Pulmonary manifestations of systemic lupus erythematosus and Sjögren's syndrome

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Purpose of review
Systemic lupus erythematosus (SLE) and Sjögren syndrome are chronic autoimmune inflammatory disorders that can present with multiorgan involvement including the lungs. This review will focus on recent literature pertaining to the epidemiology, pathogenesis, clinical presentation and diagnosis and management of SLE and Sjögren syndrome-associated pulmonary conditions.

Recent findings
Pulmonary manifestations of both disease entities have been well characterized and lung involvement can be observed during the course of the disease in most cases. Pulmonary manifestations of SLE and Sjögren syndrome can be classified based on anatomical site of involvement; and the large and small airways, lung parenchyma, lung vasculature, pleura and respiratory muscles can be involved. The pleura is most commonly involved in SLE, whereas the airways are most commonly involved in primary Sjögren's syndrome (pSS). Sleep disturbances have also been described in both entities.

Summary
Although further research into treatment strategies for the pulmonary complications seen in SLE and pSS is needed, the clinician should be aware of the risk factors and clinical presentation of the various pulmonary complications in SLE and pSS in order to identify patients who should be screened and/or have modifications in treatment strategies to mitigate the morbidity and mortality associated with these complications.

Keywords
bronchiolitis, interstitial lung disease, lymphocytic interstitial pneumonia, nonspecific interstitial pneumonia pulmonary hypertension, Sjögren's syndrome, systemic lupus erythematosus

INTRODUCTION

Pulmonary manifestations of systemic lupus erythematosus (SLE) and primary Sjögren's syndrome (pSS) are common and may result in significant morbidity and mortality. They may occur within every compartment of the respiratory system including the airways, lung parenchyma, pulmonary vasculature, respiratory muscles and pleura. We review the recent literature on the prevalence, risk factors, clinical, laboratory, physiologic, radiographic and pathologic findings as well as proposed treatment regimens for the myriad of pulmonary complications in both SLE and pSS.

SYSTEMIC LUPUS ERYTHEMATOSUS

SLE is a chronic inflammatory disease of autoimmune origin that can affect virtually every organ-system of the human body. It is characterized by the production of autoantibodies, particularly antinuclear antibodies (ANAs), and by formation and deposition of immune complexes resulting in end-organ damage [1]. SLE has a female predominance and tends to occur in women of childbearing age with a 10 : 1 female-to-male ratio [2]. SLE is chronic, relapsing and remitting in nature, and commonly presents with constitutional complaints along with skin, hematologic, renal, musculoskeletal and pulmonary manifestations. The American College of Rheumatology (ACR) proposed criteria for diagnosis in 1997 [3], and more recently a group of experts in SLE developed the Systemic Lupus International Collaborating Clinics classification criteria for SLE [4] (Table 1).

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KEY POINTS

- Any part of the pulmonary system may be involved in SLE and Sjögren's syndrome.
- SLE is the most common autoimmune disease to affect the respiratory system, and lupus pleuritis is the most common manifestation of SLE.
- The airways are the most frequently affected area of the respiratory system in pSS, with nonproductive cough the most common complaint.
- ALP may be a precursor of ILD in up to one-third of patients who survive.
- pSS–ILD is associated with significant morbidity and premature mortality. Nonspecific interstitial pneumonia is most commonly seen on surgical lung biopsy in pSS–ILD.
- Pulmonary hypertension due to SLE can fall under any of the five WHO categories of pulmonary hypertension. Immunosuppressive agents may be of added benefit in pulmonary arterial hypertension.
- Both patients with SLE and pSS have increased risk of malignancies. SLE patients have an overall increased risk of developing malignancies with non-Hodgkin lymphoma and lung cancer being common. Sjögren syndrome patients are at increased risk of lymphoma with mucosa-associated lymphoid tissue lymphomas as the most common sub-type.
- Sleep disorders are common in both SLE and pSS. Low vitamin D levels may be associated with poorer sleep quality in SLE.

Any part of the respiratory system can be affected including the airways, lung parenchyma, vasculature, pleura and respiratory musculature [5,6]. Pulmonary manifestations of SLE include airway disease, pleuritis (with or without effusion), inflammatory and fibrotic forms of interstitial lung disease (ILD), alveolar hemorrhage, acute lupus pneumonitis (ALP), pulmonary hypertension, shrinking lung syndrome (SLS) and thromboembolic disease, among others [7,8▪].

Epidemiology

SLE is the most common autoimmune disease to affect the respiratory system [9]. Pulmonary involvement is more common in men than in women and generally tends to manifest later in the course of the disease. Lung involvement is an important indicator of overall prognosis, being associated with a more than two-fold increase in mortality [6]. Pulmonary involvement in SLE also negatively impacts patient-reported outcomes and patient-performed outcomes [10▪▪].

The prevalence of pulmonary involvement varies depending on the criteria used to define lung abnormalities (e.g. clinical manifestations, imaging abnormalities or histopathologic evidence), with previous studies reporting a prevalence ranging between 20 and 90%. However, the higher end of the range may be overestimated due to imaging abnormalities as a consequence of infectious processes in this immunosuppressed population [11,12].

Nasal and airway involvement

Nasal involvement has been well documented in SLE [13,14]. In fact, the presence of nasal ulcers is one of the criteria for diagnosis of SLE [4]. The prevalence of nasal involvement is likely underestimated; however, a recent study found a prevalence of nasal involvement in 47.9% of patients [15▪▪]. The most common reported nasal symptoms included nasal congestion (31.5%), pruritus (26%), rhinorrhea (20.5%) and dryness (19.2%). Only 4/35 (11.45%) had nasal ulcers. Nasal endoscopy detected bleeding, mucositis (intranasal or nasopharynx), septal perforation, crusting, sinusitis, ulceration, dry mucosa and polypoidal mucosa.

Upper airway involvement in SLE is less common than in the other connective tissue diseases (CTDs) [7,16]. Manifestations can vary from mucosal inflammation to severe airway obstruction [17,18]. The reported incidence of laryngeal involvement in SLE patients varies from 0.3 to 30% [5]. Acute epiglottitis, laryngitis, tracheitis, vocal cord paralysis and cricoarytenoiditis have been reported. Presentation can be highly variable from asymptomatic to life-threatening respiratory compromise. Symptoms and physical exam findings include hoarseness, sore throat, dry cough, dyspnea and stridor. Most patients have an excellent response to mild-to-moderate doses of corticosteroids [16].

Lower airway involvement can also be seen in SLE, particularly in those patients with secondary Sjögren's syndrome (sSS). Most commonly, this is manifested by an obstructive ventilatory defect with decreased maximal expiratory flow rates (MEF25) less than 60% predicted [5]. Both follicular and obliterative bronchiolitis can be seen on pathology. Bronchiectasis and bronchial wall thickening have also been described [11,19].

Pleural involvement

Lupus pleuritis

Pleuritis (with or without pleural effusion) is the most common pulmonary manifestation of SLE affecting up to 60% of SLE patients during their lifetime and is

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Table 1. Diagnostic criteria for systemic lupus erythematosus [4]

ACR criteria for classification of SLE		**SLICC criteria for classification of SLE**	
4 of 11 criteria needed for diagnosis		**4 of 17 criteria, including at least one clinical criterion and one immunologic criterion; OR biopsy-proven lupus nephritis**	
Criterion	**Definition**	**Criterion**	**Definition**
Malar rash	Fixed erythema (spares the nasolabial folds)	Acute cutaneous lupus	Lupus malar rash; bullous lupus; TEN variant of SLE; etc.; photosensitive lupus rash or subacute cutaneous lupus
Photosensitivity	Skin rash as a result of sunlight exposure	Chronic cutaneous lupus	Classic discoid rash; localized or generalized or discoid lupus/lichen planus overlap
Discoid rash	Raised patches with adherent keratotic scaling; atrophic scarring in older lesions	Nonscaring alopecia	Diffuse thinning or hair fragility with visible broken hairs
Oral ulcers	Oral or nasopharyngeal ulceration, painless	Oral/nasal ulcers	Palate, buccal, tongue or nasal ulcers. Painless
Arthritis	Nonerosive arthritis involving two or more peripheral joints	Joint disease	Synovitis involving two or more joints, or tenderness in two or more joints and at least 30 min of morning stiffness
Serositis	Pleuritis and/or pericarditis	Serositis	Pleuritis and/or pericarditis
Renal disorder	Persistent proteinuria >500 mg/24 h or cellular casts	Renal disorder	Urine protein-to-creatinine ratio (or 24-h urine protein) >500-mg protein/24 h, or red blood cell cast
Neurologic disorder	Seizures or psychosis – after excluding other causes (uremia, ketoacidosis, etc.)	Neurologic disoder	Seizures; psychosis; mononeuritis multiplex or acute confusional state (excluding other causes)
Hematologic disorder	Hemolytic anemia, leucopenia, lymphopenia, thrombocytopenia (in the absence of other offending drugs)	Hematologic disorder	Hemolytic anemia, leucopenia, lymphopenia, thrombocytopenia (in the absence of other offending drugs)
ANA	An abnormal titer of ANA by IFA or an equivalent assay. Exclude: 'drug-induced lupus' syndrome	ANA	ANA level above laboratory reference range Exclude: 'drug-induced lupus' syndrome
Immunologic disorders	Anti-DNA – antibody or anti-Sm antibody or positive finding of antiphospholipid antibody (positive anticardiolipin, lupus anticoagulant, beta 2 glycoprotein I or false-positive RPR)	Anti-Sm antibody, anti-dsDNA antibody, antiphospholipid antibodies, complement levels and Coombs test (each counts as one positive criterion).	Antiphospholipid antibodies are considered positive if there is evidence of anticardiolipin antibodies, LAC, anti-B2 glycoprotein I or false-positive RPR. Complement levels include low C3, C4 and/or CH50 Coombs test counts as positive even in the absence of hemolytic anemia

ACR, American College of Rheumatology; ANA, antinuclear antibodies; IFA, immunofixation; LAC, lupus anticoagulant; OR, odds ratio; RPR, rapid plasma regain; TEN, toxic epidermal necrolysis; SLE, systemic lupus erythematosus; SLICC, Systemic Lupus International Collaborating Clinics classification.

one of the diagnostic criteria for SLE [3,8▪]. Autopsy studies demonstrate pleural involvement in 93% of patients [5]. Symptoms include pleuritic chest pain, cough, dyspnea and fever. Pertinent physical exam findings include a transient pleural friction rub and dullness to percussion. Chest imaging may reveal effusions; however, absence of effusion does not rule out the diagnosis as inflammation of the pleura may cause chest pain in the absence of effusion. Conversely, some patients may have an asymptomatic pleural effusion [11].

Pleural effusions in SLE tend to be bilateral, small to moderate in size and rarely involve more than two-thirds of the thoracic cavity [20]. It is essential to determine the underlying cause of pleural effusions; heart failure, parapneumonic effusions, malignancy and pulmonary embolism among others need to be excluded. Nevertheless, a recent Thai study of 119 patients with 127 episodes of pleuritis/pleural effusion reported SLE-related pleural effusion as the most common cause of pleural effusion is SLE patients followed by transudative effusion related to heart failure and effusions related to infection [20].

Pleural fluid may vary from serous to bloody. Effusions are generally exudative with an elevated

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lactate dehydrogenase. The total nucleated cell count is typically elevated and may reveal a neutrophilic or lymphocytic predominance depending upon the chronicity of the effusion. The pleural fluid glucose is generally low, but not as low as in patients with rheumatoid arthritis [6]. Other findings on pleural fluid analysis include a positive ANA, elevated anti-double-stranded DNA antibodies, low complement levels and lupus erythematosus cells noted on cytology. A pleural fluid ANA titer at least 1 : 160 has a sensitivity of 92% for SLE pleuritis when compared with all other causes for pleural effusions [19]. A pleural fluid to serum ANA ratio at least 1 strongly is highly suggestive as well. In the absence of SLE, an elevated ANA may be seen in paraneoplastic pleurisy [11]. Pleural biopsy might be needed in selected cases; however, it is not routinely performed [20].

Longer disease duration, late age of diagnosis of SLE (after age 50 years), greater cumulative damage and concomitant seropositivity for ribonucleoprotein (RNP) and Sm antibodies are factors that increase the risk of pleuritis by nearly two-fold [7]. Similarly, a recent review of 2390 SLE patients in the Hopkins Lupus Cohort identified fever, Raynaud phenomenon and anti-DNA antibodies as predictors for both pericarditis and pleurisy [21▪]. Data from the multicenter Latin American SLE cohort Grupo Latino Americano De Estudio del Lupus [22▪▪] suggests that nonischemic heart disease, Lupus severity of disease index more than 1 and anti-La antibody positivity at diagnosis or early in the disease course might be predictive of subsequent development of pleuropulmonary manifestations, whereas cutaneous manifestations were negatively associated. They however could not corroborate the association of anticardiolipin (aCL) antibodies, anti-RNP, anti-Ro, anti-Sm antibodies with pulmonary manifestations as described in previous investigations [5,19].

Treatment options are selected based on symptom severity and size of pleural effusion. Mild cases of SLE pleuritis typically respond to NSAIDs. Low-to-moderate doses of corticosteroids (e.g. 20–40 mg daily) are recommended for moderate-to-severe symptoms. Corticosteroid therapy may be discontinued in 3–4 weeks depending on clinical response. Pleurodesis can be considered for refractory cases, but is rarely required [6,11].

Parenchymal involvement

Acute lupus pneumonitis

ALP is a rare pulmonary manifestation with an estimated incidence of 1–4% [11,23]. It is characterized by diffuse alveolar inflammation with occasional hyaline membrane formation without evidence of vasculitis or hemorrhage. This complication is more likely to occur during an SLE flare with multisystem involvement including nephritis, serositis and arthritis [6]. Elevated anti-SSA/Ro antibodies have been associated with development of ALP [11].

ALP may be a presenting manifestation of SLE [11] or drug-induced SLE [24]. Its clinical presentation is generally nonspecific with fever, pleuritic chest pain, dyspnea, cough and rarely hemoptysis [12,23]. In patients without a history of SLE, the diagnosis of ALP can be challenging; clues to its diagnosis include lack of improvement with empiric antibiotics for pneumonia and extrapulmonary features of SLE (malar rash, alopecia, oral ulcers, serositis, nephritis, cytopenias, etc.) [23]. Patients are frequently hypoxemic with bibasilar crackles on examination. Radiologic features of ALP include bilateral alveolar infiltrates predominantly in the lower lung fields, although unilateral infiltrates have also been described. Associated pleural effusions may be present in up to 50%.

Bronchoalveolar lavage (BAL) is useful to evaluate for alternative causes such as alveolar hemorrhage and infection. Computed tomography (CT) angiography may be needed to exclude pulmonary embolism. Lung biopsy is typically reserved for patients that fail to respond to immunosuppressive therapy or in patients with a probable alternate diagnosis [5,6].

Treatment recommendations are based on clinical experience and case reports. Corticosteroids are the cornerstone of treatment for ALP with prednisone 1–2 mg/kg/day in divided doses as the initial agent of choice. Lack of improvement in 72 h and need for mechanical ventilation justify the need for intravenous pulse glucocorticoids (methylprednisolone 1 g/day for 3 consecutive days) [6]. Steroid sparing immunosuppressive agents should be started concomitantly (e.g. cyclophosphamide, azathioprine, mycophenolate mofetil) and intravenous immunoglobulin and/or plasmapheresis may be used in refractory cases [11,25]. ALP mortality rate has been reported as high as 50% [9,19,23] and may be a precursor of ILD in up to one-third of those who survive [26▪▪].

Chronic interstitial lung disease

SLE-associated ILD (SLE–ILD) is uncommon affecting approximately 1–15% of patients [27▪▪] and is usually less severe than ILD in other CTDs [19]. Risk factors for SLE–ILD include a history of ALP, longstanding disease (>10 years), Raynaud phenomenon, anti-U1 RNP antibodies, sclerodactyly and abnormal nailfold capillaroscopy [5].

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Nonspecific interstitial pneumonia (NSIP) (both cellular and fibrotic) appears to be the most common pattern seen histopathologically and/or radiographically in SLE–ILD [11,27▪▪], but usual interstitial pneumonia (UIP), organizing pneumonia, lymphocytic interstitial pneumonia (LIP), follicular bronchiolitis and nodular lymphoid hyperplasia have also been reported [28].

Patients typically present with insidious onset of dyspnea resulting in decreased exercise tolerance and a nonproductive cough; however, some patients may be asymptomatic. Physical examination typically reveals basilar crackles [8▪]. Clubbing and peripheral cyanosis, which are more commonly found in idiopathic pulmonary fibrosis, are rarely seen in SLE–ILD.

Laboratory abnormalities seen in SLE–ILD include but are not limited to hypocomplementemia, elevated high-sensitivity C-reactive protein and cryoglobulins [19]. A weak association with anti-Ro/SSA antibodies has also been reported [11].

The most common pulmonary function test (PFT) finding in SLE–ILD is a diffusion capacity for carbon monoxide (DLCO); other findings may include a restrictive pattern and/or hypoxia especially with exertion [27▪▪]. A radiographic pattern of NSIP is the most common finding on chest CT. However, the differential of ground glass opacities (GGO) includes infection, pulmonary edema, diffuse alveolar hemorrhage (DAH) and drug toxicity [6,29▪].

Treatment consists of systemic corticosteroids (prednisone 0.5–1 mg/kg/day). Steroid sparing agents commonly used in other forms of CTD–ILD (e.g. cyclophosphamide, azathioprine, mycophenolate, rituximab) have also been used for SLE–ILD, although data in SLE is limited and most recommendations come from experts [5,19,26▪▪] as there are no clinical trials in SS-ILD [27▪▪]. For ILD flares, intravenous methylprednisolone 0.5–1 g for 3 days may be needed. The prognosis of SLE–ILD is usually better than idiopathic ILDs and other CTD-associated ILDs. These patients tend to have a slow course and stabilize/improve over time.

Diffuse alveolar hemorrhage

DAH is a rare and potentially life-threatening complication of SLE affecting approximately 2% of patients. The hallmark of the disease is damage to the alveolar–capillary basement membrane in conjunction with alveolar inflammation. Risk factors for DAH include the presence of antiphospholipid antibodies (APLs) [30] and the presence of active lupus nephritis with hypocomplementemia [19].

Although DAH may be the initial manifestation of SLE, it tends to occur more frequently among patients who are already known to have lupus. Clinically, it is characterized by the triad of hemoptysis, acute anemia and diffuse alveolar infiltrates; however, hemoptysis may be absent in one-third of patients. Other symptoms and manifestations may include fever, cough, dyspnea and chest pain, hypoxemia and an increased diffusion capacity for carbon monoxide [31].

BAL is a key and preferred method for diagnosing DAH and is characterized by progressively hemorrhagic aliquots with the presence of hemosiderin laden macrophages. Lung biopsy is rarely needed for diagnosis, but if it is performed, it may show capillaritis with immune complex deposition or bland hemorrhage [31,32].

Due to the life-threatening nature of the disease, aggressive treatment with high-dose corticosteroids should be initiated promptly (methylprednisolone 0.5–1 g for 3 consecutive days or prednisone 1–2 mg/kg/day in more stable patients) followed by another immunosuppressive agent (cyclophosphamide, azathioprine, rituximab or mycophenolate) [19,31–33]. The choice of the second agent is based on disease severity, for example need for mechanical ventilation, partial or null response to intravenous steroids and so on [31]. There have also been case reports in which recombinant factor VII was successfully used for pulmonary hemorrhage refractory to standard treatment [33]. Plasmapheresis has been used, although it has not been proven to decrease mortality rates [25,32]. Finally, stem-cell transplantation has also been reported [32].

Twenty years ago, mortality rates for DAH were reported as high as 70% [34]. Recent data have shown improvement in mortality (~30–40%) perhaps related to increased use of immunosuppressive agents in addition to corticosteroids [32,35].

Respiratory muscle involvement

Shrinking lung syndrome

First described by Hoffbrand and Beck [36] in 1965 as 'unexplained dyspnea' and shrinking lungs in SLE, the SLS, also known as the 'vanishing lung' syndrome, is a rare pleuropulmonary manifestation of SLE characterized by diaphragmatic dysfunction and a restrictive pattern on pulmonary function testing with normal pulmonary parenchyma. The estimated prevalence ranges between 0.5 [37] and 10% [38,39] depending on the method and criteria used for diagnosis.

Although the cause of SLS remains controversial, multiple theories exist behind the mechanism for SLS including failure of surfactant production resulting in microatelectasis, diaphragmatic

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weakness or dysfunction with decreased transdiaphragmatic pressure, diaphragmatic myopathy due to corticosteroid use, phrenic neuropathy and pleural inflammation leading to impaired inspiration with decreased lung volume [22▪▪,38,40].

Factors associated with SLS include greater disease duration, seropositivity for anti-RNP antibodies and a history of pleuritis [19]. An association with anti-Ro/SSA antibodies has been debated [41▪▪]. SLS can be the presenting manifestation of SLE or it can present up to 2–3 decades later [38].

Clinically, patients present with progressive dyspnea that characteristically is worse when supine. Sixty-five percent of patients with SLS also have pleuritic chest pain [41▪▪]. Physical examination may reveal decreased breath sounds at the bases sometimes with associated crackles. Abdominal paradox has been described in some cases [42].

Currently, there are no standardized criteria for the diagnosis of SLS. Pulmonary function testing reveals a progressive restrictive ventilatory defect. A decrease in forced vital capacity (FVC) from sitting to supine position may also aid in diagnosis [42]. The DLCO is also often reduced. Chest radiograph and high resolution computed tomography (HRCT) reveal elevation of the hemidiaphragms, low lung volumes, basilar atelectasis, and approximately 20% of patients have pleural thickening or small pleural effusions [37,41▪▪]. The main utility of HRCT in SLS is ruling out parenchymal, interstitial or vascular lung disease. Evaluation of diaphragmatic strength is particularly useful in confirming the diagnosis of SLS. A decrease in maximal inspiratory pressure and maximal expiratory pressure is often seen, indicating global respiratory muscle weakness [43]. Electromyography with phrenic nerve conduction studies can be normal or show a decreased or absent response to stimulation [38]. Ultrasonography and fluoroscopy have also been used for diaphragmatic evaluation. The Sniff test (have the patient 'sniff' or quickly breathe in through the nose) is used to evaluate diaphragmatic motion, which is often affected in SLS patients. A paradoxical response (diaphragm moving upward with inspiration and downward with expiration) has been observed in up to 46% of SLE–SLS patients; however, a normal ultrasound does not rule out the diagnosis [41▪▪]. Dynamic contrast-enhanced lung MRI has been reported as an alternative for diagnosis [40,41▪▪].

There is no evidence supporting the use of immunosuppressive therapy for SLS, although there are case series using corticosteroids, mycophenolate mofetil, azathioprine, methotrexate, cyclophosphamide and rituximab [5,6,19,41▪▪,44,45]. Noninvasive positive pressure ventilation at night may also be beneficial [42].

Overall, the long-term prognosis is usually good with modest improvement in some cases and minor worsening occurring rarely. In a case series [38] of 55 SLE–SLS patients with a median follow-up period of 35 ± 29 months (range from 6 months to 9 years), 44 patients (80%) had significant clinical improvement with stabilization or modest improvement on PFTs after treatment, and in 10 patients, (18%) there was no functional sequelae. One patient (1.8%) died due to pneumonia, concomitant active lupus nephritis and poor medication adherence. These findings correlate with the data reported by Langenskiöld *et al.* [46] in which 20% (7/35) of patients recuperated normal lung function. Duron and Cohen-Aubart also performed a review of the literature with focus on treatment and prognosis of 155 SLE–SLS patients. Outcomes were known in 52 cases (33.5%), clinical improvement was seen in 48 patients (94%), functional improvement in 77% of cases (36/47) and imaging resolution/improvement was seen in 57% of cases (8/14).

Vascular involvement

Pulmonary hypertension

SLE is the second most common cause of CTD-related pulmonary hypertension only after the scleroderma spectrum of disease [47]. Pulmonary hypertension is a progressive and symptomatic disease characterized by an elevation in pulmonary artery pressures, which leads to right ventricular (RV) failure and death. Pulmonary hypertension is defined by a mean pulmonary artery pressure of at least 25 mmHg [48] and requires a right heart catheterization (RHC) to make the diagnosis.

The WHO divides pulmonary hypertension into five different groups based on different disease mechanisms, clinical presentation and histopathology. Patients with SLE can have pulmonary hypertension from any group or a combination of groups. Group 1, pulmonary arterial hypertension (PAH), is characterized by a lesion confined to the pulmonary arteriole. PAH also requires a normal pulmonary capillary wedge pressure (PCWP) ($\leq$15 mmHg). In group 2, the increased pulmonary artery pressures are secondary to left heart disease, namely due to systolic and diastolic dysfunction and left-sided valvular disorders. The PCWP is more than 15 mmHg in this group. Disorders of the respiratory system and hypoxemia causes group 3 pulmonary hypertension. Group 4 is secondary to chronic thromboembolic pulmonary hypertension (CTEPH). Lastly, pulmonary hypertension secondary to vasculitis has been described in SLE patients and currently falls under group 5 [49].

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Histological appearances are similar in idiopathic PAH (IPAH) and SLE–PAH [33]. Some of the pathological changes that can be seen include but are not limited to progressive arteriolar remodeling, vascular smooth muscle hypertrophy, adventitial and neointimal proliferation and in-situ thrombosis [50–53].

Endothelial damage is thought to be a key triggering factor in the pathogenesis of SLE–PAH. In one early study, antiendothelial antibodies were associated with the development of SLE–PAH [28], and evidence from animal models suggests that these antibodies may be pathogenic [54]. Others have found that endothelin levels are higher in SLE patients with PAH than in those without [29▪]. Immunoglobulin and complement deposits have been found in the pulmonary arteries of lupus patients along with the characteristic PAH vasculopathy suggesting a role for an immune complex deposition process in the pathogenesis of SLE–PAH that does not occur in PAH without CTD [4]. RhoA/Rho kinase has also been implicated in the pathophysiology of pulmonary hypertension, and Rho kinase has been shown to be upregulated in SLE patients compared with healthy controls [26▪▪]. A recent meta-analysis of 31 publications by Stéphane *et al.*, with a total of 4480 SLE patients, found that APL-positive SLE patients had a higher prevalence of PAH (12.3%) versus APL-negative SLE patients (7.3%). The overall pooled odds ratio (OR) for PAH was 2.28 [95% confidence interval (CI), 1.65–3.15] [30]. The risk of PAH was the highest amongst lupus anticoagulant-positive and IgG aCL antibody-positive patients. The presence of these antibodies creates a well known prothrombotic state [30] that can cause a four-to-five-fold increase in the risk of deep vein thrombosis and pulmonary emboli thus making SLE patients also at risk for CTEPH.

The exact prevalence of pulmonary hypertension has not been well established. Many of the case series of SLE patients with pulmonary hypertension have used echocardiography alone for diagnosis; this is a significant limitation as RHC is needed for diagnosis. For instance, in a recent Latin-American cohort of 424 SLE patients with pleuropulmonary manifestations; 2.2% (32 patients) had pulmonary hypertension [22▪▪]. Other studies have reported prevalences as low as 0.5% or as high as 14% depending on the diagnostic modality used [50,54,55▪▪,56]. Most studies using RHC for pulmonary hypertension diagnosis report an incidence less than 4% [47,55▪▪].

Clinical presentation depends on the type of pulmonary hypertension based on the WHO classification; the most common symptoms include progressive dyspnea, chest pain, peripheral edema and sometimes syncope. SLE patients with group 2 pulmonary hypertension can also have paroxysmal nocturnal dyspnea and orthopnea. A nonproductive cough associated with pleuritic chest pain can be seen in patients with pulmonary hypertension secondary to ILD (group 3 pulmonary hypertension).

Laboratory abnormalities or associations have been described in SLE-pulmonary hypertension patients. The study by Hachulla *et al.* [55▪▪] suggested that anti-U1-RNP antibodies might be a protective factor regarding survival in SLE–PAH patients, while suggesting that the presence of anti-SSA/SSB antibodies may be a risk factor for PAH. Conversely, a recent Chinese meta-analysis that included 12 studies identified anti-RNP antibody and anti-Sm antibody as risk factors for SLE-associated PAH with the pooled OR 3.68 (95% CI 2.04–6.63, $P < 0.0001$) and 1.71 (95% CI 1.06–2.76, P1/40.03), respectively. Another interesting association was reported by Castillo-Martıez *et al.* [57], who recently suggested that chronic hyperuricemia may predict the future development of pulmonary hypertension in SLE patients with normal pulmonary artery systolic pressure (PASP) at baseline.

According to the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) Guidelines for the diagnosis and treatment of pulmonary hypertension, pulmonary hypertension can be inferred if multiple different echocardiographic measurements are consistent with the diagnosis; however, when treatment modalities are being considered, echocardiography alone is not sufficient to support this treatment decision and RHC is needed [48]. Nevertheless, there have been some proposed utilities to echocardiographic evaluation. A post-hoc analysis by Hübbe-Tena *et al.* [58] from a cohort of patients with SLE followed over 6 years suggested that ESC/ERS/International Society for Heart and Lung Transplant echocardiography-based definitions of pulmonary hypertension can be useful to predict 6-year mortality in SLE patients. A Japanese cohort of SLE patients was followed over 5 years to investigate the usefulness of 6-minute walk (6-MW) stress echocardiography in detecting early pulmonary hypertension. Results suggested that 6-MW stress echocardiography might provide an incremental prognostic value of pulmonary hypertension development in CTD [59].

Once the diagnosis of PAH has been established by RHC, therapy should be started without delay. The treatment of SLE-pulmonary hypertension can be complex and most times requires a combination of immunosuppressive therapy along with vasodilators. The most commonly used vasodilators include the phosphodiesterase-5 inhibitors (PD5 inhibitors), soluble guanylate cyclase stimulators, endothelin receptor antagonists (ERAs), prostacyclin analogs and

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prostacyclin receptor agonists. A meta-analysis of nine clinical trials of CTD–PAH reported improvement in 6-MW distance with these vasodilators. The improvement with PD5 inhibitors, ERAs and prostacyclin analogs was 37–47 min, 14.1–21.7 min and 21–108 min, respectively [47].

Increasing evidence supports the use of immunosuppressive therapy in SLE–PAH; however, there are no established guidelines to guide treatment. There have been a number of case series that reported improvement in hemodynamics and functional capacity [60,61]. Most patients were treated with intravenous cyclophosphamide for 3–6 months with or without corticosteroids, and vasodilators. In these studies, patients that responded to immunosuppressive therapy tended to have less severe disease manifested by better functional capacity, higher cardiac index and/or lower pulmonary vascular resistance index at presentation. Patients are likely to respond earlier in the course of their disease potentially because those with longstanding disease can have irreversible vascular damage [62].

It has been well described that patients with CTD–PAH have poorer prognosis when compared with IPAH patients. However, SLE–PAH patients have better survival curves that patients with scleroderma associated PAH [63▪▪]. Results from the French registry reported that patients with SLE–PAH have an overall 3-year and 5-year survival rate of 89.4 and 83.9%, respectively, and anti-U1-RNP antibodies were associated with a higher survival rate [55▪▪]. The REVEAL registry reported a 2-year survival rate of 85% and a Chinese cohort reported a 3-year survival rate of 88%.

Thromboembolic disease

It has been well established that SLE patients have an increased risk of venous thromboembolic (VTE) disease as a consequence of chronic inflammation and/or the presence of APLs. Yusuf *et al.* [64] found that amongst hospitalized SLE patients, the risk for VTE was estimated to be 1.23 (95% CI 1.15–1.32) when compared with hospitalized patients without autoimmune disease. A recent Danish nationwide cohort study [65] comparing the risk of VTE in patients with cutaneous lupus erythematosus (CLE) and SLE and the general population between 1997 and 2011 found that both CLE and SLE were significant risk factors for VTE with hazard ratio 1.39 (95% CI 1.10–1.78) for CLE and hazard ratio 3.32 (95% CI 2.73–4.03) for SLE.

Malignancy

SLE is associated with an overall increase in malignancies with female patients being 10% more susceptible than their male counterparts [66]. A recent meta-analysis by Wu *et al.* of 12 studies involving a total of 57 890 SLE patients showed that there is an increased risk of lung cancer in the SLE population (OR = 1.60; 95% CI: 1.44–1.77; $P < 0.00001$).

Abnormal B-cell activation and proliferation may lead to B-cell malignancies, which may explain why non-Hodgkin lymphoma (NHL) is one of the malignancies most commonly associated with SLE [6,19]. Immunosuppressive therapy-related toxicity is also implicated in the increased risk for malignancy due to resulting cellular dysregulation and mutation.

Sleep disorders

It has been estimated that the prevalence of sleep disorders in SLE patients is as high as 85%, which is higher than that of the general population [67]. Studies in SLE have estimated the prevalence of sleep apnea to be 26–50% and periodic limb movement to be 23–50% [68,69]. Daytime sleepiness was reported in up to 51% of patients and is associated with fatigue, somnolence and daytime dysfunction [70]. Data on other sleep disorders, such as insomnia, are not available [71].

Some of the studies that have evaluated sleep in SLE patients have found increased sleep latency and decreased sleep efficiency with high levels of fragmentation and increased number of awakenings during the night when compared with healthy controls [69,72]. SLE patients have increased alpha wave intrusions into nonrapid eye movement sleep, a decrease in stages 3 and 4 of slow-wave deep sleep and a compensatory increase in stage 1 sleep [68,70]. The evidence on sleep disturbances and SLE suggest that these disturbances may be associated with worse lupus activity [73].

Although sleep disturbances are a major health problem in SLE patients [71], their underlying mechanisms are still unclear [73]. Recent studies have suggested that pain, fatigue, disease activity and psychological health disturbances, particularly depression, may play a role [71,74]. A recent retrospective analysis of 63 women with SLE assessed the role of vitamin D on sleep quality and found that low vitamin D levels in SLE patients were associated with poorer sleep quality independent of demographics, disease severity, psychological-related factors and time of the year [71].

SJÖGREN'S SYNDROME

Sjögren syndrome is a chronic inflammatory disease characterized by mononuclear cell infiltration of exocrine glands, classically the salivary and lacrimal glands. Sjögren's syndrome was first described in

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Table 2. Diagnostic criteria for Sjögren's syndrome [77]

	American-European Consensus Criteria for Sjögren's Syndrome (AECG criteria)	American College of Rheumatology Criteria for Sjögren's Syndrome (ACR criteria)
Symptoms	I. Ocular: symptoms of dry eyes for at least 3 months, foreign body sensation in the eyes and/or use of artificial tears 3 or more times per day (at least one) II. Oral: symptoms of dry mouth for at least 3 months, recurrent or persistently swollen salivary glands, need for liquids to swallow dry foods (at least one)	Does not include criteria based upon symptoms of glandular manifestations
Signs	III. Ocular: abnormal Schirmer's test, (without anesthesia; $\leq$5 mm/5 min) or positive vital dye staining of the eye surface IV. Oral: unstimulated whole salivary flow ($\leq$1.5 ml in 15 min), abnormal parotid sialography or abnormal salivary scintigraphy	i. OSS $\geq$ 3 (assuming that individual is not currently using daily eye drops for glaucoma and has not had corneal surgery or cosmetic eyelid surgery in the last 5 years) *t*
Serology	V. Positive serum anti-SSA (Ro) or anti-SSB (La), or both	ii. Positive serum anti-SSA (Ro) and/or anti-SSB (La) antibody testing OR a positive rheumatoid factor and an antinuclear antibody titer $\geq$1 : 320
Biopsy	VI. Lip biopsy showing focal lymphocytic sialoadenitis (focus score $\geq$1 per 4 mm^2)	iii. Presence of focal lymphocytic sialadenitis with a focus score $\geq$1 focus/4 mm^2 in labial salivary gland biopsy samples

AECG criteria: for diagnosis of pSS: any four of the six criteria (including serology and biopsy) or any three of the four objective criteria (all exclusion criteria met). For diagnosis of sSS: previous CTD-related diagnosis, the presence of one symptom, and two of the three objective criteria (III, IV and VI). ACR criteria require two of three criteria for diagnosis of SS (no difference between pSS versus sSS). *t* OSS, ocular staining score. This score is the sum of a 0–6 score for fluorescein staining of the cornea and a 0–3 score for lissamine green staining of the conjunctiva. ACR, American College of Rheumatology; AECG, American-European Consensus Criteria for Sjögren's Syndrome; CTD, connective tissue disease; OR, odds ratio; pSS, primary Sjögren's syndrome; sSS, secondary Sjögren's syndrome.

1926 by Henri Gougerot a French dermatologist. The estimated worldwide incidence of Sjögren syndrome is seven cases per 100 000 with higher rates reported in Europe and Asia [75].

Sjögren syndrome is divided into primary and secondary forms. pSS occurs alone, whereas sSS occurs in association with another CTD. The focus on this review will be on the pulmonary manifestations of pSS.

The etiopathogenesis includes genetic, environmental and hormonal factors. It is more commonly diagnosed in the 4th or 5th decade of life with a female-to-male ratio of 9 : 1 [76]. The ACR in collaboration with the Sjögren's International Collaborative Clinical Alliance research group revised criteria for diagnosis of Sjögren syndrome in 2012 [77] (Table 2).

Lung involvement in Sjögren's syndrome has been well described, and negatively impacts quality of life and increases mortality for patients with pSS [6,78]. The reported prevalence of lung involvement varies widely (9–75%) depending on the methods of detection and patient selection [79]. However, studies that define pulmonary involvement by respiratory symptoms associated with abnormal PFTs and/or abnormal imaging findings on HRCT [80] suggest a prevalence rate in the range of 9–22%. Some of the well described risk factors for lung disease in pSS include hypergammaglobulinemia, lymphopenia, a positive rheumatoid factor, anti-Ro/SSA and anti-La/SSB antibodies, a decreased FVC and forced expiratory volume in 1 s, history of smoking, male sex and increased age [78].

Airway involvement

The airways are likely the most frequently involved area of the respiratory system in pSS. Upper and lower airway involvement have been described in pSS and can be related either to destruction of exocrine glands or due to cell infiltration. Histopathologically, infiltration of CD4-positive T lymphocytes have been demonstrated in bronchial and bronchiolar mucosa even in the absence of imaging abnormalities or symptoms, and BAL may reveal CD4-positive lymphocytic alveolitis in up to 55% of patients with pSS.

Airway disease may involve the nasal and oral mucosa, trachea (xerotrachea), bronchi (xerobronchitis) or bronchioles [6,81▪▪]. Most pSS patients complain of a nonproductive cough; those with lower airway disease may complain of dyspnea and wheezing.

Cough

Cough is one of the most commonly reported complaint by pSS patients with a prevalence reported between 41 and 61%, and it significantly impacts

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the quality of life in over 50% of pSS. A nonproductive cough may precede the diagnosis of pSS by several years. The pathogenesis has been hypothesized to be related to airway dryness, inflammation, hyperresponsiveness and gastroesophageal reflux [81▪▪]. The severity of cough correlates with tracheal dryness. Treatment options include hypertonic (3% or 7%) nebulized saline and secretagogues such as pilocarpine and cevimeline.

Bronchiolitis

The term bronchiolitis refers to inflammation of the small airways, particularly the bronchioles, which are the airways that lead to the alveoli. Bronchiolitis is likely the most frequent airway complication in pSS. It may be isolated or associated with ILD, such as NSIP or LIP. Previous studies have shown bronchiolitis in up to 12% of pSS patients on surgical lung biopsy, and when new anatomical and radiographical criteria were used, this rate increased to 24% [82] (Fig. 1).

The most common symptoms seen with bronchiolitis are dry cough, dyspnea, wheezing and recurrent infections. On lung biopsy, follicular bronchiolitis appears to be the most common pattern seen in up to approximately 25–75% of cases [83,84]. Follicular bronchiolitis refers to the presence of hyperplastic lymphoid follicles with reactive germinal centers distributed along the bronchovascular bundles. Other types of bronchiolitis include chronic bronchiolitis with fibrosis, obliterative bronchiolitis, lymphocytic bronchiolitis and panbronchiolitis [85].

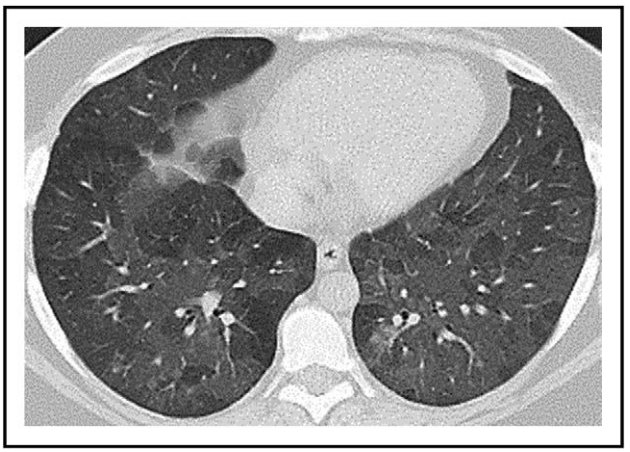


FIGURE 1. High-resolution chest computed tomography in patient with primary Sjögren's syndrome and bronchiolitis obliterans. Imaging reveals mosaic attenuation with patchwork areas of increased attenuation with lobular low attenuation suggestive of air trapping.

Treatment options include inhaled corticosteroids, rituximab and/or chronic macrolide therapy. However, these recommendations are based on low levels of scientific evidence. The prognosis of bronchiolitis is typically good with most patients improving by symptoms, imaging and PFTs; however, cases of severe bronchiolitis have been described [83,86].

Bronchiectasis

Bronchiectasis is characterized by permanent enlargement or dilatation of the airways. Patients most commonly present with chronic cough with increased mucus production. Other symptoms include dyspnea, wheezing, hemoptysis and chest pain. Nail clubbing may be seen in advanced disease. The frequency of bronchiectasis in pSS varies from 7 to 54% and is typically cylindrical as assessed by CT [19]. An older age at time of diagnosis, female sex, presence of a hiatal hernia and an elevated anti-smooth muscle antibody are associated with a higher incidence of bronchiectasis in pSS. Significantly, there is a lower frequency of anti-SSA antibody [8▪,87,88▪].

Parenchymal involvement

Interstitial lung disease

ILD is associated with significant morbidity and premature mortality in pSS [83]. Although older studies suggest a prevalence of ILD in 70% of patients with pSS [19], more recent studies suggest the prevalence is 3–11% [89]. In the largest series, 21 of 263 pSS-patients (8%) were diagnosed with ILD [90]. The time of onset of ILD in pSS is variable, and ILD may frequently precede the extrapulmonary manifestations of pSS or be diagnosed concomitantly [90]. Risk factors for pSS–ILD include the presence of high titer ANA, rheumatoid factor, anti-SSA and anti-SSB antibodies, hypergammaglobulinemia older age, the presence of Raynaud phenomenon, peripheral arthritis or esophageal involvement. Patients with these risk factors should be screened for subclinical ILD to identify patients that may benefit from earlier treatment [79,81▪▪,90]. Older age and esophageal involvement have also been associated with ILD deterioration [91]. A potential biomarker is endostatin. Higher mean levels of serum endostatin are seen in pSS compared with healthy controls, and patients with ILD have higher levels compared with those without respiratory involvement [92▪].

The most common clinical manifestations of pSS–ILD reported by European League Against Rheumatism-Sjögren Syndrome Task Force include

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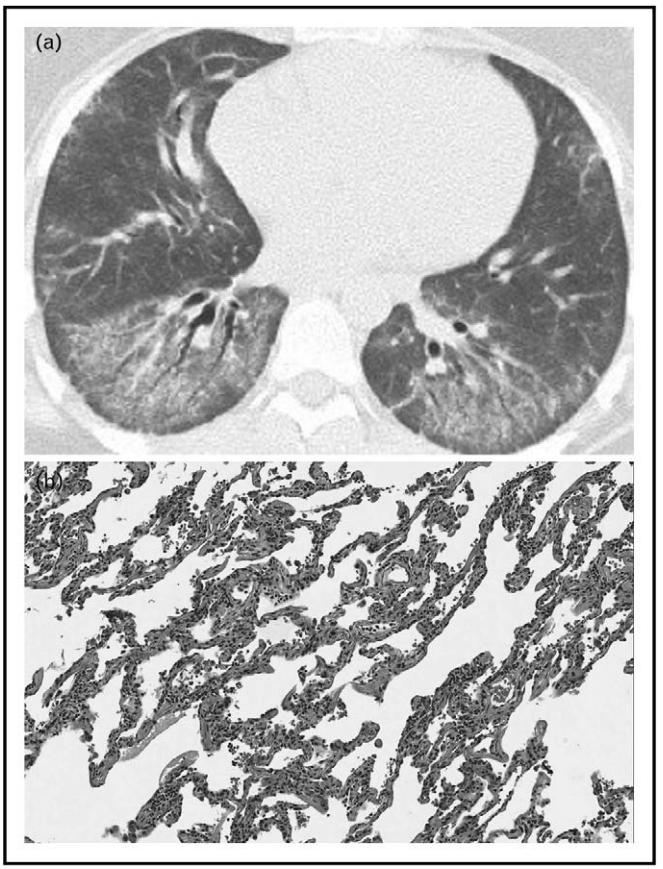


FIGURE 2. (a) High-resolution chest computed tomography of patient with primary Sjögren's syndrome and fibrotic nonspecific interstitial pneumonia. Imaging reveals lower lobe predominant ground glass opacity with traction bronchiectasis and subpleural sparing. (b) Surgical lung biopsy from patient with primary Sjögren's syndrome and nonspecific interstitial pneumonia, cellular type: alveolar walls with scattered lynmphocytes and evidence of fibrosis. (Hematoxylin and eosin, 100×).

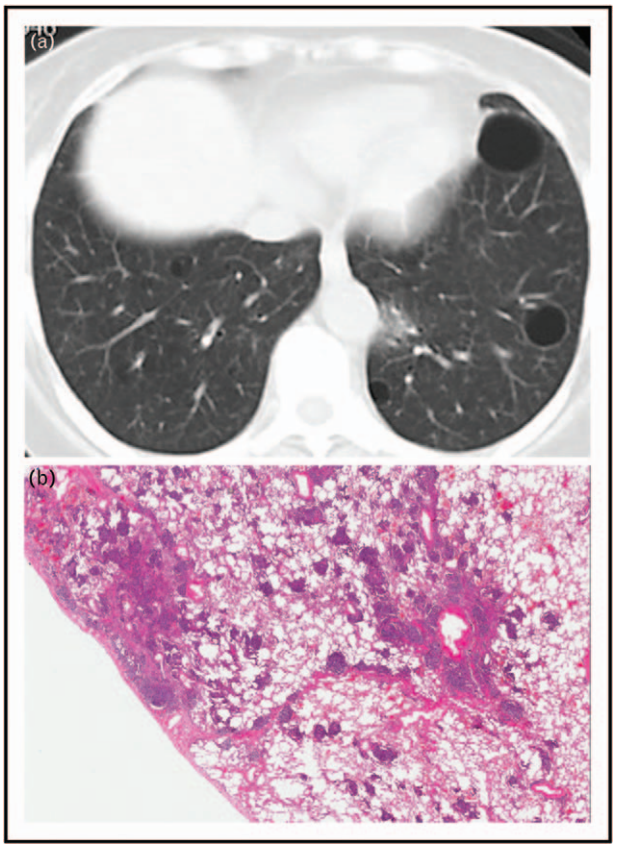


FIGURE 3. (a) High-resolution chest computed tomography of patient with primary Sjögren's syndrome and lymphocytic interstitial pneumonia. Imaging reveals lower lobe predominant perivascular subpleural cysts. (b) Surgical lung biopsy from patient with primary Sjögren's syndrome and lymphocytic interstitial pneumonia: multiple foci of benign chronic lymphocytic inflammation extending from the peribronchiolar area to the interstitium. (Hematoxylin and eosin, 15×).

dyspnea, a nonproductive cough, crackles, chest pain and fever. PFTs are usually abnormal when ILD is discovered and typically reveal a restrictive pattern with a decrease in DLCO (64% of pSS patients) an obstructive pattern (21% of patients) or a mixed restrictive and obstructive pattern (25% of patients) [79].

HRCT remains the most sensitive method for detection of parenchymal abnormalities but may also detect changes of uncertain clinical significance. Imaging abnormalities often do not correlate with PFTs or respiratory symptoms [83]. On HRCT scans, bronchial wall thickening (8–68%), nodules (6–29%), bronchiectasis (5–46%), air trapping (32%), ground-glass opacification and consolidation are the most common abnormalities [91]. Specific patterns on HRCT correlate with pulmonary histopathology. NSIP has primarily ground-glass opacities and irregular linear opacities with subpleural sparing in a peripheral and lower lobe distribution [81▪▪] (Fig. 2a). UIP is also lower lobe predominant and peripheral. It is characterized by intralobular septal thickening, honeycombing and traction bronchiectasis with the absence of significant ground glass. It is associated with increased mortality [81▪▪,93]. LIP is characterized by interlobular septal and bronchovascular bundle thickening, centrilobular and subpleural nodules, cysts and ground-glass opacities (Fig. 3a). Cysts tend to be thin-walled, vary in size and have geographic simplification of parenchymal architecture producing a 'dissolving lung appearance' [29▪,94]. Cysts can also be seen in lymphoma or amyloidosis; therefore, it is essential to make the appropriate diagnosis [83]. In organizing pneumonia, HRCT typically has patchy areas of consolidation, areas

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of ground-glass attenuation and centrilobular nodules [6,78,95].

BAL shows lymphocytic alveolitis in up to 65% of patients, even amongst those that are asymptomatic and portends a poorer prognosis than when alveolitis is absent.

Despite the classic association of pSS and LIP, NSIP appears to be the most common pathological subtype revealed by lung biopsy [80,82,89,96]. Both the cellular and fibrotic forms of NSIP may occur [5,95]. Histological features of NSIP include interstitial inflammation and fibrosis in a uniform appearance [28] (Fig. 2b). UIP is uncommon in pSS. When present, histopathology reveals temporal and spatial heterogeneity with normal lung alternating with fibrotic lung. Fibroblastic foci and honeycombing are also seen [28,95]. Approximately 25% of LIP cases are associated with pSS, and it is estimated that 1% of pSS patients will develop LIP during their lifetime [7,29▪]. LIP is characterized by benign proliferation of lymphoid cells and varying numbers of plasma cells along the alveolar septae [81▪▪,95] (Fig. 3b). Lung biopsy and assessment of clonality are essential to exclude the diagnosis of lymphoma. LIP can coexist with follicular bronchiolitis and both have the potential to progress to lymphoma [78]. Histology reveals T and B lymphocyte-rich infiltrates along with plasma cells in the interstitial septa and in the alveolar space [6,28,95]. Organizing pneumonia is characterized by alveolar fibroblast infiltration on a background of chronic inflammation in the surrounding alveoli. Histology frequently reveals NSIP-organizing pneumonia overlap [28].

Corticosteroids tend to be the mainstay of therapy followed by immunosuppressive agents such as hydroxychloroquine, azathioprine, cyclosporine, mycophenolate, cyclophosphamide, rituximab tumor necrosis factor antagonists and chlorambucil, which have been used with variable results [29▪]. Recently cases of severe pSS–ILD have been reported that were successfully treated with tociluzumab, tacrolimus and abatacept [97].

Outcomes are variable and unpredictable and are contingent on histopathology. The 5-year survival rate of NSIP in pSS is estimated to be 39–83% depending upon the case series [83,89,98]. UIP has a high risk of progression and is typically not response to immunosuppressive therapy, although no clinical trials have been performed to adequately evaluate response [6,83]. LIP and organizing pneumonia are usually corticosteroid responsive and have a good prognosis. However, fibrotic changes with cyst formation and honeycombing can occur in LIP [29▪,81▪▪]. Acute exacerbations of underlying ILD have been reported in up to 16% of pSS patients, and new areas of GGO or consolidation should raise the concern for an acute exacerbation versus infection.

Vascular involvement

Pulmonary hypertension

Pulmonary hypertension due to PAH, pulmonary veno-occlussive disease, valvular heart disease or ILD has been described in pSS-patients [78]. pSS can precede the diagnosis or can also present concurrently. The exact prevalence is unknown as there are limited studies that have assessed cardiac filling pressures by RHC [56,99]. Several case series have shown a mild elevation in RV systolic pressure as measured by echocardiography in approximately 20–25% of patients with pSS [8▪,100▪]. The described cases in the literature are composed of predominantly Asian women in their 30s or 40s presenting with dyspnea, cough and chest pain. Patients with pSS-PAH are more likely to have Raynaud phenomenon, cutaneous vasculitis and ILD [6]. They are also more likely to have a positive ANA, anti-Ro/SSA antibody, anti-RNP antibody, positive rheumatoid factor and hypergammaglobulinemia. Hypocomplementemia and cryoglobulinemia have been shown to be predictors of PASP [95].

Most pSS patients with PAH receive standard therapy for PAH (ERAs, PD5 inhibitors, prostanoids) with or without immunosuppressants; however, there is no valid evidence upon which to recommend immunosuppressive therapy as the primary treatment for pSS-related PAH [56].

Thromboembolic disease

Like other patients with connective tissue disorders, patients with pSS are at increased risk for VTE. This is thought to occur in response to chronic inflammation or due to the increased prevalence (~30%) of positive APLs [78,101]. A recent meta-analysis on the risk of VTE in rheumatic disorders revealed a cumulative VTE incidence of 2.18% (95% CI: 0.79–3.57%) in pSS patients [65]. Similarly, a Scandinavian Group that examined the incidence of thromboembolic episodes in 90 pSS patients reported an incidence rate of 3.3% over a 4.6-year follow-up [65].

Malignancy

Patients with pSS are at increased risk of developing malignancies [78]. The most common lung malignancies associated with Sjögren's syndrome are NHLs; of these, the most common subtype is mucosa-associated lymphoid tissue (MALT). pSS

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patients have a 16–44-fold increased risk of developing NHL, and 4–8% of pSS patients will develop lymphoma in the course of their disease [102]. The prevalence of primary pulmonary lymphoma is 1–2% in pSS patients; other common sites include lymph nodes, salivary glands and lacrimal glands [95].

Radiographic abnormalities include solitary or multiple nodules or masses with areas of consolidation or ground glass opacification. Lymphadenopathy and pleural effusions may also occur. A recent report of seven pSS patients with pulmonary MALT lymphoma reported an older age at diagnosis (mean 66), a female predominance, and nonspecific symptoms at presentation such as cough and dyspnea [81▪▪]. All patients were ANA-positive and anti-SSA/Ro-positive. Cryoglobulinemia, hypocomplementemia, parotid enlargement, palpable purpura and lymphopenia (particularly a decreased CD4+ and a low CD4+/CD8+ ratio) have been associated with an increased risk of NHL. MALT lymphoma tends to have a favorable course with an estimated 5-year survival with adequate hematological treatment of 65–90% [81▪▪,103].

NHL must be distinguished from pseudolymphoma, or pulmonary nodular lymphoid hyperplasia, which is a benign lesion characterized by plasma cell and mature polyclonal lymphocyte infiltration as determined by immunohistochemical and molecular studies [95]. Pseudolymphoma is more commonly seen in patients with lone sicca syndrome and usually responds to corticosteroid treatment. It rarely progresses to lymphoma.

Pulmonary amyloidosis

Pulmonary amyloidosis is a rare complication of Sjögren's syndrome that primarily occurs in female patients (95%). Patients may present with cough, dyspnea, hemoptysis and pleuritic chest pain. Thrombocytopenia, cryoglobulinemia, Raynaud phenomenon, lymphoma and APL syndrome are also reported. The most common imaging findings include nodules with or without calcification [81▪▪,95] and often on a background of LIP. The diagnosis usually requires surgical lung biopsy as lymphoma needs to be excluded. Nodular (AL) amyloidosis is the most common pathologic finding. No specific therapy has been reported to be successful; however, corticosteroids have been used in some patients [29▪].

Sarcoidosis

Sarcoidosis is systemic disease with multiorgan involvement characterized by the presence of noncaseating granulomas. The salivary and lacrimal gland may be involved and patients may experience sicca symptoms similar to pSS sometimes resulting in misdiagnosis. Nevertheless, the coexistence of sarcoidosis and pSS has been documented in many reports in the literature [104]. The estimated prevalence of sarcoidosis in patients with pSS is 1–2% [105]. In a case series of 59 patients with both diseases, 60% received their diagnosis of sarcoidosis and pSS simultaneously. The main features on presentation in this series included sicca symptoms, parotid enlargement, articular involvement, cutaneous involvement, respiratory symptoms and fatigue. Patients with sarcoidosis and coexisting pSS had a higher frequency of ANA, rheumatoid factor and anti-Ro/SSA antibodies [104].

Sleep disorders

Fatigue is one of the most common complaints of pSS patients; and sleep disturbances in pSS have been well documented [106]. A recent systematic review on the prevalence of sleep disturbances in pSS patients reported increased daytime somnolence, subjective sleep disturbances (including those related to sicca symptoms) and increased number of night awakenings. Further studies with polysomnography are needed to determine if there is a higher prevalence of sleep apnea [107▪▪].

CONCLUSION

In conclusion, any part of the respiratory system may be involved in SLE and pSS, the pleura is most commonly involved in SLE, whereas the airways are most commonly involved in pSS. The clinician should be aware of the risk factors and clinical presentation of the various pulmonary complications in SLE and pSS to identify patients who should be screened and/or have modifications in treatment strategies to mitigate the morbidity and mortality associated with these complications.

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