Therapeutic Advances in Musculoskeletal Disease Review

Diagnosis and management of lung involvement in systemic lupus erythematosus and Sjögren's syndrome: a literature review

Ther Adv Musculoskel Dis

2021, Vol. 13: 1–24

DOI: 10.1177/1759720X211040696

Roberto Depascale, Giulia Del Frate, Michela Gasparotto, Valeria Manfrè, Mariele Gatto, Luca Iaccarino, Luca Quartuccio, Salvatore De Vita and Andrea Doria

***Abstract*:** Lung involvement in systemic lupus erythematosus (SLE) and primary Sjögren's syndrome (pSS) has extensively been outlined with a multiplicity of different manifestations. In SLE, the most frequent finding is pleural effusion, while in pSS, airway disease and parenchymal disorders prevail. In both cases, there is an increased risk of pre-capillary and post-capillary pulmonary arterial hypertension (PAH) and pulmonary venous thromboembolism (VTE). The risk of VTE is in part due to an increased thrombophilic status secondary to systemic inflammation or to the well-established association with antiphospholipid antibody syndrome (APS). The lung can also be the site of an organ-specific complication due to the aberrant pathologic immune-hyperactivation as occurs in the development of lymphoma or amyloidosis in pSS. Respiratory infections are a major issue to be addressed when approaching the differential diagnosis, and their exclusion is required to safely start an immunosuppressive therapy. Treatment strategy is mainly based on glucocorticoids (GCs) and immunosuppressants, with a variable response according to the primary pathologic process. Anticoagulation is recommended in case of VTE and multi-targeted treatment regimens including different drugs are the mainstay for PAH management. Antibiotics and respiratory physiotherapy can be considered relevant complement therapeutic measures. In this article, we reviewed lung manifestations in SLE and pSS with the aim to provide a comprehensive overview of their diagnosis and management to physicians taking care of patients with connective tissue diseases.

Keywords: primary Sjogren's syndrome, pulmonary involvement, systemic inflammation, systemic lupus erythematosus, therapeutic strategies

Received: 5 May 2021; revised manuscript accepted: 3 August 2021.

Correspondence to:
Andrea Doria
Division of Rheumatology, Department of Medicine, University of Padua, Via Giustiniani, 2, 35128 Padua, Italy.
adoria@unipd.it

Roberto Depascale
Michela Gasparotto
Mariele Gatto
Luca Iaccarino
Rheumatology Unit, Department of Medicine, University of Padua, Padua, Italy

Giulia Del Frate
Valeria Manfrè
Luca Quartuccio
Salvatore De Vita
Rheumatology Unit, Department of Medicine, University of Udine, Udine, Italy

Introduction

The lungs are often affected in connective tissue diseases (CTDs), with a variable degree of severity and protean clinical presentations by virtue of the complex anatomo-functional characteristics of the respiratory apparatus. Among the CTDs, systemic sclerosis (SSc) has the highest prevalence of clinically overt pulmonary involvement with a prevalence ranging between 70% and 90% of cases;[1] similarly, in idiopathic inflammatory myopathies, and in particular anti-synthetase syndrome, the prevalence is remarkable.[2] In systemic lupus erythematosus (SLE) and primary Sjögren's syndrome (pSS), pulmonary involvement has been reported with a variable prevalence according to the diagnostic method and criteria used.[3–8] In SLE and pSS, the immune-inflammatory process may affect not only the lung parenchyma but also pleural layers, respiratory muscles, and the pulmonary vascular system with different

pathogenetic mechanisms. This often requires a comprehensive clinical and laboratory evaluation and a multi-disciplinary management to correctly characterize the extension of the organ impairment and to provide the best management. Besides, it is important to remind that the respiratory abnormalities may additionally be due to complications associated with the immunosuppressive therapy such as pulmonary drug-related toxicity[9,10] or, more frequently, recurrent infections. In pSS, they may also derive from a malignant evolution of an underlying lymphoproliferative disorder.

In this review, we provide an overview on the diagnosis and management of pulmonary manifestations in patients with SLE and pSS with the aim of raising the awareness of lung involvement among physicians taking care of SLE and pSS patients.

Search strategy

A narrative literature search was conducted to address research questions related to pulmonary manifestations in SLE and pSS patients. We considered different databases such as PubMed, Google Scholar, and Cochrane Library searching for case series, case reports, clinical trials, and review articles on lung involvement in SLE and pSS. Additional references were identified by searching the bibliographies of retrieved articles. We performed a keyword search restricted to the title of the articles, using terms relating to SLE, pSS, lung involvement, and treatment of lung involvement in CTDs. The date of publication was not used as an entry selection criterion. Articles were reviewed according to the article title and abstract, with all article types taken into consideration if they provided data relevant to the research questions.

Pulmonary involvement in SLE

SLE is a chronic autoimmune multi-systemic disease with a complex and multi-factorial pathogenesis, mostly affecting young women and characterized by a relapsing-remitting course. Organ involvement can be highly heterogeneous, and the respiratory system, along with skin, kidney, joints, and blood system, is frequently affected.[3,4]

Pleuritis is definitely the most common manifestation, but other different vascular and parenchymal abnormalities have been reported (Table 1). The prognosis greatly varies according to the type of manifestation and on the response to the currently available therapies.

Pleuritis

Pleural involvement is the most common pleuropulmonary manifestation of SLE. Pleuritis, with or without pleural effusions, has been reported in up to 50% of SLE patients during the disease course[11] and in as many as 93% of autopsy series.[12] Noteworthy, it is the only pulmonary manifestation which has been included in the 2019 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) classification criteria for SLE.[13] Long-standing disease, chronic damage, late-onset SLE, and positive anti-RNP and anti-Smith antibodies are associated with a nearly two-fold increased risk of developing pleuritis.[14] It occurs with chest pain in up to 45% to 60% of patients,[3,15] but it can be asymptomatic and fortuitously diagnosed in routine radiographs performed for other reasons. Patients may also report fever, cough, and dyspnea.[16] Pleural effusions in SLE are often bilateral, exudative, and commonly of small entity, but may occasionally be massive.[17] Fibrothorax is a rare but potentially fatal complication of lupus pleuritis, which may require pleural decortication.[18] The differential diagnosis mainly includes infections,[19] pulmonary embolism (PE), malignancy, and congestive heart failure. When infections are excluded, high levels of C-reactive protein (CRP) in SLE patients have been associated with pleural disease or other forms of serositis during disease exacerbations.[20,21] Pleural involvement is commonly observed in patients with active SLE in other organs and systems.[20] Pleural fluid analysis does not provide any specific feature; however, it can be used to rule out other conditions.[22] The fluid appearance can vary from clear, serous to bloody; physico-chemical analysis can reveal predominant polymorphonuclear cell, low glucose levels, and high levels of lactate dehydrogenase (LDH). Low complement levels and positive antinuclear antibodies (ANAs) can also be found in pleural fluid. Nonetheless, the detection of positive ANA should be interpreted with caution because a titre of ANA above 1:160 by indirect immunofluorescence has also been reported in malignant diseases.[23] Thoracoscopy may detect nodules on the visceral pleura histologically characterized by deposits of immune complexes (ICs) by immunofluorescence.[24] Treatment is mainly based on

Table 1. Lung involvement in SLE.

Type of lung involvement	Main clinical features
Lupus pleuritis	Chest, fever, cough, and dyspnea. Lupus pleuritis is often bilateral, exudative, and commonly of small/moderate entity
Parenchymal disease and airways disorders	
Acute lupus pneumonitis (ALP)	Rapid-onset pneumonia with severe respiratory illness (dyspnea, tachypnea, and hypoxiemia), fever, cough, and basilar crackles. HRCT shows patchy bilateral consolidation or ground glass opacities, frequently in conjunction with pleural effusion
Diffuse alveolar hemorrhage (DAH)	Acute or subacute dyspnea, cough, and hemoptysis. Alveolar patchy or diffuse opacities on chest radiography. The DLCO is typically increased because of extravascular hemoglobin within the alveoli. Bronchoscopy with BAL is stained with blood
Systemic lupus erythematosus–associated interstitial lung disease (SLE-ILD)	Decreased exercise tolerance, non-productive cough, dyspnea, and basilar crackles at physical examination. The most common radiologic pattern is NSIP while UIP and BOOP are unusual. PFTs are characterized by a restrictive pattern and a decreased DLCO
Pulmonary venous thromboembolism Pulmonary arterial hypertension (PAH)	They are characterized by a lack of overt clinical symptoms in the early phase and by exertional dyspnea in a more advanced disease. Physical examination could reveal a loud second pulmonary heart sound. PFTs commonly show normal lung volumes with a reduction in DLCO. Transthoracic Doppler echocardiography can be useful for screening for PAH; however, RHC is required for definitive diagnosis and to orient between PAH different etiologies
Neuromuscular disease with secondary pulmonary involvement	Dyspnea and/or chest pain, reduced lung volumes on PFTs, and diaphragm elevation on X-ray
Lung infections	They should always be excluded in patients with respiratory symptoms such as cough, fever, and dyspnea, especially in those taking immunosuppressive therapy. Chest radiograph and HRCT might show a picture indistinguishable from ALP, DAH, or ILD. Microbiological exams on serum, sputum, and BAL are therefore necessary to confirm the diagnosis

BAL, bronchioalveolar lavage; BOOP, bronchiolitis obliterans organizing pneumonia; DLCO, diffuse lung CO; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; NSIP, non-specific interstitial pneumonia; PFT, pulmonary function test; RHC, right heart catheterization; SLE, systemic lupus erythematosus; UIP, usual interstitial pneumonia.

non-steroidal anti-inflammatory drugs (NSAIDs) or systemic glucocorticoids (GCs). The latters are commonly used in case of unresponsiveness to NSAIDs and/or in moderate-severe forms. In refractory cases, immunosuppressive drugs such as azathioprine (AZA), mycophenolate mofetil (MMF),[25] and methotrexate (MTX) are recommended. Finally, the anti-BlyS monoclonal antibody belimumab resulted to be effective in some cases.[26–31]

Parenchimal disease

Acute lupus pneumonitis. Acute lupus pneumonitis (ALP) is a rare and severe manifestation of SLE affecting 1% to 4% of patients. In some series, it is reported as the initial disease presentation in up to half cases.[32] ALP is more likely to occur during SLE flares, with multi-systemic involvement, including lupus nephritis; furthermore, anti-Ro/SSA antibodies have been associated with an increased risk of ALP.[33] In one series

of 12 patients with ALP, the mortality rate was 50%, which derived from respiratory failure, infections, and thromboembolic events; among the survivors, up to one third developed chronic interstitial lung disease (ILD).[32] The clinical picture of ALP is not specific and is usually characterized by a rapid-onset severe respiratory illness, fever, cough, and dyspnea. Physical examination typically shows tachycardia, tachypnea, hypoxemia, and basilar crackles. Chest radiographs are characterized by bilateral, acinar infiltrates in the lower lobes, while high-resolution computed tomography (HRCT) shows patchy consolidation or ground glass opacities, frequently in conjunction with pleural effusion.[34] Histopathologic findings include diffuse alveolar damage, hyaline membranes, and inflammatory cells infiltrates. By immunofluorescence, granular deposits of IgG and C3 can be found within the alveolar septa.[35,36]

As clinical manifestations of ALP are non-specific, diagnosis can be very challenging. Viral, bacterial, and fungal infections need to be ruled out, especially the opportunistic ones if the patient is immunocompromised. Notably, in the current times, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia should be excluded as well.[37,38] Other alternative diagnoses include organizing pneumonia (OP), PE, drug toxicity, diffuse alveolar hemorrhage (DAH) and malignancy. If clinical or microbiological tests are non-diagnostic, lung biopsy is recommended to confirm the diagnosis. No controlled trials have been carried out for the treatment of lupus pneumonitis and the therapeutic recommendations mainly derive from case reports and clinical practice. Broad spectrum antibiotics, including those covering encapsulated organisms, should be administrated in all patients while awaiting microbiological results. The cornerstone of treatment is represented by systemic prednisone at the dose of 1 mg/kg/day. If no response is obtained within 72 hours, intravenous (IV) pulses of GCs (i.e. 1 g of methylprednisolone per day for three consecutive days) should be administered. Steroid-sparing immunosuppressive agents, such as AZA, MMF, or cyclophosphamide (CYC), should be concomitantly started. Intravenous immunoglobulins (IVIGs) and plasmapheresis may be useful in refractory cases.[33]

DAH. DAH is an uncommon but potentially fatal manifestation of SLE, occurring in less than 2% of patients,[39] in most cases during the disease course rather than at the time of the diagnosis.[40] Despite aggressive immunosuppressive therapy, the mortality rate from DAH is still high, mainly for its rapid onset and fast progression over a few days.[33] DAH is most commonly reported in young women, especially in the setting of a serologically and clinically active disease.[41,42] The most relevant risk factor associated with the development of DAH is active renal disease, especially class III or IV lupus nephritis.[41–44] Furthermore, a recent case-control study reported that anti-Ro/SSA antibodies, thrombocytopenia, and elevated CRP may significantly be associated with lupus DAH.[45] Antiphospholipid antibodies (aPL) are also supposed to be contributory in some patients.[46] DAH is characterized by acute or subacute dyspnea, cough, and hemoptysis in the setting of a drop in blood hemoglobin level and bilateral alveolar opacities, patchy, or diffuse, on chest radiography. The diffusing capacity for carbon monoxide (DLCO) is typically increased because of the presence of extravascular hemoglobin within the alveoli. Bronchoscopy with bronchoalveolar lavage (BAL) is commonly performed in order to confirm DAH and to rule out infections and malignancies. BAL fluid is invariably stained with blood and does not clear with continuous lavage. Hemosiderin-laden macrophages in BAL fluid are an additional common finding. The two most frequent histologic patterns described in lupus DAH include bland pulmonary hemorrhage and vasculitis of the small arterioles.[41,47] Bland pulmonary hemorrhage has been suggested to be the most common cause of DAH in some series.[48] It is commonly associated with a predominant monocyte infiltration in the alveolar wall and arterial IC deposition.[48] Inflammation and necrosis of the alveolar and capillaries with a predominant pericapillary neutrophil infiltration are instead the common features of the inflammatory vasculitic pattern.[49] Since DAH may be life threatening, most patients are treated with a high dose of systemic GCs, especially IV pulses of methylprednisolone (Figure 1(a) and (b)). Some studies reported a better survival rate in patients receiving a higher dose of methylprednisolone than that conventionally used (4–8 g instead of 3 g).[50] Administration of CYC has demonstrated to improve survival,[51] also in the most severe cases requiring mechanical ventilation;[41] the combination of methylprednisolone and CYC is associated with an even increased survival rate.[52] Plasma exchange and IVIG are considered rescue therapies for refractory disease, although supportive data are limited.[48] The anti-CD20 monoclonal antibody rituximab (RTX), in addition to GCs, has proven to be effective in case reports or in

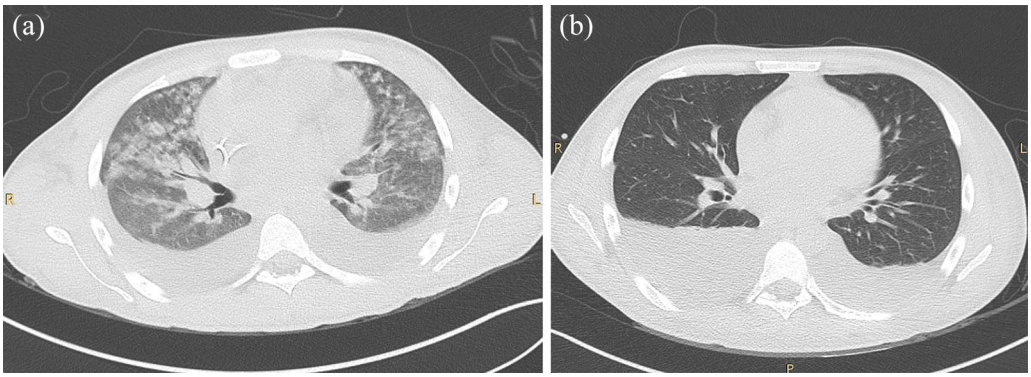

Figure 1. Areas of bilateral parenchymal consolidations with a peribronchovascular distribution localized in the inferior lobes on high-resolution computed tomography (a) and the corresponding chest radiography image (b) in a patient with organizing pneumonia in systemic lupus erythematosus.

registries;[53] however, if the clinical picture is from mild to moderate, MMF or AZA may be reasonably used.[54,55]

SLE-associated ILD. Chronic systemic lupus erythematosus–associated interstitial lung disease (SLE-ILD) is a rare manifestation of the disease, which affects up to 9% of patients.[3,56–58] SLE-ILD can occur after one or more episodes of ALP or in a more insidious fashion.[32] Although no clinical or serologic markers have strongly been associated with the development of chronic SLE-ILD,[59] a recent systematic review demonstrated a potential association with late-onset disease.[60,61] Non-specific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), OP, lymphocytic interstitial pneumonia (LIP), follicular bronchiolitis, and nodular lymphoid hyperplasia have all been reported in association with SLE.[62] NSIP is the most common radiologic pattern,[58] while UIP and OP are fairly unusual[62,63] (Figure 2(a) and (b)). SLE-ILD commonly occurs with a decreased exercise tolerance, non-productive cough, dyspnea, and basilar crackles at physical examination.[64] The diagnosis is often based on clinical and radiological findings, but it is crucial to rule out other possible causes of respiratory symptoms, such as infections, malignancy, and congestive heart failure. Pulmonary function tests (PFTs) are characterized by a restrictive pattern, defined by a decrease in forced vital capacity (FVC), total lung capacity, and DLCO. Chest radiographs may show the presence of ILD, but HRCT is the milestone for confirming lung interstitial involvement and for defining its radiologic pattern, which in turn correlates with a specific histopathologic diagnosis.

In recent years, novel serum biomarkers have been tested for evaluating ILD in SLE and other CTDs.[65] Among them it has to be mentioned Krebs von den Lungen-6 (KL-6), surfactant protein-A (SP-A), surfactant protein-D (SP-D), CC-chemokine ligand 18 (CCL18), and matrix metalloproteinase 7 (MMP7). In the future, they may be used for diagnosis, assessing the severity of disease, prediction of progression, and treatment responses in CTDs-ILD.[65]

There are no definite guidelines for the management of SLE-ILD, and the therapeutic approach depends on the type, severity, and rate of progression of lung involvement. Patients with fibrotic ILD are less likely to benefit from anti-inflammatory or immunosuppressive therapy, while they may take advantage from the use of antifibrotic agents. A recent clinical trial in patients with progressive fibrosing ILDs of different etiologies, including autoimmune diseases, showed a decrease in the rate of decline of lung function with the use of the antifibrotic agent nintedanib.[66,67] With exception of fibrosing forms, the mainstay of therapy is high-dose prednisone (1 mg/kg/day) followed by gradual tapering. In a case series,[58] the treatment with prednisone was associated with an improvement of respiratory symptoms and DLCO in the majority of patients. Steroid-sparing agents commonly used for the treatment of ILD in CTDs include AZA, MMF, RTX, and CYC. However, data on the use of immunosuppressive drugs in SLE-ILD are insubstantial.[68–70] For patients affected with mild to moderate forms, AZA or MMF may be considered, while in the severe or rapidly progressive cases, CYC or RTX should be preferred. In the

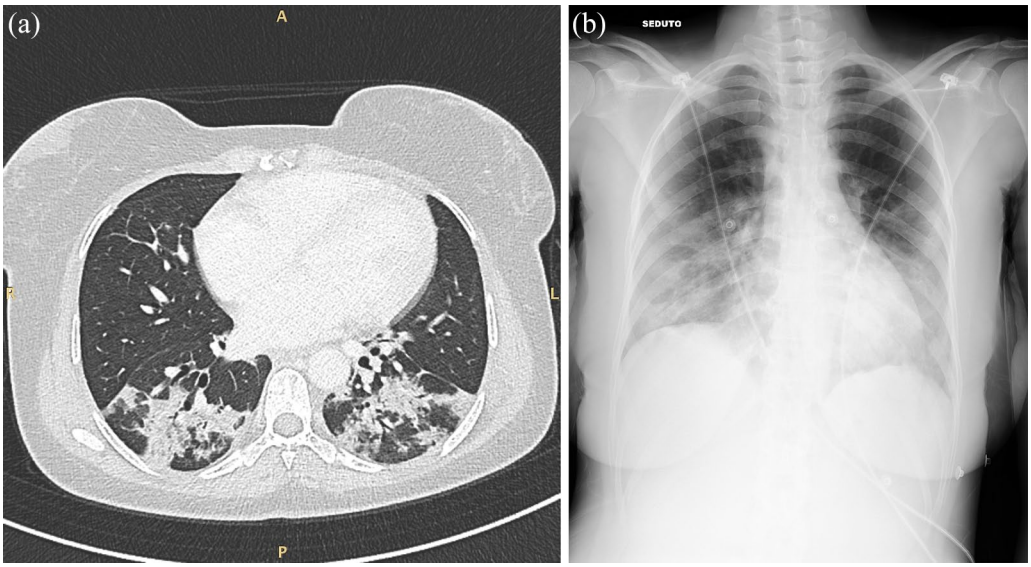

Figure 2. Diffuse ground glass opacities, air-bronchogram images, and bilateral pleural effusion on high-resolution computed tomography in a patient with hemorragic alveolitis in systemic lupus erythematosus before (a) and after (b) methylprednisolone pulses and high-dose intravenous glucocorticoid therapy.

setting of a severe ILD flare, characterized by hypoxemia and marked impairment by PFTs, high dose of systemic GCs (i.e. methylprednisolone 1 g for 3 days) should be administered, in association with RTX or CYC, switching to another immunosuppressive agent such as AZA or MMF for maintenance therapy.[70]

Pulmonary thromboembolic disease

Notably, SLE patients have an increased risk of developing venous thromboembolic events in the pulmonary circulation.[71,72] Yusuf *et al.*[71] found that among hospitalized patients the risk of pulmonary venous thromboembolism (VTE) is higher in SLE patients compared to those without autoimmune diseases. Membranous nephropathy and aPL positivity are well-established risk factors for VTE, in particular the presence of aPL carries a six-fold increased risk of VTE.[73] Indeed, thrombotic events frequently occur in the setting of antiphospholipid antibody syndrome (APS), whose prevalence in SLE is estimated to be around 30%.[74–76] Noteworthy, recurrent episodes of VTE may lead to chronic thromboembolic pulmonary disease and, eventually, pulmonary arterial hypertension (PAH). Therapy of pulmonary thromboembolism is mainly based on anti-coagulants. Initial management does not differ if the patient is aPL positive or negative.[33]

PAH

PAH is a rare and life-threatening pulmonary manifestation of SLE, much more frequent in SSc or mixed connective tissue disease (MCTD).[77] It is defined, on right heart catheterization (RHC), by a mean pulmonary artery pressure greater than 25 mmHg at rest and a normal pulmonary capillary wedge pressure when classified as pre-capillary.[78] Pulmonary hypertension can be secondary to a variety of diseases, such as ILD leading to hypoxemia, thromboembolic disease, pulmonary veno-occlusive disease (PVOD),[79] left-heart-sided valvulopathies, and sleep apnea disorder. On this regard, the World Health Organization has proposed a classification of the different forms of pulmonary hypertension into five groups based on the underlying cause.[80] In a cross-sectional study of 283 patients with SLE, pulmonary hypertension was observed in 4% of patients, based on Doppler echocardiography, while severe PAH (pulmonary systolic pressure by echocardiography >40 mmHg) was noted in about 1%.[81] In most cases, SLE diagnosis precedes the detection of PAH but its early prevalence may be underestimated due to the lack of overt clinical symptoms in the early phase.[82] The strongest association of PAH in the setting of SLE is with Raynaud's phenomenon (RP), occurring in up to 60% of cases.[83] Other reported associations are with positive rheumatoid factor (RF), anti-ribonucleoprotein (RNP) antibodies, and serum

endothelin-1 levels.[84,85] The clinical picture of PAH is characterized by exertional dyspnea, fatigue, non-productive cough, and, in advanced disease, symptoms of cor pulmonale. Physical examination findings commonly include a loud second pulmonary heart sound and a left parasternal lift. A chest radiography can show cardiomegaly and a pronounced pulmonary artery segment. PFTs in PAH commonly show normal lung volumes with a decrease in DLCO. The six-minute walk distance (6MWD) is reduced, in association with oxygen desaturation ⩾5%, often with an inflated heart rate response.[86] When PAH is caused by advanced ILD, lung volumes will show a restrictive pattern. Transthoracic Doppler echocardiography can be useful for PAH screening because it allows to estimate pulmonary artery pressures and right atrial and right ventricular size and function.[81] However, RHC is required for a definitive diagnosis. Common histological findings in SLE-related PAH are represented by thickening of the arterial media and subintima in addition with angiomatoid lesions of the pulmonary muscular arteries and IC deposition in the arterial wall.[87,88] Rare cases of pulmonary vasculitis have been reported.[89] The management of SLE-associated PAH is similar to that of other CTDs or the idiopathic form.[90] General measures for patients affected with PAH may include oxygen, exercise, and diuretics. The main pharmacological approach is based on endothelin receptor antagonists, phosphodiesterase type-5 inhibitors (PDE5 inhibitors), and vasodilators. Monotherapy with a single-class agent can be administered, although the combination of oral drugs belonging to different classes is preferred in clinical practice to obtain a synergic effect and, at the same time, to reduce the risk of adverse effects by administering lower doses of each drug. Among the endothelin receptor antagonists used for PAH, there are the non-selective agents, bosentan, and macitentan, and the selective agent ambrisentan. Sildenafil, tadalafil, and vardenafil are PDE5 inhibitors with vasodilatory effects. A study examining the effect of oral sildenafil in 19 patients with SLE-associated PAH found that sildenafil-treated patients had a mean increase in 6MWD of 42 meters compared with a decrease of 13 meters in the placebo group after 12 weeks of treatment.[91] The combination of ambrisentan and tadalafil has been associated with a significant decrease in the rate of clinical failure compared to monotherapy with either drugs alone.[92] Data on the use of immunosuppressive therapy in SLE-associated PAH are inconclusive, but those patients with PAH secondary to ILD or pulmonary vasculitis may benefit from immunosuppressive agents.[93] In this regard, single studies reported a successful treatment of PAH with CYC[94] or RTX[95] but randomized clinical trials are needed to confirm these findings.[96]

Shrinking lung syndrome

Shrinking lung syndrome (SLS) is an uncommon but well-recognized complication of SLE and other autoimmune diseases[97] such as SSc, pSS, and rheumatoid arthritis (RA).[98] SLS affects from 0.5% to 1.53% of all lupus patients,[99] in most cases 4 to 5 years after the initial diagnosis.[100] Pleural involvement, positive anti-double-stranded-DNA (dsDNA), and anti-RNP antibodies are associated with the development of SLS.[101] Different etiologies have been proposed, but the precise pathophysiological mechanism has yet to be demonstrated.[102] It is possible that myopathy or myositis of the diaphragms may lead to muscular disfunction;[103] however, this hypothesis is in contrast with some reports suggesting a normal diaphragm function in most patients with SLS.[104] Another hypothesis postulates a phrenic nerve damage or paralysis.[105,106] Some other reports suggest a possible role of chronic pleural inflammation leading to lung hypo-inflation and altered lung compliance.[107,108] SLS commonly occurs with dyspnea and/or chest pain, reduced lung volumes by PFTs, and diaphragm elevation by X-ray. For establishing the diagnosis of SLS parenchymal diseases, infections and PE need to be excluded. GC therapy and immunosuppressants are reported to improve both pulmonary function and symptoms.[108–110] RTX and CYC have been successfully used for the treatment of SLS,[111–113] while the efficacy of theophylline or other beta-adrenergic agonists is still controversial.[114] Finally, physiotherapy for pulmonary rehabilitation may also be helpful.[103]

Lung infections

Lung infections can be considered one of the most relevant causes of morbidity and mortality among hospitalized patients affected with SLE[115] and one of the most common causes of lung involvement in SLE patients. High disease activity, disease duration, and use of immunosuppressants are recognized risk factors for the development of lung infections.[116] Furthermore, a mean daily dose of 15 mg of prednisolone at the onset of pneumonia is reported to be an adjunctive threatening of death.[117] Deficiencies in the complement system,

impaired chemotaxis and phagocytosis of macrophages, and homozygosity for mannose-binding lectin variant polymorphisms put SLE patients at high risk for a variety of bacterial (especially encapsulated organisms) and opportunistic lung infections.[117–119] Nevertheless, functional asplenia, which is reported in up to 5% of SLE patients, may also play a role.[120] The most common causes of lung infection in a Canadian study were *P. aeruginosa*, *H. influenzae*, *S. marcescens*, *K. pneumoniae*, and *Legionella species*;[121] other potential causes include *Cytomegalovirus*, disseminated *Herpes simplex*, and *Pneumocystis jirovecii*.[122,123] According to EULAR recommendations, vaccination against pneumococcal disease and influenza should be strongly encouraged for most people with SLE and other autoimmune rheumatic diseases.[124]

Pulmonary involvement in pSS

pSS is defined as an autoimmune epithelitis specifically characterized by impairment of exocrine glands (mainly lacrimal and salivary) due to inflammatory infiltrate.[125] It also shows extraglandular, multi-organ involvement[126,127] and respiratory manifestations (Table 2) are among the most prevalent extra-glandular complications affecting 9% to 75% of patients[128] according to the detection methods and patient selection criteria.[129–131] Upper airway disorders with dryness in nasal and oropharyngeal mucosa are definitely among the most frequent manifestations and are due to mucosal dryness, mucus viscosity disorders, and impaired mucociliary clearance caused by the long-standing inflammation that finally leads to atrophy of the submucosal glands of the airway mucosa.[132] Chronic obstructive pulmonary disease[133–136] and bronchial hyperresponsiveness[137,138] have also an increased prevalence in pSS patients in respect to general population. Respiratory and lung involvement have proven to significantly decrease the quality of life and are associated with increased mortality.[8,139]

Airway disorders

Bronchiolitis. Bronchiolitis is the most frequent airway disease in pSS, and it is classified into three main types: follicular bronchiolitis, chronic bronchiolitis, and bronchiolitis obliterans. Lung biopsy–proven prevalence reaches 12% of cases (29% of patients have histopathologic changes consistent with follicular bronchiolitis, 21% with chronic bronchiolitis, and 7% with bronchiolitis obliterans), but frequency increases to 29% with HRCT evaluation.[140] It traditionally occurs with cough and dyspnea, which may be the first manifestation of pSS in up to 36% of patients.[141] The course of bronchiolitis in pSS is typically fairly mild; however, severe cases have been reported.[141,142] Follicular bronchiolitis has been specifically linked to CTDs, such as pSS and RA. It traditionally occurs with cough and dyspnea, even without objective clinical signs of lung involvement. PFT findings may be normal or show either a restrictive or obstructive pattern. Radiographically, it appears as a reticular or reticulonodular pattern on HRCT[143] (Figure 3(a) and (b)), while histopathologically, it is characterized by the presence of hyperplastic lymphoid follicles with reactive germinal centers distributed along bronchovascular bundles.[144] Bronchiolitis obliterans is defined by a mosaic pattern with air trapping on HRCT.[142] Chronic bronchiolitis and bronchiolitis obliterans present with a spectrum of histological changes such as lymphocytic infiltration of small airways, bronchiolar smooth muscle hypertrophy, obstruction of bronchioles with mucus or even complete obliteration of bronchioles with scarring; these aspects are often indistinguishable from other etiologies.[139] There are scant data on the effect of therapy on bronchiolitis in pSS. Macrolides (most commonly azithromycin 250 mg 3 days a week for 2–3 months[145]), inhaled GCs and inhaled bronchodilators may strongly improve the respiratory status of patients.[146] GCs and RTX could be an option for follicular bronchiolitis[147–149] while a combination of hydroxychloroquine and MMF had been administered to patients with constrictive bronchiolitis showing stability or slight improvement of respiratory function.[142]

Bronchiectasis. Radiographically evident bronchiectasis has been described in 23% to 54% of patients with pSS.[150,151] Patients with bronchiectasis tend to be older at pSS diagnosis, have a higher frequency of hiatal hernia and a lower prevalence of anti-Ro/SSA antibodies but increased presence of anti-smooth muscle cell antibodies.[152] Most patients usually show cylindrical shape bronchiectasis and have lower lobe–predominant disease.[152] Clinical symptoms are variable and non-specific: dry cough, isolated dyspnea, and hemoptysis in rare occasions. In addition, patients with bronchiectasis have a higher frequency of respiratory infections (56% vs 3%) and pneumonia (29% vs 3%).[152] Treatment is based on strategies to relief from secretions[145] like mucolytic agents and expectorants, nebulized saline or

Table 2. Lung involvement in pSS.

Type of lung involvement	Main clinical features
Airways disorders	
Upper airways inflammation	Dryness in nasal and oropharyngeal mucosa finally leading to atrophy of the submucosal glands of the airway mucosa
Chronic obstructive pulmonary disease and reactive airway disease	Shortness of breath, chronic dry cough, or wheezing due to airway hyperresponsiveness. PFTs allow the distinction of the two patterns
Bronchiolitis (follicular bronchiolitis, chronic bronchiolitis, and bronchiolitis obliterans)	It traditionally presents with cough and dyspnea. PFT findings may be normal or show either a restrictive or obstructive pattern. It appears as a reticular or reticulonodular pattern on HRCT
Bronchiectasis	Dry cough, isolated dyspnea, and hemoptysis in rare occasions. Patients with bronchiectasis have a higher frequency of respiratory infections and pneumonia
Parenchymal disease	
Interstitial lung disease	Non-productive cough and dyspnea are present in half of patients, the remaining are completely asymptomatic. On auscultation, it is characterized by fine bibasilar end-inspiratory "velcro-like" crackles. The most common ILD pattern is NSIP, followed by UIP, OP, and LIP. In early involvement, it is easy to observe a reduction of DLCO (alveolar inflammation) with a preserved FVC (normal lung volumes)
Lymphoma and pseudolymphoma	Cough, slowly progressive dyspnea, and traditional B symptoms (fever, night sweats, and weight loss) are characteristic of lung lymphoma. Parenchymal radiographic findings are often associated to mediastinal lymphadenopathy and pleural effusions Pseudolymphoma is generally asymptomatic, and it usually appears as a solitary nodule or mass
Pulmonary amyloidosis	Cough or dyspnea along with fatigue, weakness, hemoptysis, and pleuritic chest pain. Radiologically it is characterized by large, calcified, randomly distributed, irregular, smooth-bordered nodules alone, or in association with LIP
Sarcoidosis	Asymptomatic or presenting with exertional dyspnea or dry cough. Heerfordt's syndrome is defined by the characteristic parotid enlargement and the presence of uveitis. Radiographic abnormalities include bilateral hilar lymphadenopathy, pulmonary infiltrates, or fibrosis
Cystic lung disease	Mostly subclinical. Cysts are usually bilateral with the majority located in the middle lung
Pulmonary venous thromboembolism Pulmonary arterial hypertension (PAH)	They are characterized by a lack of overt clinical symptoms in the early phase and by exertional dyspnea in a more advanced disease. Physical examination could reveal a loud second pulmonary heart sound. PFTs commonly show normal lung volumes with a reduction in DLCO. Transthoracic Doppler echocardiography can be useful for screening for PAH however, RHC is required for definitive diagnosis and to orient between PAH different etiologies
Lymphocytic pleuritis	Rare manifestation in pSS characterized by chest, fever, cough, dyspnea, and exudative pleural effusion
Neuromuscular disease with secondary pulmonary involvement	Dyspnea, persistent episodes of chest pain, restrictive syndrome, and the absence of significant interstitial and/or pleural disease

DLCO, diffuse lung CO; FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; LIP, lymphocytic interstitial pneumonia; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia; PAH, pulmonary arterial hypertension; PFT, pulmonary function test; pSS, primary Sjogren's syndrome; RHC, right heart catheterization; UIP, usual interstitial pneumonia.

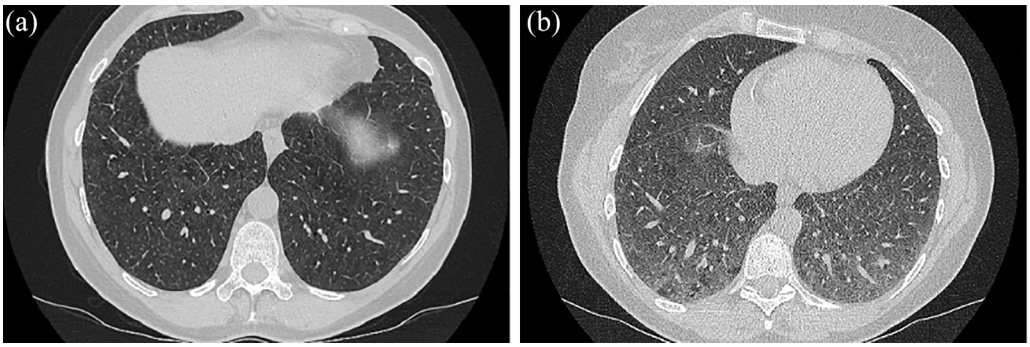

Figure 3. Reticular pattern during inspiration (a) and expiration (b) on high-resolution computed tomography in a patient affected with follicular bronchiolitis in primary Sjögren's syndrome.

hypertonic saline, oscillatory positive expiratory pressure, postural drainage, and mechanical high-frequency chest wall oscillation therapies. Chronic administration of macrolides in patients without non-tuberculous mycobacterium colonization or infection is also advisable.[145]

Parenchymal involvement

Interstitial lung disease (pSS-ILD). ILD prevalence among pSS patients is around 20% when defined by HRCT or reduced FVC and/or DLCO. Besides HRCT, which is the gold standard, quantitative CT (QCT) analysis may be a promising tool to assess pSS-ILD and its severity. It is based on software providing highly accurate and operator-independent measurements, termed QCT indices, which have been rapidly validated in systemic autoimmune diseases. Quantitative lung assessment methods are capable of distinguishing limited ILD from extensive ILD, which is responsible for poor prognosis in pSS.[153] ILD prevalence increases along with the disease duration (10% after 1 year from diagnosis, up to 47% after 15 years of disease) but in 10% to 51% of patients, it occurs years before pSS onset.[154]

Symptoms as non-productive cough and dyspnea are observed in 40% to 66% of patients but are not specific; 24% to 48% of patients are completely asymptomatic.[154,155] Physical examination is often unremarkable but fine bibasilar end-inspiratory "velcro-like" crackles at auscultation may lead to ILD suspicion.[156] Digital clubbing, weight loss, focus score $\geqslant$4 in minor salivary gland biopsy, lower albumin-to-globulin ratio, higher levels of IgM, LDH, Erythrocyte Sedimentation Rate (ESR), and positive anti-Ro52 antibodies are frequently found in pSS-ILD patients.[157,158] Older age, smoking, increased ANA titer and CRP level, and RF have been reported as potential risk factors for the development of ILD.[157] Patients with non-sicca-onset pSS-ILD less commonly have hypergammaglobulinemia, increased RF or positive anti-SSA, and anti-SSB antibodies compared with patients with sicca-onset pSS-ILD,[159] making ILD recognition challenging. In a patient with pSS and suspected ILD, an oximetry testing is part of the patient's initial evaluation; further investigations include HRCT with expiratory views and PFTs with DLCO measurement which should be performed and followed initially at 3- to 6-month intervals for at least 1 year because of variable natural history of the disease progression.[145] Discordance between baseline PFT abnormalities, degree of symptoms, and HRCT findings can be observed:[160] the incidence of parenchymal HRCT changes appear to be earlier and greater in frequency than what clinical symptoms would indicate; moreover, HRCT findings are not always accompanied by substantial alterations in PFTs.[160] In early involvement, it is easy to observe a decrease in DLCO with a preserved FVC because inflammation, affecting the alveolar membrane, causes an impairment of gas-exchange function with preserved lung volumes.[154]Therefore, DLCO is highly sensitive to predict the presence of ILD while FVC is more useful for assessing the disease extent.[161] A novel non-invasive tool based on lung ultrasound examination could be helpful for screening of pSS-ILD involvement[154] because plain chest radiographs are insufficient to detect early abnormalities.[160] Imaging features of pSS-ILD are complex and include variable combination of ground glass opacities, reticular abnormalities, consolidation, honeycombing, cysts, nodules, and also bronchiectasis.[140] Surgical lung biopsy is not routinely recommended but may be considered in neoplastic

and non-neoplastic lymphoproliferative disorder for ruling out cancers, amyloidosis, suspected infection failing empiric therapies, and when less invasive testing is not diagnostic.[145] Notably, there are cases of lymphoma and amyloidosis presenting with a radiographic pattern similar to LIP; thus, tissue biopsy is essential to ascertain a LIP diagnosis.[162–164] The most common ILD pattern is NSIP, found in 41% to 45% of pSS-ILD patients,[162] followed by UIP in 10%, OP in 4%, and LIP which has been classically linked to pSS and occurring in 4% to 9% of cases.[156,158] The remaining have combined HRCT patterns.[158] Guidelines for evaluation and management of pulmonary disease in pSS have recently been published.[145] No standard definition exists for staging, but EULAR Sjogren's syndrome disease activity index (ESSDAI), imaging, and PFTs could drive the initiation of therapy.[165] No treatment or serial observations is suggested for mild disease activity; for moderate-severe disease activity, oral corticosteroids plus MMF, or AZA as first-line GCs-sparing or as adjunctive agents is recommended.[165] If there is no satisfactory response, it is advisable to perform a critical review of HRCT to determine whether the primary pattern is fibrotic or inflammatory; in the latter case, RTX, calcineurin inhibitors, tacrolimus over cyclosporine A (CsA), or CYC are available options.[145] For progressive fibrotic ILD, it is possible to consider an antifibrotic therapy, such as nintedanib, which is approved by the Food and Drug Administration (FDA) for progressive fibrotic lung disease in SSc.[145] More specifically, NSIP pattern shows good response to GCs (0.5–1 mg/kg/day tapered over months to 5–7.5mg/day) associated with other drugs as AZA or CYC[149] while UIP is considered as an irreversible lung disease with a high risk of progression despite immunosuppressive therapy.[162,166] In patients with OP, it is reported a good initial response to GC therapy using adjunctive immunosuppressive agents such as AZA, CsA, infliximab, RTX, and tocilizumab in refractory cases.[140,165,167,168] LIP seems to be a reversible lung disease with a potential risk of progression through the development of honeycombing[164] although the majority of patients with LIP treated with GCs remain clinically stable or improve. Other immunosuppressive agents such as AZA or CYC have been used but with variable response[169] and RTX has been reported as effective.[149] Other experimental therapies are under study for pSS and may be of potential usefulness also for lung involvement in light of the common systemic immunological mechanisms underlying the disease. Belimumab could be an option in consideration of the critical role of B-cell activating factor (BAFF) and of B-cells in the pathogenesis of pSS. Moreover, the combination of RTX and belimumab, based on previous experience[26,170–172] is currently being explored for pSS and may be considered for patients with severe lung involvement;[173] belimumab given immediately before RTX should be useful against tissue lymphoid inflammation because the first drug, by depleting local BAFF, can facilitate the action of the second.[174]

Ianalumab, an IgG1 monoclonal antibody against BAFF-R, is currently under study for salivary gland invovement.[175] Abatacept, a CTLA-4 monoclonal antibody that modulates T-cell co-stimulation, has been shown to give some benefit in pSS improving disease activity scores and reducing lymphocytic foci, local T-cells and gammaglobulins;[176] it might be also beneficial in pulmonary pSS. Iscalimab, a monoclonal antibody targeting CD40/CD40 L pathway which is key factor in the organization of the germinal centers, could become a viable option.[177] Direct inhibition of inflammatory cytokines may be of potential benefit in pulmonary pSS as well. Interleukin (IL)-17 has shown to play an important role in the pathogenesis of pSS because an increased number of IL-17 Ralfa-expressing T-cells have been found in minor salivary glands in pSS patients.[178] Type-I interferon has in turn a key role in pSS pathogenesis and could be a potential target in pulmonary pSS.[179–181] In addition, blocking downstream signaling of pro-inflammatory cytokines through use of Janus kinase (JAK) inhibitors may be effective as recent evidence suggests it may also influence BAFF signaling.[182] There is some evidence on the efficacy of JAK inhibitors in chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis (IPF). It would be important to explore their role even in pulmonary pSS.[139,183,184] Data on prognosis of pSS-ILD are heterogeneous. Risk factors associated with death are decreased FVC and forced expiratory volume (FEV_1), severe lung involvement,[185] and higher number of reticulations on HRCT, number of lymphoblastic foci in biopsy, and high CO_2 arterial pressure.[154] By multivariate analysis, low O_2 arterial pressure, presence of microscopic honeycombing,[140] and severity of fibroblastic foci on surgical lung biopsy[186] seem to be independently associated with worse survival. Patients with pre-existing ILD are at risk of acute exacerbation.[187] UIP pattern is at higher risk for this complication[188] with a rate of mortality up to 50% at 3 months from onset.[189] Treatment of acute exacerbations is

commonly based on high-dose GCs in monotherapy or in association with CYC, oral tacrolimus, or CsA usually along with broad spectrum antibiotic therapy because of the challenging differential diagnosis with bilateral pneumonia. Recently, reduction of acute exacerbations risk in IPF employing nintedanib has been reported.[156,190]

Lymphoma and pseudolymphoma. Patients with pSS are at higher risk for developing non-Hodgkin lymphoma[191] with a relative risk of 44.4[191,192] and a lifetime risk around 5% to 10%.[69] The mucosa-associated lymphoid tissue (MALT) lymphoma is the most common subtype,[193–195] secondary to lymphocytic infiltration of polyclonal B- and T-cells evolving into a monoclonal B-cell proliferation.[194,196] Well-known risk factors include purpura, parotid enlargement, hypocomplementemia, type-II cryoglobulinemia,[197–199] CD4 T-cell lymphopenia, and low CD4/CD8 ratio.[193,194] Lymphoma is more frequently described in salivary and lacrimal glands and in the lymph nodes. Pulmonary localization comprises 20% of all lymphomas in patients with pSS,[149] and it is usually a low-grade extra nodal marginal B-cell lymphoma of the MALT type.

However, even if it is not routinely searched, it may also originate from a salivary gland B-cell clone previously expanded in that microenvironment, and then further expanding and becoming malignant by a second trigger in the lung microenvironment.[200]

Symptoms generally include cough, slowly progressive dyspnea, and traditional B symptoms (fever, night sweats, and weight loss). Radiographic findings comprise solitary or multi-focal nodules or masses, bilateral alveolar infiltrates, interstitial opacities, airspace consolidation, or ground glass attenuation, all having been described with a mild predilection for the lower lobes.[201] Mediastinal lymphadenopathy and pleural effusions may accompany parenchymal abnormalities. Biopsy is necessary for definitive diagnosis[202,203] because HRCT features in MALT lymphoma can be indistinguishable from benign lymphoproliferative processes. The average 5-year survival rate is 65% to 90%[204] and watchful waiting without specific treatment is reserved for asymptomatic cases. Treatment is indicated for patients with bulky lymphadenopathies and/or splenomegaly, risk of local compressive disease resulting in organ dysfunction, significant cytopenia from bone marrow compromise, and/or rapid disease progression.[205] Overt lymphomas require specific hematological treatment based on RTX and chemotherapy regimens.[165,206]

Pseudolymphoma, or pulmonary nodular lymphoid hyperplasia, is a localized lymphoproliferative non-malignant disease[207] characterized by infiltration of mature polyclonal lymphocytes and plasma cells.[164] It is typically asymptomatic, although it can present with cough and dyspnea and is most commonly seen in patients with isolated sicca symptoms.[130] It generally appears as a solitary nodule or mass on HRCT.[208] If mediastinal lymphadenopathy or the presence of pleural effusions is noted, a diagnosis of lymphoma should be considered, and histological confirmation is mandatory. Pseudolymphoma generally regresses after treatment with GCs or immunosuppressive therapy but rarely it progresses to lymphoma.[209,210]

Pulmonary amyloidosis. Amyloidosis is a heterogeneous group of disorders associated with extracellular deposition of fibrillar plasma proteins[211] whose type is determinant for clinical classification. Pulmonary involvement in pSS occurs in light-chain (AL) amyloidosis, whereas reactive (AA) and hereditary forms are uncommon. The two commonly seen patterns include nodular and septal amyloidosis. It is a rare complication of pSS,[130] and a literature review[212] reports 37 cases identified with a median delay of 7 years from pSS diagnosis. Most patients are symptomatic presenting cough or dyspnea[212] along with fatigue, weakness,[213] hemoptysis,[214] and pleuritic chest pain.[215] Identified associated abnormalities include immune thrombocytopenia,[216] cryoglobulinemia,[213] RP,[130] APS,[217] renal disease,[218] and lymphoma.[212,216] The most common form of pSS-related pulmonary amyloidosis is the localized nodular type;[212] it usually occurs alone but may also be associated with pulmonary lymphoma,[219] reflecting the localized clonal proliferation of B-lymphocytes or plasma cells secreting light chains.[220] Radiologically, it presents with large, calcified, randomly distributed, irregular, smooth-bordered nodules[221] alone or in association with LIP.[140,213,215] Surgical lung biopsy is generally required to establish the diagnosis.[212,222] The prognosis is unknown, and there are no data to support any definitive therapeutic option. Observation alone may be sufficient in patients with localized nodular amyloidosis. The efficacy of GCs is anecdotal, and the improvement observed may reflect a favorable response of the underlying NSIP or LIP to GCs therapy.[212]

Cystic lung disease (CLD). Lung cysts are defined by the presence of clearly demarcated airspaces surrounded by thin (<2 mm) walls. CLD has been noted in up to 20% patients with pSS, being mostly subclinical and with limited impact on outcome. Cysts are mostly bilateral with the majority located in the middle lung.[139,223] Association between anti-SSB/La antibodies and the presence of lung cysts has been reported:[224] anti-SSB/La has a higher diagnostic specificity for pSS than does anti-SSA/Ro alone, supporting the fact that CLD is a specific feature of pSS even though the pathogenic role of anti-La/SSB antibodies remains to be determined.[225] Lung cysts have been associated with LIP, amyloidosis, or MALT B-cell lymphoma. As lung cysts in pSS are not attributable to active disease, they do not require immunosuppressive therapy.[225]

Sarcoidosis. The prevalence of sarcoidosis in patients with pSS has been estimated at between 1% and 2%.[226,227] Parotid enlargement can be part of a rare sarcoid manifestation, called Heerfordt's syndrome and characterized by the presence of facial nerve palsy, parotid gland enlargement, anterior uveitis, and low-grade fever. It is important to differentiate if sarcoidosis mimics or coexist with pSS even though making a differential diagnosis may be difficult due to similar clinical manifestations at onset including respiratory symptoms.[228] Hence, it is necessary focusing on three specific aspects: the existence of extra-glandular features, the immunologic profile, and the histologic analysis of minor salivary glands.[227]

Recently, the ultrasound-guided parotid biopsy in pSS allows differentiation with sarcoidosis.[229]

The correct diagnosis has important therapeutic and prognostic implications: lung sarcoidosis frequently resolves spontaneously without significant residual functional impairment, whereas pSS pulmonary involvement frequently requires immunosuppressive treatment beyond GCs[228] and often leads to permanent defects.

Pulmonary VET

Patients with pSS are thought to be at increased risk for deep vein thrombosis and PE with the highest risk during the first year after pSS diagnosis.[230,231] Inflammation can contribute to the development of VTE because it favors clotting, decreases the activity of natural anti-coagulant mechanisms, and impairs the fibrinolytic system. Thrombosis might be related also to the presence of antiphospholipid antibodies, being lupus anticoagulant (LAC) an important marker for APS.[232] Treatment of PE is based on anticoagulation while the role of immunosuppressive therapy has yet to be established.

PAH

PAH is a rare but severe complication of pSS. Pre-capillary PAH is characterized by vascular proliferation and remodeling of the small pulmonary arteries resulting in a progressive increase in pulmonary vascular resistance and ultimately in right ventricular failure and death.[233] PAH in pSS can also occur as a result of PVOD,[234] valvular heart diseas,[235] or ILD.[233] The exact prevalence of PAH in pSS is unknown; one study reported echocardiographic evidence of PAH in 22% of patients,[236] nevertheless RHC represents the gold standard for the diagnosis.[237] In a recent Chinese case-control study with a cohort of 103 patients with pSS-PAH diagnosed by RHC,[238] the 1-, 3-, and 5-year survival rates were 94.0%, 88.8%, and 79.0%, respectively; a low cardiac index and an increased damage index were significantly and independently associated with survival. The main symptom is exertional dyspnea[233] which is very unspecific and sometime misleadingly associated to ILD. This determines a delay between dyspnea onset and PAH diagnosis greater than 1 year in 69% of patients.[233,239] pSS-PAH has worse hemodynamic profiles on RHC than SSc-PAH and SLE-PAH, probably because diagnosis is performed in a more advanced stage of the illness.[240] Recognized associations with pSS-PAH include hypergammaglobulinemia, positive ANA, high RF level, anti-RNP antibodies, and RP.[240] Histological examination of the lungs has shown intimal and medial hypertrophy associated with plexiform lesions in the pulmonary arteries, whereas vasculitis and inflammatory infiltrates are not usually observed.[241] However, an immunologic etiology is suggested by the presence of IC in the pulmonary vessel walls of pSS–PAH patients.[241] Treatment with PAH-targeted drugs (endothelin receptor antagonists, PDE5 inhibitors, and epoprostenol) is the backbone of therapy.[233] The benefits of immunosuppressive agents such as CYC, MTX, leflunomide, tacrolimus, or AZA[231] plus GCs have been reported in several cases[242] but their effectiveness combined with PAH-target drugs requires further study.

Lymphocytic pleuritis

Pleural effusion has rarely been described in pSS.[243,244] The presence of a coexisting autoimmune disease, such as RA or SLE must be excluded.[245] The pleural fluid is a lymphocytic-predominant exudate with increased levels of RF, anti-SSA, anti-SSB autoantibodies,[245] and low levels of complement. Lymphocytic infiltration of the pleura was found on pleural biopsies.[208] Controlling the systemic inflammation and use of steroid therapy is the mainstay of therapy.[244]

Neuromuscular diseases with secondary lung involvement

Neuromuscular diseases with secondary pulmonary involvement have also been described in pSS.[246–249] SLS, although traditionally associated with SLE, has been very rarely reported.[246] Pathogenesis is still unknown: micro atelectasis and hyaline membranes caused by surfactant deficiency, diaphragmatic myopathy or phrenic nerve neuropathy have been proposed as putative hypothesis. It is commonly characterized by dyspnea, persistent episodes of chest pain, restrictive syndrome, and the absence of significant interstitial and/or pleural disease. In one case report, it has been successfully treated with RTX.[246] Hypokalemic periodic paralysis associated with a distal renal tubular acidosis, which occurs in up to 5% of patients with pSS, can sufficiently severe to cause respiratory muscle weakness.[247] Finally, lung involvement could be secondary to proximal skeletal myopathy;[248] a case of pSS complicated with inflammatory myopathy and ILD responsive to corticosteroids therapy has been reported.[249]

Author contributions

Roberto Depascale and Giulia Del Frate equally contributed to this work.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Andrea Doria https://orcid.org/0000-0003-0548-4983

References

1. Zanatta E, Codullo V, Avouac J, *et al*. Systemic sclerosis: recent insight in clinical management. *Joint Bone Spine* 2020; 87: 293–299.
2. Gasparotto M, Gatto M, Saccon F, *et al*. Pulmonary involvement in antisynthetase syndrome. *Curr Opin Rheumatol* 2019; 31: 603–610.
3. Keane MP and Lynch JP III. Pleuropulmonary manifestations of systemic lupus erythematosus. *Thorax* 2000; 55: 159–166.
4. Gatto M, Zen M, Ghirardello A, *et al*. Emerging and critical issues in the pathogenesis of lupus. *Autoimmun Rev* 2013; 12: 523–536.
5. Quadrelli S, Alvarez C, Arce S, *et al*. Pulmonary involvement of systemic lupus erythematosus: analysis of 90 necropsies. *Lupus* 2009; 18: 1053–1060.
6. Flament T, Bigot A, Chaigne B, *et al*. Pulmonary manifestations of Sjogren's syndrome. *Eur Respir Rev* 2016; 25: 110–123.
7. Luppi F, Sebastiani M, Sverzellati M, *et al*. Lung complications of Sjogren syndrome. *Eur Respir Rev* 2020; 29: 200021.
8. Palm Ø, Garen T and Enger TB. Clinical pulmonary involvement in primary Sjögren's syndrome: prevalence, quality of life and mortality—a retrospective study based on registry data. *Rheumatology* 2013; 52: 173–179.
9. Malik SW, Myers JL, DeRemee RA, *et al*. Lung toxicity associated with cyclophosphamide use. Two distinct patterns. *Am J Respir Crit Care Med* 1996; 154: 1851–1856.
10. Lateef O, Shakoor N and Balk RA. Methotrexate pulmonary toxicity. *Expert Opin Drug Saf* 2005; 4: 723–730.
11. Orens JB, Martinez FJ and Lynch JP III. Pleuropulmonary manifestations of systemic lupus erythematosus. *Rheum Dis Clin North Am* 1994; 20: 159–193.
12. Haupt HM, Moore GW and Hutchins GM. The lung in systemic lupus erythematosus. Analysis of the pathologic changes in 120 patients. *Am J Med* 1981; 71: 791–798.
13. Fanouriakis A, Kostopoulou M, Alunno A, *et al*. Update 19 of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis* 2019; 78: 736–745.
14. Mittoo S and Fell C. Pulmonary manifestations of systemic lupus erythematosus. *Semin Respir Crit Care Med* 2014; 35: 249–254.

15. Palavutitotai N, Buppajarntham T and Katchamart W. Etiologies and outcomes of pleural effusions in patients with systemic lupus erythematosus. *J Clin Rheumatol* 2014; 20: 418–421.

16. Hellman DB, Kirsch CM, Whiting-O'Keefe Q, *et al.* Dyspnea in ambulatory patients with SLE: prevalence, severity, and correlation with incremental exercise testing. *J Rheumatol* 1995; 22: 455–461.

17. Bouros D, Panagou P, Papandreou L, *et al.* Massive bilateral pleural effusion as the only first presentation of systemic lupus erythematosus. *Respiration* 1992; 59: 173–175.

18. Sharma S, Smith R and Al-Hameed F. Fibrothorax and severe lung restriction secondary to lupus pleuritis and its successful treatment by pleurectomy. *Can Respir J* 2002; 9: 335–337.

19. Rojas-Serrano J, Pedroza J, Regalado J, *et al.* High prevalence of infections in patients with systemic lupus erythematosus and pulmonary hemorrhage. *Lupus* 2008; 17: 295–299.

20. Man BL and Mok CC. Serositis related to systemic lupus erythematosus: prevalence and outcome. *Lupus* 2005; 14: 822–826.

21. ter Borg EJ, Horst G, Limburg PC, *et al.* C-reactive protein levels during disease exacerbations and infections in systemic lupus erythematosus: a prospective longitudinal study. *J Rheumatol* 1990; 17: 1642–1648.

22. Good JT Jr, King TE, Antony VB, *et al.* Lupus pleuritis. Clinical features and pleural fluid characteristics with special reference to pleural fluid antinuclear antibodies. *Chest* 1983; 84: 714–718.

23. Porcel JM, Ordi-Ros J, Esquerda A, *et al.* Antinuclear antibody testing in pleural fluid for the diagnosis of lupus pleuritis. *Lupus* 2007; 16: 25–27.

24. Pandya MR, Agus B and Grady RF. In vivo LE phenomenon in pleural fluid. *Arthritis Rheum* 1976; 19: 962–963.

25. Iaccarino L, Rampudda M, Canova M, *et al.* Mycophenolate mofetil: what is its place in the treatment of autoimmune rheumatic diseases? *Autoimmun Rev* 2007; 6: 190–195.

26. Depascale R, Gatto M, Zen M, *et al.* Belimumab: a step forward in the treatment of systemic lupus erythematosus. *Expert Opin Biol Ther* 2021; 21: 563–573.

27. Iaccarino L, Andreoli L, Bocci EB, *et al.* Clinical predictors of response and discontinuation of belimumab in patients with systemic lupus erythematosus in real life setting. Results of a large, multicentric, nationwide study. *J Autoimmun* 2018; 86: 1–8.

28. Trentin F, Gatto M, Zen M, *et al.* Effectiveness, tolerability, and safety of belimumab in patients with refractory SLE: a review of observational clinical-practice-based studies. *Clin Rev Allergy Immunol* 2018; 54: 331–343.

29. Doria A, Stohl W, Schwarting A, *et al.* Efficacy and safety of subcutaneous belimumab in anti-double-stranded DNA-positive, hypocomplementemic patients with systemic lupus erythematosus. *Arthritis Rheum* 2018; 70: 1256–1264.

30. Gatto M, Saccon F, Zen M, *et al.* Early disease and low baseline damage as predictors of response to belimumab in patients with systemic lupus erythematosus in a real-life setting. *Arthritis Rheum* 2020; 72: 1314–1324.

31. Carrión-Barberà I, Salman-Monte TC, Castell S, *et al.* Successful treatment of systemic lupus erythematosus pleuropericarditis with belimumab. *Eur J Rheumatol* 2019; 6: 150–152.

32. Matthay RA, Schwarz MI, Petty TL, *et al.* Pulmonary manifestations of systemic lupus erythematosus: review of twelve cases of acute lupus pneumonitis. *Medicine* 1975; 54: 397–409.

33. Tselios K and Urowitz MB. Cardiovascular and pulmonary manifestations of systemic lupus erythematosus. *Curr Rheumatol Rev* 2017; 13: 206–218.

34. Ahuja J, Arora D, Kanne JP, *et al.* Imaging of pulmonary manifestations of connective tissue diseases. *Radiol Clin North Am* 2016; 54: 1015–1031.

35. Swigris JJ, Fischer A, Gillis J, *et al.* Pulmonary and thrombotic manifestations of systemic lupus erythematosus. *Chest* 2008; 133: 271–280.

36. Rodríguez-Iturbe B, García R, Rubio L, *et al.* Immunohistologic findings in the lung in systemic lupus erythematosus. *Arch Pathol Lab Med* 1977; 101: 342–344.

37. Kichloo A, Aljadah M, Albosta M, *et al.* COVID-19 and acute lupus pneumonitis: diagnostic and treatment dilemma. *J Investig Med High Impact Case Rep* 2020; 8: 2324709620933438.

38. Zen M, Fuzzi E, Astorri D, *et al.* SARS-CoV-2 infection in patients with autoimmune rheumatic diseases in northeast Italy: a cross-sectional study on 916 patients. *J Autoimmun* 2020; 112: 102502.

39. Badsha H, Teh CL, Kong KO, *et al.* Pulmonary hemorrhage in systemic lupus erythematosus. *Semin Arthritis Rheum* 2004; 33: 414–421.

40. Andrade C, Mendonca T, Farinha F, *et al*. Alveolar hemorrhage in systemic lupus erythematosus: a cohort review. *Lupus* 2016; 25: 75–80.

41. Zamora MR, Warner ML, Tuder R, *et al*. Diffuse alveolar hemorrhage and systemic lupus erythematosus. Clinical presentation, histology, survival, and outcome. *Medicine* 1997; 76: 192–202.

42. Lara AR and Schwarz MI. Diffuse alveolar hemorrhage. *Chest* 2010; 137: 1164–1171.

43. Hughson MD, He Z, Henegar J, *et al*. Alveolar hemorrhage and renal microangiopathy in systemic lupus erythematosus. *Arch Pathol Lab Med* 2001; 125: 475–483.

44. Bajema IM, Wilhelmus S and Alpers CE. Revision of the International Society of Nephrology/Renal Pathology Society classification for lupus nephritis: clarification of definitions, and modified National Institutes of Health activity and chronicity indices. *Kidney Int* 2018; 93: 789–796.

45. Sun Y, Zhou C, Zhao J, *et al*. Systemic lupus erythematosus-associated diffuse alveolar hemorrhage: a single-center, matched case-control study in China. *Lupus* 2020; 29: 795–803.

46. Cartin-Ceba R, Peikert T, Ashrani A, *et al*. Primary antiphospholipid syndrome-associated diffuse alveolar hemorrhage. *Arthritis Care Res* 2014; 66: 301–310.

47. Myers JL and Katzenstein AA. Microangiitis in lupus-induced pulmonary hemorrhage. *Am J Clin Pathol* 1986; 85: 552–556.

48. Al-Adhoubi NK and Bystrom J. Systemic lupus erythematosus and diffuse alveolar hemorrhage, etiology and novel treatment strategies. *Lupus* 2020; 29: 355–363.

49. Zhuang H, Han S, Lee PY, *et al*. Pathogenesis of diffuse alveolar hemorrhage in murine lupus. *Arthritis Rheum* 2017; 69: 1280–1293.

50. Barile LA, Jara LJ, Medina-Rodriguez F, *et al*. Pulmonary hemorrhage in systemic lupus erythematosus. *Lupus* 1997; 6: 445–448.

51. Ednalino C, Yip J and Carsons SE. Systematic review of diffuse alveolar hemorrhage in systemic lupus erythematosus: focus on outcome and therapy. *J Clin Rheumatol* 2015; 21: 305–310.

52. Virdi RP, Bashir A, Shahzad G, *et al*. Diffuse alveolar hemorrhage: a rare life-threatening condition in systemic lupus erythematosus. *Case Rep Pulmonol* 2012; 2012: 836017.

53. Iaccarino L, Bartoloni E, Carli L, *et al*. Efficacy and safety of off-label use of rituximab in refractory lupus: data from the Italian Multicentre Registry. *Clin Exp Rheumatol* 2015; 33: 449–456.

54. Hannah JR and D'Cruz DP. Pulmonary complications of systemic lupus erythematosus. *Semin Respir Crit Care Med* 2019; 40: 227–234.

55. Gatto M, Zen M, Iaccarino L, *et al*. New therapeutic strategies in systemic lupus erythematosus management. *Nat Rev Rheumatol* 2019; 15: 30–48.

56. Cheema GS and Quismorio FP Jr. Interstitial lung disease in systemic lupus erythematosus. *Curr Opin Pulm Med* 2000; 6: 424–429.

57. Wiedemann HP and Matthay RA. Pulmonary manifestations of systemic lupus erythematosus. *J Thorac Imaging* 1992; 7: 1–18.

58. Weinrib L, Sharma OP and Quismorio FP Jr. A long-term study of interstitial lung disease in systemic lupus erythematosus. *Semin Arthritis Rheum* 1990; 20: 48–56.

59. Yee CS, Hussein H, Skan J, *et al*. Association of damage with autoantibody profile, age, race, sex and disease duration in systemic lupus erythematosus. *Rheumatology* 2003; 42: 276–279.

60. Medlin JL, Hansen KE, McCoy SS, *et al*. Pulmonary manifestations in late versus early systemic lupus erythematosus: a systematic review and meta-analysis. *Semin Arthritis Rheum* 2018; 48: 198–204.

61. Pons-Estel GJ, Ugarte-Gil MF and Alarcón GS. Epidemiology of systemic lupus erythematosus. *Expert Rev Clin Immunol* 2017; 13: 799–814.

62. Tansey D, Wells AU, Colby TV, *et al*. Variations in histological patterns of interstitial pneumonia between connective tissue disorders and their relationship to prognosis. *Histopathology* 2004; 44: 585–596.

63. Takada H, Saito Y, Nomura A, *et al*. Bronchiolitis obliterans organizing pneumonia as an initial manifestation in systemic lupus erythematosus. *Pediatr Pulmonol* 2005; 40: 257–260.

64. Hedgpeth MT and Boulware DW. Interstitial pneumonitis in antinuclear antibody-negative systemic lupus erythematosus: a new clinical manifestation and possible association with anti-Ro (SS-A) antibodies. *Arthritis Rheum* 1988; 31: 545–548.

65. Bao Y, Zhang W, Shi D, *et al*. Correlation between serum tumor marker levels and connective tissue disease-related interstitial lung disease. *Int J Gen Med* 2021; 14: 2553–2560.

66. Flaherty KR, Wells AU, Cottin V, *et al*. Nintedanib in progressive fibrosing interstitial lung diseases. *N Engl J Med* 2019; 381: 1718–1727.

67. Wells AU, Flaherty KR, Brown KK, *et al*. Nintedanib in patients with progressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. *Lancet Respir Med* 2020; 8: 453–460.
68. Lim SW, Gillis D, Smith W, *et al*. Rituximab use in systemic lupus erythematosus pneumonitis and a review of current reports. *Intern Med J* 2006; 36: 260–262.
69. Okada M, Suzuki K, Matsumoto M, *et al*. Intermittent intravenous cyclophosphamide pulse therapy for the treatment of active interstitial lung disease associated with collagen vascular diseases. *Mod Rheumatol* 2007; 17: 131–136.
70. Swigris JJ, Olson AL, Fischer A, *et al*. Mycophenolate mofetil is safe, well tolerated, and preserves lung function in patients with connective tissue disease-related interstitial lung disease. *Chest* 2006; 130: 30–36.
71. Yusuf HR, Hooper WC, Grosse SD, *et al*. Risk of venous thromboembolism occurrence among adults with selected autoimmune diseases: a study among a U.S. cohort of commercial insurance enrollees. *Thromb Res* 2015; 135: 50–57.
72. Yusuf HR, Hooper WC, Beckman MG, *et al*. Risk of venous thromboembolism among hospitalizations of adults with selected autoimmune diseases. *J Thromb Thrombolysis* 2014; 38: 306–313.
73. Wahl DG, Guillemin E, de Maistre E, *et al*. Risk for venous thrombosis related to antiphospholipid antibodies in systemic lupus erythematosus—a meta-analysis. *Lupus* 1997; 6: 467–473.
74. Ghirardello A, Doria A, Ruffatti A, *et al*. Antiphospholipid antibodies (aPL) in systemic lupus erythematosus. Are they specific tools for the diagnosis of aPL syndrome? *Ann Rheum Dis* 1994; 53: 140–142.
75. Larosa M, Iaccarino L, Gatto M, *et al*. Advances in the diagnosis and classification of systemic lupus erythematosus. *Expert Rev Clin Immunol* 2016; 12: 1309–1320.
76. Zen M, Martinez ML, Benvenuti F, *et al*. Prevalence, outcome and management of patients with SLE and secondary antiphospholipid antibody syndrome after aPL seroconversion. *Rheumatology* 2021; 60: 1313–1320.
77. Johnson SR and Granton JT. Pulmonary hypertension in systemic sclerosis and systemic lupus erythematosus. *Eur Respir Rev* 2011; 20: 277–286.
78. Pope J. An update in pulmonary hypertension in systemic lupus erythematosus—do we need to know about it? *Lupus* 2008; 17: 274–277.
79. Montani D, Achouh L, Dorfmüller P, *et al*. Pulmonary veno-occlusive disease: clinical, functional, radiologic, and hemodynamic characteristics and outcome of 24 cases confirmed by histology. *Medicine* 2008; 87: 220–233.
80. Zanatta E, Polito P, Famoso G, *et al*. Pulmonary arterial hypertension in connective tissue disorders: pathophysiology and treatment. *Exp Biol Med* 2019; 244: 120–131.
81. Prabu A, Patel K, Yee CS, *et al*. Prevalence and risk factors for pulmonary arterial hypertension in patients with lupus. *Rheumatology* 2009; 48: 1506–1511.
82. Doria A, Iaccarino L, Sarzi-Puttini P, *et al*. Cardiac involvement in systemic lupus erythematosus. *Lupus* 2005; 14: 683–686.
83. Li EK and Tam LS. Pulmonary hypertension in systemic lupus erythematosus: clinical association and survival in 18 patients. *J Rheumatol* 1999; 26: 1923–1929.
84. Shen JY, Chen SL, Wu XY, *et al*. Pulmonary hypertension in systemic lupus erythematosus. *Rheumatol Int* 1999; 18: 147–151.
85. Guillevin L. Vasculopathy and pulmonary arterial hypertension. *Rheumatology* 2009; 48(Suppl. 3): iii54–iii57.
86. Yang GL, Guo J, Pudasaini B, *et al*. Value of heart rate recovery in female patients with pulmonary arterial hypertension due to systemic lupus erythematosus. *Clin Respir J* 2019; 13: 545–554.
87. Quismorio FP Jr, Sharma O, Koss M, *et al*. Immunopathologic and clinical studies in pulmonary hypertension associated with systemic lupus erythematosus. *Semin Arthritis Rheum* 1984; 13: 349–359.
88. Dhala A. Pulmonary arterial hypertension in systemic lupus erythematosus: current status and future direction. *Clin Dev Immunol* 2012; 2012: 854941.
89. Roncoroni AJ, Alvarez C and Molinas F. Plexogenic arteriopathy associated with pulmonary vasculitis in systemic lupus erythematosus. *Respiration* 1992; 59: 52–56.
90. Maron BA and Galiè N. Diagnosis, treatment, and clinical management of pulmonary arterial hypertension in the contemporary era: a review. *JAMA Cardiol* 2016; 1: 1056–1065.

91. Badesch DB, Hill NS, Burgess G, *et al*. Sildenafil for pulmonary arterial hypertension associated with connective tissue disease. *J Rheumatol* 2007; 34: 2417–2422.

92. Galiè N, Barberà JA, Frost AE, *et al*. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med* 2015; 373: 834–844.

93. Jais X, Launay D, Yaici A, *et al*. Immunosuppressive therapy in lupus- and mixed connective tissue disease-associated pulmonary arterial hypertension: a retrospective analysis of twenty-three cases. *Arthritis Rheum* 2008; 58: 521–531.

94. Gonzalez-Lopez L, Cardona-Muñoz EG, Celis A, *et al*. Therapy with intermittent pulse cyclophosphamide for pulmonary hypertension associated with systemic lupus erythematosus. *Lupus* 2004; 13: 105–112.

95. Hennigan S, Channick RN and Silverman GJ. Rituximab treatment of pulmonary arterial hypertension associated with systemic lupus erythematosus: a case report. *Lupus* 2008; 17: 754–756.

96. Bardoxolone methyl in patients with connective tissue disease-associated pulmonary arterial hypertension, 2016, https://clinicaltrials.gov/ct2/show/NCT02657356?term=connective+tissue+disease&cond=Pulmonary+Arterial+Hypertension&draw=2&rank=1

97. Smyth H, Flood R, Kane D, *et al*. Shrinking lung syndrome and systemic lupus erythematosus: a case series and literature review. *QJM* 2018; 111: 839–843.

98. Uslu S, Avşar AK, Erez Y, *et al*. Shrinking lung syndrome in primary Sjögren syndrome. *Balkan Med J* 2020; 37: 351–352.

99. Borrell H, Narváez J, Alegre JJ, *et al*. Shrinking lung syndrome in systemic lupus erythematosus: a case series and review of the literature. *Medicine* 2016; 95: e4626.

100. Munoz ML, Gelber AC and Houston BA. Into thin air: shrinking lung syndrome. *Am J Med* 2014; 127: 711–713.

101. Allen D, Fischer A, Bshouty Z, *et al*. Evaluating systemic lupus erythematosus patients for lung involvement. *Lupus* 2012; 21: 1316–1325.

102. Carmier D, Diot E and Diot P. Shrinking lung syndrome: recognition, pathophysiology and therapeutic strategy. *Expert Rev Respir Med* 2011; 5: 33–39.

103. Rubin LA and Urowitz MB. Shrinking lung syndrome in SLE—a clinical pathologic study. *J Rheumatol* 1983; 10: 973–976.

104. Hawkins P, Davison AG, Dasgupta B, *et al*. Diaphragm strength in acute systemic lupus erythematosus in a patient with paradoxical abdominal motion and reduced lung volumes. *Thorax* 2001; 56: 329–330.

105. Laroche CM, Mulvey DA, Hawkins PN, *et al*. Diaphragm strength in the shrinking lung syndrome of systemic lupus erythematosus. *Q J Med* 1989; 71: 429–439.

106. Hardy K, Herry I, Attali V, *et al*. Bilateral phrenic paralysis in a patient with systemic lupus erythematosus. *Chest* 2001; 119: 1274–1277.

107. Henderson LA, Loring SH, Gill RR, *et al*. Shrinking lung syndrome as a manifestation of pleuritis: a new model based on pulmonary physiological studies. *J Rheumatol* 2013; 40: 273–281.

108. Toya SP and Tzelepis GE. Association of the shrinking lung syndrome in systemic lupus erythematosus with pleurisy: a systematic review. *Semin Arthritis Rheum* 2009; 39: 30–37.

109. Karim MY, Miranda LC, Tench CM, *et al*. Presentation and prognosis of the shrinking lung syndrome in systemic lupus erythematosus. *Semin Arthritis Rheum* 2002; 31: 289–298.

110. Soubrier M, Dubost JJ, Piette JC, *et al*. Shrinking lung syndrome in systemic lupus erythematosus. A report of three cases. *Rev Rhum Engl Ed* 1995; 62: 395–398.

111. Benham H, Garske L, Vecchio P, *et al*. Successful treatment of shrinking lung syndrome with rituximab in a patient with systemic lupus erythematosus. *J Clin Rheumatol* 2010; 16: 68–70.

112. Peñacoba Toribio P, Córica Albani ME, Mayos Pérez M, *et al*. Rituximab in the treatment of shrinking lung syndrome in systemic lupus erythematosus. *Reumatol Clin* 2014; 10: 325–327.

113. Langenskiöld E, Bonetti A, Fitting JW, *et al*. Shrinking lung syndrome successfully treated with rituximab and cyclophosphamide. *Respiration* 2012; 84: 144–149.

114. Muñoz-Rodríguez FJ, Font J, Badia JR, *et al*. Shrinking lungs syndrome in systemic lupus erythematosus: improvement with inhaled beta-agonist therapy. *Lupus* 1997; 6: 412–414.

115. Navarro-Zarza JE, Alvarez-Hernández E, Casasola-Vargas JC, *et al*. Prevalence of community-acquired and nosocomial infections in hospitalized patients with systemic lupus erythematosus. *Lupus* 2010; 19: 43–48.

116. Zen M, Saccon F and Gatto M. Prevalence and predictors of flare after immunosuppressant

discontinuation in patients with systemic lupus erythematosus in remission. *Rheumatology* 2020; 59: 1591–1598.

117. Doria A, Iaccarino L, Ghirardello A, *et al.* Long-term prognosis and causes of death in systemic lupus erythematosus. *Am J Med* 2006; 119: 700–706.

118. Petri M and Genovese M. Incidence of and risk factors for hospitalizations in systemic lupus erythematosus: a prospective study of the Hopkins Lupus Cohort. *J Rheumatol* 1992; 19: 1559–1565.

119. Doria A, Canova M, Tonon M, *et al*. Infections as triggers and complications of systemic lupus erythematosus. *Autoimmun Rev* 2008; 8: 24–28.

120. Piliero P and Furie R. Functional asplenia in systemic lupus erythematosus. *Semin Arthritis Rheum* 1990; 20: 185–189.

121. Duffy KN, Duffy CM and Gladman DD. Infection and disease activity in systemic lupus erythematosus: a review of hospitalized patients. *J Rheumatol* 1991; 18: 1180–1184.

122. Ramos-Casals M, Cuadrado MJ, Alba P, *et al.* Acute viral infections in patients with systemic lupus erythematosus: description of 23 cases and review of the literature. *Medicine* 2008; 87: 311–318.

123. Weng CT, Liu MF, Weng MY, *et al.* Pneumocystis jirovecii pneumonia in systemic lupus erythematosus from southern Taiwan. *J Clin Rheumatol* 2013; 19: 252–258.

124. Furer V, Rondaan C, Heijstek MW, *et al.* 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis* 2020; 79: 39–52.

125. Tincani A, Andreoli L, Cavazzana I, *et al.* Novel aspects of Sjögren's syndrome in 2012. *BMC Med* 2013; 11: 93.

126. Baldini C, Pepe P, Quartuccio L, *et al.* Primary Sjögren's syndrome as a multi-organ disease: impact of the serological profile on the clinical presentation of the disease in a large cohort of Italian patients. *Rheumatology* 2014; 53: 839–844.

127. Manfrè V, Cafaro G, Riccucci I, *et al.* One year in review 2020: comorbidities, diagnosis and treatment of primary Sjögren's syndrome. *Clin Exp Rheumatol* 2020; 38(Suppl. 126): 10–22.

128. Jin Y, Zhang T, Ye W, *et al.* Clinical profile and associated factors of pulmonary involvement in primary Sjögren's syndrome. *Med Clin* 2019; 153: 305–311.

129. Manuel RC, Pilar BZ, Raphaèle S, *et al.* Characterization of systemic disease in primary Sjögren's syndrome: EULAR-SS Task Force recommendations for articular, cutaneous, pulmonary and renal involvements. *Rheumatology* 2015; 54: 2230–2238.

130. Strimlan CV, Rosenow EC, Divertie MB, *et al*. Pulmonary manifestations of Sjögren's syndrome. *Chest* 1976; 70: 354–361.

131. García-Carrasco M, Ramos-Casals M, Rosas J, *et al*. Primary Sjögren syndrome. *Medicine* 2002; 81: 270–280.

132. Natalini JG, Johr C and Kreider M. Pulmonary involvement in Sjögren syndrome. *Clin Chest Med* 2019; 40: 531–544.

133. Heus A, Arends S, Van Nimwegen JF, *et al.* Pulmonary involvement in primary Sjögren's syndrome, as measured by the ESSDAI. *Scand J Rheumatol* 2020; 49: 38–46.

134. Mandl T, Diaz S, Ekberg O, *et al*. Frequent development of chronic obstructive pulmonary disease in primary SS—results of a longitudinal follow-up. *Rheumatology* 2012; 51: 941–946.

135. Strevens Bolmgren V, Olsson P, Wollmer P, *et al*. Respiratory symptoms are poor predictors of concomitant chronic obstructive pulmonary disease in patients with primary Sjögren's syndrome. *Rheumatol Int* 2017; 37: 813–818.

136. Kampolis CF, Fragkioudaki S, Mavragani CP, *et al*. Prevalence and spectrum of symptomatic pulmonary involvement in primary Sjögren's syndrome. *Clin Exp Rheumatol* 2018; 36(Suppl. 112): 94–101.

137. Gudbjornsson B, Hedenstrom H, Stalenheim G, *et al*. Bronchial hyperresponsiveness to methacholine in patients with primary Sjogren's syndrome. *Ann Rheum Dis* 1991; 50: 36–40.

138. Shen TC, Chen HJ, Wei CC, *et al.* Risk of asthma in patients with primary Sjögren's syndrome: a retrospective cohort study. *BMC Pulm Med* 2016; 16: 152.

139. Gupta S, Ferrada MA and Hasni SA. Pulmonary manifestations of primary Sjögren's syndrome: underlying immunological mechanisms, clinical presentation, and management. *Front Immunol* 2019; 10: 1327.

140. Ito I, Nagai S, Kitaichi M, *et al*. Pulmonary manifestations of primary Sjogren's syndrome: a clinical, radiologic, and pathologic study. *Am J Respir Crit Care Med* 2005; 171: 632–638.

141. Borie R, Schneider S, Debray MP, *et al.* Severe chronic bronchiolitis as the presenting feature of

primary Sjögren's syndrome. *Respir Med* 2011; 105: 130–136.

142. Wight EC, Baqir M and Ryu JH. Constrictive bronchiolitis in patients with primary Sjögren syndrome. *J Clin Rheumatol* 2019; 25: 74–77.

143. Wells AU and Du Bois RM. Bronchiolitis in association with connective tissue disorders. *Clin Chest Med* 1993; 14: 655–666.

144. Ryu JH, Myers JL and Swensen SJ. Bronchiolar disorders. *Am J Respir Crit Care Med* 2003; 168: 1277–1292.

145. Lee AS, Scofield RH, Hammitt KM, *et al.* Consensus guidelines for evaluation and management of pulmonary disease in Sjögren's. *Chest* 2021; 159: 683–698.

146. Stojan G, Baer AN and Danoff SK. Pulmonary manifestations of Sjögren's syndrome. *Curr Allergy Asthma Rep* 2013; 13: 354–360.

147. Gottenberg JE, Cinquetti G, Larroche C, *et al.* Efficacy of rituximab in systemic manifestations of primary Sjögren's syndrome: results in 78 patients of the AutoImmune and Rituximab registry. *Ann Rheum Dis* 2013; 72: 1026–1031.

148. Aerni MR, Vassallo R, Myers JL, *et al.* Follicular bronchiolitis in surgical lung biopsies: clinical implications in 12 patients. *Respir Med* 2008; 102: 307–312.

149. Flament T, Bigot A, Chaigne B, *et al.* Pulmonary manifestations of Sjögren's syndrome. *Eur Respir Rev* 2016; 25: 110–123.

150. Gardiner P, Ward C, Allison A, *et al.* Pleuropulmonary abnormalities in primary Sjögren's syndrome. *J Rheumatol* 1993; 20: 831–837.

151. Lohrmann C, Uhl M, Warnatz K, *et al.* High-resolution CT imaging of the lung for patients with primary Sjogren's syndrome. *Eur J Radiol* 2004; 52: 137–143.

152. Soto-Cardenas MJ, Perez-De-Lis M, Bove A, *et al.* Bronchiectasis in primary Sjögren's syndrome: prevalence and clinical significance. *Clin Exp Rheumatol* 2010; 28: 647–653.

153. Silva M, Milanese G, Seletti V, *et al.* Pulmonary quantitative CT imaging in focal and diffuse disease: current research and clinical applications. *Br J Radiol* 2018; 91: 20170644.

154. Sambataro G, Ferro F, Orlandi M, *et al.* Clinical, morphological features and prognostic factors associated with interstitial lung disease in primary Sjögren's syndrome: a systematic review from the Italian Society of Rheumatology. *Autoimmun Rev* 2020; 19: 102447.

155. Roca F, Dominique S, Schmidt J, *et al.* Interstitial lung disease in primary Sjögren's syndrome. *Autoimmun Rev* 2017; 16: 48–54.

156. Luppi F, Sebastiani M, Silva M, *et al.* Interstitial lung disease in Sjögren's syndrome: a clinical review. *Clin Exp Rheumatol* 2020; 38(Suppl. 126): 291–300.

157. Wang Y, Hou Z, Qiu M, *et al.* Risk factors for primary Sjögren syndrome-associated interstitial lung disease. *J Thorac Dis* 2018; 10: 2108–2117.

158. Dong X, Zhou J, Guo X, *et al.* A retrospective analysis of distinguishing features of chest HRCT and clinical manifestation in primary Sjögren's syndrome-related interstitial lung disease in a Chinese population. *Clin Rheumatol* 2018; 37: 2981–2988.

159. Gao H, Zou YD, Zhang XW, *et al.* Interstitial lung disease in non-sicca onset primary Sjögren's syndrome: a large-scale case-control study. *Int J Rheum Dis* 2018; 21: 1423–1429.

160. Uffmann M, Kiener HP, Bankier AA, *et al.* Lung manifestation in asymptomatic patients with primary Sjögren syndrome: assessment with high resolution CT and pulmonary function tests. *J Thorac Imaging* 2001; 16: 282–289.

161. Ciancio N, Pavone M, Torrisi ES, *et al.* Contribution of pulmonary function tests (PFTs) to the diagnosis and follow up of connective tissue diseases. *Multidiscip Respir Med* 2019; 14: 17, https://mrmjournal.biomedcentral.com/articles/10.1186/s40248-019-0179-2

162. Parambil JG, Myers JL, Lindell RM, *et al.* Interstitial lung disease in primary Sjögren syndrome. *Chest* 2006; 130: 1489–1495.

163. Watanabe Y, Koyama S, Miwa C, *et al.* Pulmonary mucosa-associated lymphoid tissue (MALT) lymphoma in Sjögren's syndrome showing only the LIP pattern radiologically. *Intern Med* 2012; 51: 491–495.

164. Travis WD. Rare diseases bullet 13: non-neoplastic pulmonary lymphoid lesions. *Thorax* 2001; 56: 964–971.

165. Ramos-Casals M, Brito-Zerón P, Bombardieri S, *et al.* EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies. *Ann Rheum Dis* 2020; 79: 3–18.

166. Flaherty KR, Thwaite EL, Kazerooni EA, *et al.* Radiological versus histological diagnosis in UIP and NSIP: survival implications. *Thorax* 2003; 58: 143–148.

167. Matteson EL and Ike RW. Bronchiolitis obliterans organizing pneumonia and Sjögren's syndrome. *J Rheumatol* 1990; 17: 676–679.

168. Justet A, Ottaviani S, Dieudé P, *et al.* Tocilizumab for refractory organising pneumonia associated with Sjögren's disease. *BMJ Case Rep* 2015; 2015: bcr2014209076.

169. Cha SI, Fessler MB, Cool CD, *et al.* Lymphoid interstitial pneumonia: clinical features, associations and prognosis. *Eur Respir J* 2006; 28: 364–369.

170. De Vita S, Quartuccio L, Salvin S, *et al.* Sequential therapy with belimumab followed by rituximab in Sjögren's syndrome associated with B-cell lymphoproliferation and overexpression of BAFF: evidence for long-term efficacy. *Clin Exp Rheumatol* 2014; 32: 490–494.

171. Saadoun D, Ghembaza A, Riviere S, *et al.* Rituximab plus belimumab in non-infectious refractory cryoglobulinemia vasculitis: a pilot study. *J Autoimmun* 2021; 116: 102577.

172. Chevalier K, Belkhir R, Seror R, *et al.* Efficacity of a sequential treatment by anti-CD 20 monoclonal antibody and belimumab in type II cryoglobulinaemia associated with primary Sjögren syndrome refractory to rituximab alone. *Ann Rheum Dis* 2020; 79: 1257–1259.

173. Safety and efficacy study of subcutaneous belimumab and intravenous rituximab co-administration in subjects with primary Sjogren's syndrome, 2015, https://clinicaltrials.gov/ct2/show/NCT02631538

174. Gandolfo S and De Vita S. Double anti-B cell and anti-BAFF targeting for the treatment of primary Sjögren's syndrome. *Clin Exp Rheumatol* 2019; 37(Suppl. 118): 199–208.

175. Safety and efficacy of VAY736 in patients with primary Sjogren's syndrome (pSS), 2016, https://clinicaltrials.gov/ct2/show/NCT02962895

176. Mavragani CP and Moutsopoulos HM. Sjögren's syndrome: old and new therapeutic targets. *J Autoimmun* 2020; 110: 102364.

177. Safety, pharmacokinetics and preliminary efficacy study of CFZ533 in patients with primary Sjögren's syndrome, 2014, https://clinicaltrials.gov/ct2/show/NCT02291029

178. Mieliauskaite D, Dumalakiene I, Rugiene R, *et al.* Expression of IL-17, IL-23 and their receptors in minor salivary glands of patients with primary Sjögren's syndrome. *Clin Dev Immunol* 2012; 2012: 187258.

179. Brkic Z, Maria NI, van Helden-Meeuwsen CG, *et al.* Prevalence of interferon type I signature in CD14 monocytes of patients with Sjögren's syndrome and association with disease activity and BAFF gene expression. *Ann Rheum Dis* 2013; 72: 728–735.

180. Furie R, Khamashta M, Merrill JT, *et al.* Anifrolumab, an anti-interferon-α receptor monoclonal antibody, in moderate-to-severe systemic lupus erythematosus. *Arthritis Rheum* 2017; 69: 376–386.

181. Del Papa N, Minniti A, Lorini M, *et al.* The role of interferons in the pathogenesis of Sjögren's syndrome and future therapeutic perspectives. *Biomolecules* 2021; 11: 251.

182. Lee J, Lee J, Kwok SK, *et al.* JAK-1 inhibition suppresses interferon-induced BAFF production in human salivary gland: potential therapeutic strategy for primary Sjögren's syndrome. *Arthritis Rheum* 2018; 70: 2057–2066.

183. Barnes PJ. Kinases as novel therapeutic targets in asthma and chronic obstructive pulmonary disease. *Pharmacol Rev* 2016; 68: 788–815.

184. Milara J, Hernandez G, Ballester B, *et al.* The JAK2 pathway is activated in idiopathic pulmonary fibrosis. *Respir Res* 2018; 19: 24.

185. Chen MH, Chou HP, Lai CC, *et al.* Lung involvement in primary Sjögren's syndrome: correlation between high-resolution computed tomography score and mortality. *J Chin Med Assoc* 2014; 77: 75–82.

186. Enomoto Y, Takemura T, Hagiwara E, *et al.* Prognostic factors in interstitial lung disease associated with primary Sjögren's syndrome: a retrospective analysis of 33 pathologically–proven cases. *PLoS ONE* 2013; 8: e73774.

187. Kolb M, Bondue B, Pesci A, *et al.* Acute exacerbations of progressive-fibrosing interstitial lung diseases. *Eur Respir Rev* 2018; 27: 180071.

188. Spagnolo P, Distler O, Ryerson CJ, *et al.* Mechanisms of progressive fibrosis in connective tissue disease (CTD)-associated interstitial lung diseases (ILDs). *Ann Rheum Dis* 2021; 80: 143–150.

189. Leuschner G and Behr J. Acute exacerbation in interstitial lung disease. *Front Med* 2017; 4: 176.

190. Richeldi L, Cottin V, du Bois RM, *et al.* Nintedanib in patients with idiopathic pulmonary fibrosis: combined evidence from the TOMORROW and INPULSIS® trials. *Respir Med* 2016; 113: 74–79.

191. Kassan SS, Thomas TL, Moutsopoulos HM, *et al.* Increased risk of lymphoma in sicca syndrome. *Ann Intern Med* 1978; 89: 888–892.

192. Borie R, Wislez M, Thabut G, *et al*. Clinical characteristics and prognostic factors of pulmonary MALT lymphoma. *Eur Respir J* 2009; 34: 1408–1416.

193. Voulgarelis M, Dafni UG, Isenberg DA, *et al*. Malignant lymphoma in primary Sjögren's syndrome: a multicenter, retrospective, clinical study by the European Concerted Action on Sjögren's syndrome. *Arthritis Rheum* 1999; 42: 1765–1772.

194. De Vita S and Gandolfo S. Predicting lymphoma development in patients with Sjögren's syndrome. *Expert Rev Clin Immunol* 2019; 15: 929–938.

195. Yachoui R, Leon C, Sitwala K, *et al*. Pulmonary MALT lymphoma in patients with Sjögren's syndrome. *Clin Med Res* 2017; 15: 6–12.

196. Tzioufas AG and Voulgarelis M. Update on Sjögren's syndrome autoimmune epithelitis: from classification to increased neoplasias. *Best Pract Res Clin Rheumatol* 2007; 21: 989–1010.

197. Quartuccio L, Isola M, Corazza L, *et al*. Performance of the preliminary classification criteria for cryoglobulinaemic vasculitis and clinical manifestations in hepatitis C virus-unrelated cryoglobulinaemic vasculitis. *Clin Exp Rheumatol* 2012; 30(1, Suppl. 70): S48–S52.

198. Quartuccio L, Isola M, Baldini C, *et al*. Biomarkers of lymphoma in Sjögren's syndrome and evaluation of the lymphoma risk in prelymphomatous conditions: results of a multicenter study. *J Autoimmun* 2014; 51: 75–80.

199. Chen W, Cao H, Lin J, *et al*. Biomarkers for primary Sjögren's syndrome. *Genomics Proteomics Bioinformatics* 2015; 13: 219–223.

200. Gasparotto D, De Vita S, De Re V, *et al*. Extrasalivary lymphoma development in Sjögren's syndrome: clonal evolution from parotid gland lymphoproliferation and role of local triggering. *Arthritis Rheum* 2003; 48: 3181–3186.

201. Bae YA, Lee KS, Han J, *et al*. Marginal zone B-cell lymphoma of bronchus-associated lymphoid tissue. *Chest* 2008; 133: 433–440.

202. Papiris SA, Kalomenidis I, Malagari K, *et al*. Extranodal marginal zone B-cell lymphoma of the lung in Sjögren's syndrome patients: reappraisal of clinical, radiological, and pathology findings. *Respir Med* 2007; 101: 84–92.

203. Egashira R, Kondo T, Hirai T, *et al*. CT findings of thoracic manifestations of primary Sjögren syndrome: radiologic-pathologic correlation. *Radiographics* 2013; 33: 1933–1949.

204. Graham BB, Mathisen DJ, Mark EJ, *et al*. Primary pulmonary lymphoma. *Ann Thorac Surg* 2005; 80: 1248–1253.

205. Gribben JG. How I treat indolent lymphoma. *Blood* 2007; 109: 4617–4626.

206. Brito-Zerón P, Baldini C, Bootsma H, *et al*. Sjögren syndrome. *Nat Rev Dis Primers* 2016; 72: 16047.

207. De Vita S, Boiocchi M, Sorrentino D, *et al*. Characterization of prelymphomatous stages of B cell lymphoproliferation in Sjögren's syndrome. *Arthritis Rheum* 1997; 40: 318–331.

208. Chung A, Wilgus ML, Fishbein G, *et al*. Pulmonary and Bronchiolar Involvement in Sjogren's syndrome. *Semin Respir Crit Care Med* 2019; 40: 235–254.

209. Song MK, Seol YM, Park YE, *et al*. Pulmonary nodular lymphoid hyperplasia associated with Sjögren's syndrome. *Korean J Intern Med* 2007; 22: 192–196.

210. Hansen LA, Prakash UBS and Colby TV. Pulmonary lymphoma in Sjögren's syndrome. *Mayo Clin Proc* 1989; 64: 920–931.

211. Milani P, Basset M, Russo F, *et al*. The lung in amyloidosis. *Eur Respir Rev* 2017; 26: 170046.

212. Rajagopala S, Singh N, Gupta K, *et al*. Pulmonary amyloidosis in Sjogren's syndrome: a case report and systematic review of the literature. *Respirology* 2010; 15: 860–866.

213. Bonner H Jr, Ennis RS, Geelhoed GW, *et al*. Lymphoid infiltration and amyloidosis of lung in Sjögren's syndrome. *Arch Pathol* 1973; 95: 42–44.

214. Srinivas P, Liam CK and Jayaram G. Localised nodular pulmonary amyloidosis in a patient with sicca syndrome. *Med J Malaysia* 2000; 55: 385–387.

215. Desai SR, Nicholson AG, Stewart S, *et al*. Benign pulmonary lymphocytic infiltration and amyloidosis: computed tomographic and pathologic features in three cases. *J Thorac Imaging* 1997; 12: 215–220.

216. Subcutaneous masses and adenopathy in a 77-year-old man with Sjögren's syndrome and amyloidosis. *Am J Med* 1989; 86: 585–590, https://www.semanticscholar.org/paper/Subcutaneous-masses-and-adenopathy-in-a-77-year-old/c43c8b74e0355e9d886a95c86af9572abec1ccd6#citing-papers

217. Hosono T, Bando M, Suzuki E, *et al*. Sjögren's syndrome with multiple bullae due to pulmonary nodular amyloidosis. *Nihon Kokyuki Gakkai Zasshi* 2007; 45: 869–873.

218. Niepolski L, Grzegorzewska AE and Szymaś J. Nodular pulmonary amyloidosis and Sjögren's syndrome in a patient treated with intermittent hemodialysis. *Hemodial Int* 2007; 11: 406–410.

219. Lantuejoul S, Moulai N, Quetant S, *et al.* Unusual cystic presentation of pulmonary nodular amyloidosis associated with MALT-type lymphoma. *Eur Respir J* 2007; 30: 589–592.

220. Wu CW and Chien YC. Sjögren's syndrome with nodular pulmonary amyloidosis. *Respirol Case Rep* 2020; 9: e00699.

221. Jeong YJ, Lee KS, Chung MP, *et al.* Amyloidosis and lymphoproliferative disease in Sjögren syndrome: thin-section computed tomography findings and histopathologic comparisons. *J Comput Assist Tomogr* 2004; 28: 776–781.

222. Nakamura N, Yamada G, Itoh T, *et al.* Pulmonary MALT lymphoma with amyloid production in a patient with primary Sjögren's syndrome. *Intern Med* 2002; 41: 309–311.

223. Srivali N, Ungprasert P, Cheungpasitporn W, *et al.* Lung cavities in Sjögren's syndrome. *QJM* 2016; 109: 135–136.

224. Watanabe M, Naniwa T, Hara M, *et al.* Pulmonary manifestations in Sjögren's syndrome: correlation analysis between chest computed tomographic findings and clinical subsets with poor prognosis in 80 patients. *J Rheumatol* 2010; 37: 365–373.

225. Lechtman S, Debray MP, Crestani B, *et al.* Cystic lung disease in Sjögren's syndrome: an observational study. *Joint Bone Spine* 2017; 84: 317–321.

226. Gal I, Kovacs J and Zeher M. Case series: coexistence of Sjögren's syndrome and sarcoidosis. *J Rheumatol* 2000; 27: 2507–2510.

227. Ramos-Casals M, Brito-Zerón P, García-Carrasco M, *et al.* Sarcoidosis or Sjögren syndrome? *Medicine* 2004; 83: 85–95.

228. Santiago T, Santiago M, Rovisco J, *et al.* Coexisting primary Sjögren's syndrome and sarcoidosis: coincidence, mutually exclusive conditions or syndrome? *Rheumatol Int* 2014; 34: 1619–1622.

229. Zabotti A, Zandonella Callegher S, Lorenzon M, *et al.* Ultrasound-guided core needle biopsy compared with open biopsy: a new diagnostic approach to salivary gland enlargement in Sjögren's syndrome? *Rheumatology* 2021; 60: 1282–1290.

230. Aviña-Zubieta JA, Jansz M, Sayre EC, *et al.* The risk of deep venous thrombosis and pulmonary embolism in primary Sjögren syndrome: a general population-based study. *J Rheumatol* 2017; 44: 1184–1189.

231. Quartuccio L. Risk of thrombosis in Sjögren syndrome: the open question of endothelial function immune-mediated dysregulation. *J Rheumatol* 2017; 44: 1106–1108.

232. Pasoto SG, Chakkour HP, Natalino RR, *et al.* Lupus anticoagulant: a marker for stroke and venous thrombosis in primary Sjögren's syndrome. *Clin Rheumatol* 2012; 31: 1331–1338.

233. Launay D, Hachulla E, Hatron PY, *et al.* Pulmonary arterial hypertension: a rare complication of primary Sjögren syndrome: report of 9 new cases and review of the literature. *Medicine* 2007; 86: 299–315.

234. Naniwa T and Takeda Y. Long-term remission of pulmonary veno-occlusive disease associated with primary Sjögren's syndrome following immunosuppressive therapy. *Mod Rheumatol* 2011; 21: 637–640.

235. Vassiliou VA, Moyssakis I, Boki KA, *et al.* Is the heart affected in primary Sjögren's syndrome? An echocardiographic study. *Clin Exp Rheumatol* 2008; 26: 109–112.

236. Kobak S, Kalkan S, Kirilmaz B, *et al.* Pulmonary arterial hypertension in patients with primary Sjögren's syndrome. *Autoimmune Dis* 2014; 2014: 710401.

237. Galiè N, Humbert M, Vachiery JL, *et al.* ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J* 2016; 37: 67–119.

238. Wang J, Li M, Wang Q, *et al.* Pulmonary arterial hypertension associated with primary Sjögren's syndrome: a multicentre cohort study from China. *Eur Respir J* 2020; 56: 1902157.

239. Yan S, Li M, Wang H, *et al.* Characteristics and risk factors of pulmonary arterial hypertension in patients with primary Sjögren's syndrome. *Int J Rheum Dis* 2018; 21: 1068–1075.

240. Zhao J, Wang Q, Liu Y, *et al.* Clinical characteristics and survival of pulmonary arterial hypertension associated with three major connective tissue diseases: a cohort study in China. *Int J Cardiol* 2017; 236: 432–437.

241. Nakagawa N, Osanai S, Ide H, *et al.* Severe pulmonary hypertension associated with primary Sjögren's syndrome. *Intern Med* 2003; 42: 1248–1252.

242. Liu Z, Yang X, Tian Z, *et al.* The prognosis of pulmonary arterial hypertension associated with

primary Sjögren's syndrome: a cohort study. *Lupus* 2018; 27: 1072–1080.

243. Hwang JA, Yang TH, Lee JY, *et al.* Severe pulmonary hypertension in primary Sjögren's syndrome. *Korean Circ J* 2013; 43: 504–507.

244. Makimoto G, Asano M, Fujimoto N, *et al.* Bilateral pleural effusions as an initial presentation in primary Sjögren's syndrome. *Case Rep Rheumatol* 2012; 2012: 640353.

245. Teshigawara K, Kakizaki S, Horiya M, *et al.* Primary Sjogren's syndrome complicated by bilateral pleural effusion. *Respirology* 2008; 13: 155–158.

246. Blanco Pérez JJ, Pérez González A, Guerra Vales JL, *et al.* Shrinking lung in primary Sjogrën syndrome successfully treated with rituximab. *Arch Bronconeumol* 2015; 51: 475–476.

247. Martínez-Granados R, Delgado-García G, Wah-Suárez M, *et al.* Primary Sjögren's syndrome first presenting as hypokalemic quadriparesis. *Arch Rheumatol* 2017; 32: 257–259.

248. Sorajja P, Poirier MK, Bundrick JB, *et al.* Autonomic failure and proximal skeletal myopathy in a patient with primary Sjögren syndrome. *Mayo Clin Proc* 1999; 74: 695–697.

249. Koga T, Kouhisa Y, Nakamura H, *et al.* A case of primary Sjögren's syndrome complicated with inflammatory myopathy and interstitial lung disease. *Rheumatol Int* 2012; 32: 3647–3649.