratory volume in one second [FEV1]) were detected in patients with uncomplicated clinical features. A decrease in FEV1 was described...
in 11% of SS patients [13] and in 14% of 100 patients at SS diagnosis [11].

CT scan studies have clearly demonstrated the high frequency of proximal airway disease (table 1) associated with distal airway involvement: bronchial airway thickening (8–68%), centrolobular nodules (6–29%), bronchiectasis (5–46%) and air trapping (32%) [13,14,34–37], (figure 2). The high frequency of radiological patterns related to airway disease confirms the predilection of SS for the bronchial tree. The variability of frequency reported in the different studies may be linked to differences in patient inclusion criteria.

The initial presentation of SS may mimic non-allergic asthma. As SS mainly occurs in women over the age of 50 years, dry cough, wheezing and asthenia may be lead to the disease being misdiagnosed as late onset asthma.

**Distal airway disease in Sjögren’s syndrome**

The frequency of distal airway disease in SS is difficult to evaluate. Bronchiolitis secondary to extraglandular lesions may be isolated or associated with interstitial disease (LIP, NSIP, and lymphoma). Follicular bronchiolitis is the main pathological pattern in SS and is similar to that described in rheumatoid arthritis patients. The main symptoms associated with bronchiolitis are dry cough, recurrent “bronchitis” and dyspnea. Evaluating distal airway disease with pulmonary function tests is difficult. Measuring the flow related to distal airways (less than 2 mm in diameter) is technically challenging. Indeed, values for maximum expiratory flow from 25 to 75% of vital capacity (MEF25–75%) and forced expiratory flow from 50% of vital capacity (FEF50%) below the lower limit of normal suggest possible distal airway involvement. Nevertheless, when expiratory time is optimal in a patient with normal VC and an FEV1 of more than 80%, these values may be relevant for distal airway function evaluation. Pulmonary hyperinflation, defined as a higher residual volume to total lung capacity ratio (RV:TLC), was reported in half of the patients with primary SS and was associated with diminished peripheral airflow [38]. Other tools such as the forced oscillation technique to measure resistance or the exhaled fraction of nitric oxide (FeNO) measurement should be considered [39,40]. Some studies have reported distal airway function without controls. Papiris et al. showed a decrease in FEF50% and FEF25% (less than 75% of theoretical values in 87 and 97%, respectively, of pSS non smoker patients) [13]. Constantopoulos et al. reported in eight of 36 patients with pSS small airways obstruction with significantly diminished maximal expiratory flows at 25% of forced VC (MEF25) [12]. Mialon et al. evaluated 18 primary SS patients for a period ranging from 26 to 137 months and reported a reduction in MEF25 values in 72% of patients, a finding consistent with the development of peripheral airways obstruction [32]. Most studies have reported a frequency of 22 to 46% of distal airway disease in SS [12,26,41].

![figure 2](HRCTscan showing centrolobular nodules in a patient with SS and follicular bronchiolitis)
After 10 years of follow-up, Davidson et al. reported in 30 patients with pSS, a great variation in TLCO in time and concluded that TLCO was relatively an insensitive technique to detect subclinical pulmonary disease in those patients [8]. An ongoing prospective study in our center is designed to evaluate the clinical characteristics of respiratory manifestations in primary SS patients. Patients are included in the study if a self-questionnaire screening respiratory symptoms is positive. As of November 2010, 53 pSS patients are included of whom 77% had respiratory symptoms. Among patients with airway disease, 24% presented chronic cough and 52% had a bronchial obstruction. Interestingly, 56% of patients had a TLCO less than 80% and 65% of these patients had a bronchial obstruction without interstitial disease, pulmonary hypertension or cardiac disease. The latter patients had more severe dyspnea, an impairment of quality of life, a decrease in capillary volume, a lower MEF25–75% value and inspiratory capacity and a decrease in capillary volume. The pulmonary capillary volume was calculated using a method evaluating the lung diffusing capacity for nitric oxide (DLNO). Fibrosis and destruction of bronchiar and peribronchiar areas, including the distal vessels, may explain the decrease in TLCO and in capillary volume. As a consequence, bronchiolitis may be associated with an isolated decrease in TLCO in SS patients. Data on follow-up of bronchiolitis lesions and of pulmonary function tests are currently lacking. Some studies showed that the bronchial and bronchiolar disease is stable in SS [11,32,42]. Lymphoid infiltration may be associated with an atelectasis responsible for a middle lobe syndrome [43]. Except in rheumatoid arthritis with sSS, constrictive bronchiolitis is rare in SS [44]. Rare cases of panbronchiolitis have been described [45]. Crestani et al. reported six cases of pSS and predominant bronchiolar manifestations [46]. Five of the six had recurrent bronchial infections, bronchial obstruction, hypoxemia and centrilobular nodules compatible with diffuse bronchiolitis. Three of the six patients were treated with macrolides for a duration of 6 to 24 months. The outcome was favorable in two patients with this treatment.

**Bronchial hyperresponsiveness**

Bronchial hyperresponsiveness is frequently described in SS. It is characterized by symptoms reported by patients such as an increase in cough after exposure to smoke, sprays, air-conditioning, etc. Its severity is correlated with tracheal dryness [29]. Bronchial hyperresponsiveness is reported to occur in 42 to 60% of SS patients [29,47–49]. This frequency is higher compared to controls. The mechanisms involved in bronchial hyperresponsiveness in SS are unknown but are likely to be different from those identified in asthma. There are no eosinophils in bronchial mucosa, and the bronchial reactivity differs: patients with SS have a higher response to metacholine and a lower response to adenosine monophosphate, cold or hyperventilation [50]. The intensity of bronchial hyperresponsiveness does not appear to depend on SS severity or duration, and bronchial hyperresponsiveness is not correlated with salivary gland lymphocytic infiltration [49] or with exhaled NO level [51]. Nevertheless, no study has evaluated the bronchial structure-function relationship in SS. Bronchial hyperresponsiveness is rarely described in systemic diseases other than SS and systemic sclerosis [48].

**Other manifestations**

Recurrent respiratory infections are reported in 10 to 35% of patients [7,27,52]. The decrease in mucoiliary clearance, local immunity impairment, and parodontopathy related to the sicca syndrome may facilitate infections. A tracheal lymphoma responsible for corticosteroid-resistant severe tracheal obstruction has been described in SS. Cysts on high-resolution CT (HRCT) scan, isolated or associated with LIP or lymphoma, may be due to a peribronchial infiltration leading to sequelae of fibrosis and a thin walled cyst. Lymphoid infiltration associated with amyloid deposition within the bronchial tree has been described in SS [45].

**Interstitial lung diseases**

Various histological patterns of ILDs have been associated with pSS, such as NSIP, usual interstitial pneumonia (UIP), OP, LIP, primary pulmonary lymphoma and diffuse interstitial amyloidosis (Box 2). In addition more than one type of pattern of ILD may be observed [53]. SS is consequently at the crossroads between autoimmune diseases and lymphoproliferative disorders.

**Clinical manifestations**

Parenchymal lung involvement in SS is usually manifested by cough and dyspnea, although some patients may be asymptomatic with a normal chest X-ray. In a series of 61 consecutive patients diagnosed with pSS, 41% noted a "sicca cough" whereas only 7% noted dyspnea upon effort [13] and 14% had bibasilar rales. Cough of variable intensity may be observed in up to 50% of patients [33].

**Radiological features**

Radiological abnormalities in SS vary widely depending on the methodologies used to investigate the disease. The chest X-ray usually reveals a fine reticular or nodular pattern. Bilateral lung infiltrates were the most common pattern seen on chest radiography [19]. In patients with both pSS and pSS, 22% had chest radiography abnormalities, with linear and reticular opacities being the most frequent finding [15]. HRCT findings in SS include both interstitial and airway abnormalities and both ILD and bronchiolar inflammatory changes are common abnormal findings seen in pSS [15,34,35,54]. Koyama et al. reviewed chest HRCT findings of 60 patients with pSS and showed that the most common findings were ground-glass opacities (92%), centrilobular nodules (78%), nonseptal linear opacities (75%), interlobular septal thickening (55%), bronchectasis (38%), and cysts (30%) [35]. Indeed, ground-glass

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Pulmonary manifestations of Sjögren’s syndrome

Bronchoalveolar lavage findings

Bronchoalveolar lavage (BAL) fluid in patients with pSS typically reveals an increased inflammatory cells, in particular excess lymphocytes counts. In a series of studies, Wallaert et al. first examined patients with primary and secondary Sjögren’s syndrome with and without clinical pulmonary disease [63]. Half of the patients with pSS and no clinical, radiographic, or lung function evidence of pulmonary disease had an abnormal lavage cellular differential. Two patterns of BAL cellular yield were identified: a pure lymphocyte predominant alveolitis (18% lymphocytes in 69% of the abnormal lavages) and a mixed neutrophil and lymphocytic alveolitis (4% neutrophils in 25% of the abnormal lavages). Patients with abnormal BAL findings tended to have more severe Sjögren’s disease with extensive extraglandular disease (myositis, lymphadenopathy, renal or hepatic involvement), higher serum gamma globulin and serum beta-2-microglobulin, and higher prevalence of rheumatoid factor and antinuclear antibodies. Non-smokers with pSS syndrome in the absence of clinical or radiographic evidence of pulmonary disease had a significantly increased percentage of lymphocytes in BAL fluid [64,65]. In particular, patients with pSS syndrome had an increase in CD4+ helper/inducer and CD8+ cytotoxic/suppressor cells in the lungs similar to findings reported from other mucous surfaces of these patients. A particularly interesting finding in this study was the demonstration that patients with a neutrophilic alveolitis tended to have a marked increase in the CD8 suppressor/cytotoxic population in their BAL fluid [64]. In addition, alveolar macrophages from patients with pSS are activated, as assessed by the detection of neutrophil chemotactic activity from alveolar macrophage in culture, fibronectin secretion and spontaneous release of increased amounts of superoxide anion [64]. Unfortunately, it is not known if these abnormalities predict the development of clinically relevant lung disease. The prognostic value of BAL alveolitis in SS is unknown. None of the patients with an abnormal BAL fluid at presentation was shown to develop clinical evidence of lung disease [63,66]. Even when ILD is present, a BAL lymphocytosis tends to predict a relatively good prognosis. In contrast, patients with other defined connective tissue diseases had a neutrophil alveolitis, often associated with a poorer clinical outcome and clinical deterioration in untreated patients [61,63,64,67].

Patients with lymphocytic alveolitis had more cough, dyspnea, roentgenologic evidence of ILD, and abnormal pulmonary function (lower TLC and diffusing capacity). Lymphocyte subtyping studies revealed a reduced T-helper/suppressor (CD4/CD8) ratio. In a series of 18 patients with pSS but no radiographic disease or respiratory symptoms, 14 patients had a pure lymphocytic alveolitis, whereas four had a mixed neutrophilic and lymphocytic alveolitis [61]. On repeat BAL after 2 years’ observation, nearly half of the patients with lymphocytosis had a normal BAL whereas the other patients (with a lymphocytic alveolitis or mixed alveolitis) had no change in their differential. At the time of the second lavage, the patients with abnormal HRCT scans had greater BAL cellularity, a greater percentage of neutrophils and lymphocytes, but no difference in the CD4/CD8 ratio or percentage of activated (DR+) lymphocytes. Interestingly, the patients with lymphocytic alveolitis had a smaller loss of their DLCO 2 years later compared with those patients with a mixed (neutrophilic and lymphocytic) alveolitis. Otherwise there were no differences in patients’ extraglandular involvement or serologies based on BAL (cell differential) or radiographic (disease present or absent) differences. Thus the detection of these forms of pulmonary inflammation may be useful in the management of these disease processes.

Diffuse interstitial pneumonias in Sjögren’s syndrome

A UIP (figure 3) pattern is rather uncommon in patients with SS. In the series of 343 patients studied by Strimlan et al., pulmonary involvement in systemic diseases.
fibrosis was histopathologically diagnosed in only two patients [7]. In this series, no distinction was made between the primary and secondary forms of SS. Since then, most reports of interstitial pulmonary fibrosis have been on patients with sSS [26]. Pulmonary fibrosis has also been described in patients with pSS, although the histopathological changes have been poorly documented and the diagnosis was usually based on radiological and functional data alone [26]. Deheinzelin et al. performed open lung biopsy in 12 patients with pSS and found a spectrum of interstitial lung disease ranging from follicular bronchiolitis and LIP to UIP [68]. Yamadori et al. performed surgical biopsies in nine patients with pSS and found six patients with UIP histology and three with NSIP [69]. Recently, Parambil et al. studied lung biopsies in 18 patients with pSS and interstitial lung disease in light of the recent classification of idiopathic interstitial pneumonias [19]: the main histopathological patterns observed included NSIP, OP, UIP, and LIP in 5, 4, 3, and 3 patients, respectively.

**Organizing pneumonitis (OP)**

OP is characterized by concentric stenosis of bronchiolar lumen and by the filling of alveoli with tissue composed of fibroblasts, myofibroblasts, and mononuclear cells. OP may be associated with drug use, infections (in particular viral infections) or with systemic autoimmune diseases such as rheumatoid arthritis and lupus erythematosus. Although rarely reported in the course of SS, OP does not seems to be exceptional: in two studies of cases with interstitial pneumonia during SS, with histopathological examination of lung tissue, OP was found in four out of 18 cases in one study and in three out of 33 cases in the other [19,24]. The clinical presentation is similar to that of community-acquired pneumonia, with irregular alveolar opacities, usually bilateral, with air bronchograms sometimes associated with linear or nodular interstitial infiltration. The diagnosis is suggested if antibiotics prove ineffective in such cases of pneumonia. In most of these published cases, the OP revealed SS [70–73] and regressed with corticosteroid therapy without sequelae.

Cystic lesions have been reported during the course of SS [74]. Diffuse interstitial lesions with cysts may be indistinguishable from other benign lesions, such as lymphoid interstitial pneumonia [57]. Young et al. described a patient with SS and Wegener’s granulomatosis who presented with cavitary lung disease [75]. Interestingly, SS may be complicated by both multiple bullae and pulmonary nodular amyloidosis (figure 4) [76–78]. In a recent study of 80 patients, lung cysts were observed in 22 patients (39%) with pSS and eight patients (33%) with sSS and were significantly associated with anti-SSB/La seropositivity and clonally derived lymphoproliferative disorders. The presence of lung cysts revealed by chest CT might be a prognostic clinical feature, a clue, or a predictor of clonally derived lymphoproliferative disorders in patients with SS [79].

**Lymphoproliferative disorders**

Diffuse lymphoid hyperplasia of the lungs

Follicular bronchiolitis may present as a separate disease [80], but in patients with primary SS follicular bronchiolitis usually
coexists with lymphocytic bronchitis/bronchiolitis or LIP, or both. Histopathologically, it is characterized by lymphoid hyperplasia surrounding terminal bronchioles, resulting in narrowing of lumina. HRCT usually demonstrates diffuse ground-glass opacities (figure 5) or nodular bronchiolocentric opacities.

In a few cases, follicular bronchiolitis is associated with airway obstruction, which may induce cystic changes (bullae) in the lung parenchyma [28].

LIP is a diffuse infiltrative lung disorder, first described by Liebow and Carrington [81]. It is a classic but uncommon component of SS. Histologically, it is characterized by an interstitial polyclonal infiltrate of mature lymphocytes, plasma cells, and other lymphoreticular elements, which expand to the interstitial septa and fill the alveolar spaces (figure 6). Interstitial lymphoid nodules with germinal centers may be visible in some areas. LIP frequently coexists with follicular bronchiolitis [82] and the overlapping list of etiologies of the two conditions suggests a close relationship. Patients with LIP may be asymptomatic or present with cough and progressive dyspnea. Systemic symptoms such as fever, night sweats, and weight loss are less common. Lung auscultation often reveals bibasilar fine rales. Clubbing is almost always absent. The chest roentgenogram shows a diffuse interstitial or patchy alveolar pattern with lower lobe predominance. HRCT usually identifies thickened bronchovascular bundles, nodules of varying sizes, ground-glass opacities, and interstitial or alveolar opacities (figure 7) [54,83]. Pulmonary function tests typically reveal a restrictive ventilatory defect. Lung biopsy is necessary for diagnosis. Transbronchial biopsy is often insufficient to make a diagnosis of LIP and recourse to open lung biopsy is frequently necessary. Given its frequent association, HIV testing should be...
performed in cases of LIP. The natural history of LIP is unknown; some patients may have a favorable course (stabilization or improvement), whereas others may evolve to bronchus-associated lymphoid tissue (BALT) lymphoma.

Lymphomas

In addition to the common pulmonary complications, patients with pSS have a high risk of developing B-cell lymphoma, which may affect the lungs in 20% of cases [84,85]; indeed, among 50 SS patients with lymphoma, Hansen et al. found 10 patients with pulmonary localization [85]. The lungs are also the second extra-nodal localization of lymphoma in pSS [3,4]. Typically, these lymphomas are mostly composed of mucosa-associated lymphoid tissue (MALT, 50%) and marginal zone B-cell lymphoma (MZBCL, 40%) with low-grade malignancy. High-grade B-cell lymphomas associated with increased mortality have also been reported (<10%). The prognosis is usually good, with an average 5-year survival rate of 65 to 90% [85–88]. Pulmonary pSS lymphomas are often pauci-symptomatic and were detected in a routine or occasional examination in most of the reported cases; dry cough of mild intensity and slowly progressive dyspnea were the most commonly reported pulmonary symptoms [84–87,89,90]. Associated systemic symptoms and biological parameters include those previously reported as associated with a high risk of lymphoma in pSS and may include cutaneous vasculitis, recurrent parotidomégaly, lymphopenia, hypogammaglobulinemia, low C4 levels and presence of a type II cryoglobulinemia [86].

Radiological findings in pulmonary pSS lymphoma are entirely non-specific. Chronic alveolar opacities, reticular or reticulo-nodular opacities, diffuse nodular lesions, or pleural effusion have previously been reported. Bilateral disease is present in 25 to 50% of cases. Mediastinal involvement is rarely described [89,90]. The diagnosis of primary pulmonary lymphoma in pSS may be made by CT-guided biopsy of the pulmonary lesion, reported as successful in only 25% of cases. Other studies have reported utility with BAL, but BAL alone does not allow the immunopathological analysis and clonal detection necessary to make a specific diagnosis [91]. Diagnostic operative procedures range from lymph node biopsy to wedge biopsy or lobectomy. Anatomopathological analysis must include clonal detection by molecular analysis. After pulmonary lymphoma has been diagnosed, appropriate staging including bone marrow biopsy and CT scan of the abdomen should be performed to rule out extrathoracic disease. If the pathological diagnosis is MALT lymphoma without evidence of higher-grade transformation and staging finds no disease elsewhere, a complete resection may be considered definitive and no further therapy is required [92]. If there is residual disease, disease in the contralateral chest, or extrathoracic disease, chemotherapy regimens including rituximab and/or radiotherapy may be considered [88].

The nature and existence of pseudolymphoma, a tumor-like aggregate of lymphoid cells that does not meet the criteria for malignancy, is currently debated. Indeed, the description of pseudolymphoma in pSS was made 30 years ago, and such cases may have in fact represented low-grade lymphomas that could not be definitively classified as such with diagnosis tools from that era [93].

Pleural involvement

Pleural involvement seems to be rare in primary SS. The presence of a pleural effusion should prompt a further evaluation for the underlying etiology. Kelly et al. reported pleuritis in one out of 43 patients with pSS [11] and Gardner et al. reported pleural thickening in three out of 16 patients [26]. Only one study is discordant, in which the retrospective examination of CT scans in patients with pSS found pleural thickening in 36% (20/56 patients) [79].

More interesting are the rarely reported presentations of uni- or bilateral pleuritis revealing SS. The pleuritis was attributed to SS because no other etiology was found, and because of the presence in the pleural effusion of lymphocytes and anti-SSA and SSB antibodies [94–96]. Shrink lung syndrome has commonly been reported in patients with systemic lupus erythematosus, but recently the case of a woman with pSS who developed shrinking lung was reported [97].

Pulmonary amyloidosis

Pulmonary amyloidosis associated with SS is rare and there is a paucity of data on its clinical and radiological features. A recent publication identified 33 well-described cases in the literature [98]. Women accounted for 96.5% of cases (male:female ratio 1:27, compared to 1:9 for Sjögren’s syndrome alone). The median age of the patients was 59 years (range: 29–79) and most were symptomatic (72.7%, n = 22). The most common symptoms were cough (n = 9/33) and dyspnea (n = 9/33). Other symptoms included fatigue, weakness, hemoptysis and pleuritic chest pain. Significant weight loss was uncommon, but often indicated lymphoma complicating SS and pulmonary amyloidosis. Most cases of pulmonary amyloidosis occurred in primary SS (91%). Lymphoma was associated with Sjögren’s syndrome-related pulmonary amyloidosis in 9%. The diagnosis of pulmonary amyloidosis usually followed that of SS. Pulmonary amyloidosis was reported with a variable delay from the diagnosis of SS (median 7 years, range 0–30, n = 18). Pulmonary amyloidosis in SS is reported to be associated with diffuse septal and nodular infiltrates [19,99]. In the review by Rajagopala et al. [98], multiple nodules were the most common radiological abnormality (78.8%). The nodular pattern was frequently the sole radiological finding (33.3%), or occurred in association with a lymphoid interstitial pneumonia pattern (45.5%), with multiple cysts, septal thickening and nodules.
The nodules are relatively large, irregular, have smooth margins and are randomly distributed, with frequent calcification without cavitation. The cysts are not numerous and are randomly distributed without zonal predominance. Diffuse septal amyloidosis occurred in 12% (n = 4/33) of patients. Isolated diffuse septal AA amyloidosis [19,99] and diffuse septal AL amyloidosis with systemic AL amyloidosis [100] have been reported in patients with SS. Spirometry may indicate obstructive or restrictive lung disease. In the review by Raja-gopala et al. [98] most patients required surgical lung biopsy for the diagnosis of pulmonary amyloidosis and to exclude associated lymphoma, tuberculosis or fungal infection. Transbronchial lung biopsy, CT-guided aspiration and biopsy were also used for evaluation. The nodular forms were frequently reported as localized AL amyloidosis. Pathophysiologically, this may reflect contiguous clonal cells arising locally and excreting light chains. Pulmonary AA amyloidosis has also been associated with SS, without evidence of amyloid deposition elsewhere [19,99]. Localized AA amyloidosis may be an organ-specific deposition abnormality related to local inflammation [101]. Most patients, especially those with nodular amyloidosis, were observed without administration of any specific therapy. Five patients were treated with corticosteroids, with improvement reported in four. However, data on objective spirometric or radiological improvement, and in particular the rate of occurrence of lymphoma in those with LIP-generalized nodular amyloidosis, have not been reported.

Figure 8
Diffuse nodular amyloidosis is the most common radiological pattern (a), occurring alone or in association with cysts of varying size (b)

Pulmonary hypertension
Pulmonary hypertension (PH) is defined as a mean pulmonary arterial pressure (mPAP) greater than 25 mmHg at rest as assessed by right heart catheterization (RHC) [102]. An updated clinical classification of PH [103] distinguishes pulmonary arterial hypertension (PAH), pulmonary veno-occlusive disease, PH due to left heart disease, PH due to lung disease and/or hypoxia and chronic thromboembolic PH. Within PAH, there is a subgroup of patients with PAH associated with connective tissue diseases. This subgroup accounts for up to 10–15% of PAH cases [104,105]. The main connective tissue diseases that can be complicated by PAH are systemic sclerosis [106] followed by systemic lupus erythematosus and mixed connective tissue disease [107]. For instance, 5–10% of systemic sclerosis patients may present with PAH [108]. Some other connective tissue diseases can also occur in association with PAH, though far more rarely: dermatomyositis and rheumatoid arthritis [107]. PAH has not been reported as a complication of pSS in large cohorts of patients [2,109,110]. However, a recent report of several cases and an extensive literature review [111] reported 41 pSS patients with PH [26,112–137]. Among them, 13 were in the non-English literature and RHC data were available in only 17 patients. The importance of right heart catheterization for diagnosis and prognosis evaluation of PAH must again be emphasized. Data were sufficient for analysis for 28 patients with pSS-associated PH [111]. That study found that PH was a possible complication of pSS but appeared to be rare, even if possibly overlooked. This contrasts with the relatively high frequency of pSS in the general population. Most patients with pSS-associated PH had pSS-associated PAH [111]. Interestingly, some patients also had portal hypertension. One patient had a chronic thromboembolic PH and two patients had PH due to lung disease. There are no reported cases of pulmonary veno-occlusive disease in the context of pSS.
The majority of patients with pSS-associated PH are women but the proportion is reported to be the same as in pSS without PH [111]. Mean age at diagnosis of PH is 50 ± 11 years in the literature [111]. The first symptom of PH (exertional dyspnea or syncope in all cases) precedes the diagnosis of PAH by 34 months, which suggests that PH is underdiagnosed in pSS patients with dyspnea, most likely because of its rarity. The clinical presentation of pSS-associated PH is usually severe, with more than 80% of patients presenting with New York Heart Association (NYHA) functional class III or IV and a low mean 6-minute walk distance of 330 m, which is consistent with a late diagnosis [111]. Nearly half of the patients in the literature review had evidence of right heart failure [111]. When performed (n = 17 patients), hemodynamics revealed moderate to severe PAH (mPAP: 44 mmHg, cardiac index: 2.9 Lmin⁻¹m⁻², total pulmonary resistance: 11 Woods units). Among the 10 patients in whom acute vasoreactivity testing using inhalation of nitric oxide was performed, none were responders as recently defined [138]. Histological examination is available in six patients [111]. Intimal and medial hypertrophy was common whereas vasculitis or inflammatory infiltrates was not described. Where available, immunofluorescence findings showed deposits of immunoglobulins and complement in the pulmonary arteriolar walls in two out of three patients. It must be emphasized that lung biopsy is generally not performed in PH patients as it is unnecessary for diagnosis and may be dangerous.

In pSS-associated PH, the diagnosis of pSS can precede diagnosis of PH in nearly half of the patients or both diagnoses can be made concomitantly. Glandular manifestations in patients with pSS-associated PH are similar to those of patients with primary SS and no PH. Conversely, when compared to the cohort examined by GC et al. [2], patients with pSS-associated PH appear to have significantly more frequently Raynaud’s phenomenon and to a lesser extent cutaneous vasculitis. These findings reinforce the probable role of vasculopathy in the pathogenesis of PH in these patients. Interstitial lung disease is also more frequently found in pSS-associated PH (26 vs. 9% in patients without PH) [111]. Patients with pSS-associated PH have significantly more frequently antinuclear, anti-Ro/SSA and anti-RNP antibodies as well as positive rheumatoid factor and hypergammaglobulinemia than pSS patients without PH. These immunological findings could suggest both an activation of B cells and a role of autoantibodies, such as anti-RNP antibodies [139], or other antibodies, such as anti-endothelial cell antibodies [140] in the pathogenesis of pSS-associated PAH.

In conclusion, PH is a rare but quite severe complication of pSS, which should be searched for in cases of unexplained dyspnea, and/or syncope. Although echocardiography is a useful initial investigative tool for suspected PH, RHC is mandatory to confirm the diagnosis. Patients with pSS-associated PH appear to have more frequently a vasculopathy, interstitial lung disease, and B cell activation markers (antinuclear antibodies, anti-Ro/SSA, anti-RNP antibodies and hypergammaglobulinemia) than pSS patients without PH. Standard PH therapy and immunosuppressants can be efficient in some patients. The best treatment algorithm remains to be defined and the prognosis appears to be poor.

**Treatment**

Treatment and prognosis of airway disease in SS have yet to be defined. Extraglandular lesions (lymphocytic infiltration) may respond to corticosteroids [43]. In symptomatic and/or severe bronchial manifestations, systemic steroid treatment may be indicated. In severe broncholitis, corticosteroids and immunosuppressive drugs have been tested in single cases, without evidence for efficacy [24]. In case of severe bronchial or bronchiolar disease, decisions on whether such treatments should be continued should be based on assessment of objective parameters such as HCRT or lung function testing. Due to the side effects, if the treatment response is not clear, treatment should be discontinued. Erythromycin has shown some efficacy for the treatment of broncholitis associated with rheumatoid arthritis, and this approach might be considered in SS, though convincing data supporting the benefit of this strategy in pSS are lacking [45,53]. Indications for inhaled bronchodilator and corticosteroids may be tested in cases of obstructive bronchial disease and/or bronchial hyperresponsiveness, even if one study in SS was negative [50]. Inhibition of B lymphocytes by rituximab may represent an alternative in case of aggressive airway disease in SS [141–143].

Corticosteroids are the most widely used treatment for OP. In patients with UIP and NSIP, low-dose corticosteroids and azathioprine are usually recommended though there is no definitive evidence that this approach alters the course of the disease [144]. Indeed corticosteroid and immunosuppressive drugs are usually used in patients with extraglandular involvement. In a series of 11 patients treated with an azathioprine-based regimen, a significant improvement in forced VC was observed after at least 6 months when compared with non-treated patients [68]. Unfortunately, no control studies have been done; thus, therapy has so far been empirical. The treatment of LIP is based on anecdotal experience. Corticosteroids are the traditional primary therapy, but other immunosuppressive agents such as cyclophosphamide, chlorambucil, and azathioprine have been used, with variable results. Some patients improve without therapy, while others progress to advanced interstitial fibrosis despite immunosuppression [145]. The treatment of PAH in SS is very heterogeneous as are the evaluation criteria used to assess their efficacy. Among the 19 case reports in the literature with data concerning treatment, some patients had no treatment and two patients were treated with calcium channel blockers alone [111]. Six patients were treated with immunosuppressive therapy either alone or preceded by standard PH therapy or followed by standard PH therapy. Seven patients received a standard PH therapy as
first-line treatment (bosentan, $n = 3$, IV epoprostenol, $n = 2$, oral prostacyclin, $n = 1$, sildenafil, $n = 1$) with some benefit but possible short-term failure. First-line immunosuppressive therapy may transiently improve clinical and hemodynamic status in some patients with pSS-associated PAH. However, sustained benefits with this approach alone are unusual as is the case in other forms of CTD-associated PAH and standard PAH treatment is most often required. Moreover, it must be kept in mind that failure of immunosuppressive therapy is most likely underestimated. However, the data are both retrospective and too weak at this time. Only prospective studies (difficult considering the rare combination of primary SS and PAH) would be able to clarify the role of immunosuppressive treatment in PAH associated with pSS. The best treatment strategy remains therefore to be defined. Among the 28 patients, information on survival is available in all patients but one. Overall, 15 out of 27 patients were alive at the last evaluation. Twelve patients died, 11 from PAH and one from pneumonia. Estimated survival rates were 73 and 66% at 1 and 3 years, respectively [111].

**Conclusion**

Pulmonary involvement is common in pSS patients, but only about 10% of them are symptomatic. The main pulmonary manifestations are sicca cough, and mild to moderate airways obstruction. However, more severe lung involvement may occur, such as various patterns of interstitial diseases, lymphoproliferative disorders, or pulmonary amyloidosis and lung cysts, needing specific therapy. Systematic and regular pulmonary evaluation of SS patients, even asymptomatic ones, with a minimum of pulmonary function testing and plain chest radiography is appropriate.

**Conflict of interests:** None.

**References**

patients with primary Sjögren’s syndrome. 


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