



Review

Pulmonary Manifestations of Collagen Diseases[☆]

Luis Gómez Carrera,* Gema Bonilla Hernan

Servicio de Neumología, IdiPAZ, Hospital Universitario La Paz, Madrid, Spain

ARTICLE INFO

Article history:

Received 2 March 2012

Accepted 20 November 2012

Available online 2 May 2013

Keywords:

Collagen diseases

Diffuse interstitial pulmonary disease

Rheumatoid arthritis

Scleroderma

Systemic erythematous lupus

Inflammatory myopathies

Mixed connective tissue disease

Undifferentiated connective tissue disease

ABSTRACT

Collagen diseases are a large group of systemic inflammatory diseases of autoimmune etiology. The etiopathogenesis of collagen diseases is multifactorial. There is genetic susceptibility, as many connective tissue disorders show family history, and environmental factors may trigger the disease. Collagen diseases can affect almost all the organs of the body. The respiratory system is one of the most frequently affected, although the prevalence of pulmonary disease is not precisely known for the different collagen disorders. Any structure of the respiratory tract can be affected, but perhaps the most frequent is pulmonary parenchymal disease in the form of pneumonitis, which can be produced in any of the idiopathic interstitial pneumonitis patterns. The pleura, pulmonary vessels, airways and respiratory muscles may also be affected. The frequency of lung disease associated with collagen diseases is on the rise. This is in due part to the better diagnostic methods that are available to us today (such as high-resolution computed tomography) and also to the appearance of new forms of pneumonitis associated with the new treatments that are currently used. The objective of this article is to offer a global vision of how collagen diseases can affect the lungs according to the latest scientific evidence.

© 2012 SEPAR. Published by Elsevier España, S.L. All rights reserved.

Manifestaciones pulmonares de las enfermedades del colágeno

RESUMEN

Las enfermedades del colágeno constituyen un gran grupo de enfermedades inflamatorias sistémicas de etiología autoinmune. La etiopatogenia de las enfermedades del colágeno es multifactorial. Existe una susceptibilidad genética, y muchos trastornos del tejido conectivo muestran una agregación familiar, sobre la que actúan factores ambientales que desencadenan la enfermedad. En las enfermedades del colágeno se pueden afectar casi todos los órganos del cuerpo. El sistema respiratorio es uno de los más frecuentemente afectados, aunque no se conoce con exactitud la prevalencia de enfermedad pulmonar en las diferentes enfermedades del colágeno. Cualquier estructura del aparato respiratorio puede estar afectada. Quizá lo más frecuente sea la enfermedad del parénquima pulmonar en forma de neumonitis, que puede manifestarse como cualquiera de los patrones de neumonitis intersticiales idiopáticas. Pero también pueden afectarse la pleura, los vasos pulmonares, la vía aérea y la musculatura respiratoria. La frecuencia de enfermedad pulmonar asociada a las enfermedades del colágeno está aumentando, por una parte gracias a los mejores métodos de diagnóstico de que disponemos hoy en día, como la tomografía computarizada de alta resolución, y también por la aparición de nuevas formas de neumonitis asociadas a los nuevos tratamientos empleados en la actualidad. El objetivo de este artículo es ofrecer una visión en conjunto de cómo las enfermedades del colágeno pueden afectar el pulmón, de acuerdo con las nuevas evidencias científicas.

© 2012 SEPAR. Publicado por Elsevier España, S.L. Todos los derechos reservados.

Palabras clave:

Enfermedades del colágeno

Enfermedad pulmonar intersticial difusa

Artritis reumatoide

Esclerodermia

Lupus eritematoso sistémico

Miopatías inflamatorias

Enfermedad mixta del tejido conectivo

Enfermedad indiferenciada del tejido conectivo

[☆] Gómez Carrera L, Bonilla Hernan G. Manifestaciones pulmonares de las enfermedades del colágeno. Arch Bronconeumol. 2013;49:249–60.

* Corresponding author.

E-mail address: lgomezcarrera@gmail.com (L. Gómez Carrera).

Introduction

Collagen diseases are a heterogeneous group of systemic inflammatory diseases of autoimmune origin that affect a wide range of organs and systems. The respiratory tract is one of those that are most often affected. Any of the structures of the respiratory system can be affected: lung parenchyma, pleura, pulmonary vessels, respiratory muscles and bone structures. The frequency and way in which the respiratory system is affected depend on each type of collagen disease.^{1–3} As well as being affected by the disease itself, it should also be taken into account that the treatments used can also cause lung disease due to toxicity.^{4–6} The most common lung condition in every case is pneumonitis,⁷ which appears in all the histopathological patterns of idiopathic interstitial pneumonitis.⁸ Moreover, connective tissue diseases (in themselves and especially due to the immunosuppression produced by the drugs used in their treatment) have an increased prevalence of infections, among them respiratory system infections, mainly with the new biological treatments used today. These have also been related with the development of pneumonitis,^{6,9} in some cases with fatal consequences. In any event, the onset of pulmonary complications increases morbidity and mortality in patients with connective tissue diseases.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune disease of unknown cause and chronic evolution that mainly affects the joints, causing chronic symmetric erosive synovitis. Its estimated prevalence in Spain is 0.5%.¹⁰ It may have other extra-articular manifestations, such as subcutaneous nodules, vasculitis, pericarditis, neuropathies, episcleritis and pleuropulmonary involvement. The two most common extra-articular manifestations in RA are pulmonary involvement and cutaneous vasculitis. Eighteen percent (18%) of the mortality in RA is due to pulmonary causes, and approximately 5% of patients with RA present clinical manifestations of pulmonary involvement. RA can affect the lung in different ways: interstitial lung disease (ILD), pleuritis, pleural effusion, rheumatoid nodules associated or not with pneumoconiosis (Caplan's syndrome), airway obstruction, vasculitis, pulmonary hypertension (PH), and involvement of the chest wall and respiratory muscles.^{1,11} Pulmonary involvement has been related to smoking and with some clinical features of patients, such as male gender, severe erosive joint disease, positive rheumatoid factor (RF) and the presence of other clinical manifestations, such as subcutaneous rheumatoid nodules.

Parenchymal Involvement

Interstitial Lung Disease

ILD is the most common pulmonary manifestation in RA. The presenting form of ILD in RA is similar to that seen in idiopathic interstitial pneumonias (IIP), and the histological patterns of interstitial disease that we can find in RA are the same as those in IIP. These include usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), cryptogenic organizing pneumonia (COP), desquamative interstitial pneumonia (DIP), respiratory bronchiolitis-associated ILD (RB-ILD), acute interstitial pneumonia (AIP) and lymphoid interstitial pneumonia (LIP) (Table 1).^{8,12} Most lung diseases associated with RA occur in the first 5 years after onset of the disease. At the time of RA onset, pulmonary complications can appear in 10%–20% of cases, and the presence of pulmonary fibrosis has been demonstrated in 14% of patients with a history of RA of less than 2 years. The prevalence of ILD varies depending on the

Table 1
Idiopathic Interstitial Pneumonias.

Usual interstitial pneumonia (UIP)
Nonspecific interstitial pneumonia (NSIP)
Organizing pneumonia (OP)
Desquamative interstitial pneumonia (DIP)
Respiratory bronchiolitis-associated interstitial lung disease (RB-ILD)
Acute interstitial pneumonia (AIP)
Lymphoid interstitial pneumonia (LIP)

criteria used to establish the diagnosis. The presence of clinically significant ILD has been described in approximately 7% of patients,⁷ while studies carried out in autopsies show an ILD prevalence of 35%.¹³ In studies in which chest high resolution computed tomography (HRCT) scanning was used to screen for ILD in RA patients, a prevalence of almost 20% was observed.¹⁴ In others where pulmonary function tests (PFT) were carried out, restrictive changes were observed in up to 40% of patients. In the Spanish RA registry, ILD has a prevalence of 3.7% when only chest X-ray is considered, and increases to 80% if the histological findings of lung biopsies are taken into account.¹⁵ In a study conducted in 2008 in RA patients without respiratory symptoms, in which HRCT scanning was performed, ILD was found in 21 of the 64 patients studied (33%).¹⁶

It has been observed that ILD, like other extra-articular manifestations, is more common in men than in women. The relationship of smoking with the development of ILD is not clear at present; some have viewed smoking as potential risk factor for the development of ILD, while others have associated it independently with the development of ILD.^{15,16} The presence of anti-citrulline antibodies (anti-CCP) or IgA and/or IgM rheumatoid factor (RF) increases the risk of developing extra-articular manifestations, and high RF titers have been associated with the presence of ILD and with a reduction in the carbon monoxide diffusing capacity (DLCO).¹⁷ The relationship between anti-CCP and lung disease is unknown. Other factors that have been associated with the onset of ILD in patients with RA are advanced age at diagnosis, disease activity and severity markers, appearance of rheumatoid nodules and more severe functional classification.¹⁸ The mean survival of patients with ILD and RA is less than 40% at 5 years. Bongartz et al.¹⁸ found a mean survival of 2.6 years after the diagnosis of ILD in their series.

The clinical manifestations are non-specific and the most common symptom is dyspnea on exertion, followed by non-productive cough. Chest pain is rare. Fever is a very uncommon symptom. The physical examination may be normal in the initial stages of lung involvement. Dry "Velcro" crackles subsequently appear on the pulmonary auscultation, and acropachy can be observed in advanced stages.

The diagnosis of ILD in RA is based on the combination of symptomatology suggestive of lung disease, consistent PFTs and typical radiological findings; in some cases a histological study may be necessary. Fibrobronchoscopy and bronchoalveolar lavage (BAL) may be useful for making the differential diagnosis with other interstitial diseases, and for discarding lung infections or drug-induced diseases.

PFTs are essential in the evaluation of pulmonary involvement in RA. They may be altered even in asymptomatic patients. The first parameter altered is the DLCO, as this is the most sensitive test; it may be reduced in 40% of patients, even with a normal plain chest X-ray, and in 82% of patients with abnormal HRCT scans, even if they are asymptomatic.¹³ DLCO correlates well with the degree of disease extension on the HRCT scan and also has prognostic value: a DLCO <54% of the expected value can predict disease progression.¹⁹ A restrictive pattern is later observed, with a reduction in the total lung capacity (TLC) and forced vital capacity (FVC),

and an increase in the alveolar-arterial oxygen gradient. In some cases, a mixed pattern can be observed with obstructive changes, especially in smokers. In advanced stages of the disease, desaturation can be observed with physical exercise, and even hypoxemia at rest.

In many cases, the chest X-ray is normal. It is not a very sensitive technique for diagnosing early stage interstitial lung disease.¹⁴ Reticulonodular patterns, basal opacities, ground glass, a honeycomb pattern and, in advanced stages, signs of PH can be observed.

HTCT scanning is much more sensitive for detecting the abnormalities that occur in the lung, even in asymptomatic patients. The findings are very varied, but the most common are: reticular images, ground glass pattern, bronchial wall thickening, bronchial dilatation, consolidation, micronodules and a honeycomb pattern.²

Depending on the type of lung involvement, the radiological findings differ, adopting different patterns. Some of these are characteristic of certain histological patterns, and enable diagnostic and therapeutic decisions to be taken without having to perform a lung biopsy.³

In the UIP HRCT pattern, the most common findings are reticulation and a honeycomb pattern, predominantly in bases and peripheral zones, accompanied by traction bronchiectasis and small areas of ground glass opacities. In the NSIP HRCT pattern, ground glass opacities predominate and reticulation predominates in peripheral and basal areas; traction bronchiectasis and a little honeycombing can also appear. The bronchiolitis pattern is characterized by centrilobular or peribronchial nodules and bronchial dilatation may coexist with bronchiectasis. In the COP pattern, airspace consolidation can be observed with ground glass opacities, and there may be centrilobular nodules.²⁰

BAL does not have a specific value in diagnosis. Its main interest lies in excluding other diseases such as opportunistic infections, drug reactions and neoplasms.³ In RA, the cellularity of BAL is increased, and in general an increase can be observed in neutrophils and occasionally eosinophils. In early stages, in sub-clinical phases, there may be a predominance of lymphocytes, which is associated with a better prognosis and response to treatment.^{21,22}

Any of the defined IIP histological patterns can be found in RA^{8,12} (Table 1). The histological pattern most often seen in RA-associated ILD is UIP,^{23,24} unlike in other collagen diseases, in which the NSIP pattern is more common; this is the second most frequently observed pattern in RA; in third place is COP. Other patterns can also be found, but with much lower prevalence: respiratory bronchiolitis (RB-ILD), DIP, LIP and diffuse alveolar damage (DAD).

Drug-Induced Interstitial Lung Disease

The drugs used in the treatment of RA can have diverse side effects. They can also affect the lung and cause interstitial disease. Methotrexate (MTX) is the drug that is most commonly associated with lung disease in RA. MTX-pneumonitis is an idiosyncratic rather than dose-dependent reaction. Its onset has no relation with the cumulative dose, and it can even occur weeks after treatment ends. The presence of previous interstitial disease, advanced age, and abnormal PFTs are risk factors for the development of MTX-pneumonitis. However, in some studies, low-dose MTX treatments have not been observed to cause deterioration of ILD.²⁵ Its diagnosis is difficult, as the symptoms are non-specific and can be confused with infection. Several criteria have been proposed for its diagnosis.^{26,27} Moreover, since a previous lung disease can be a risk factor for its development, algorithms have also been designed to minimize the risk of its use.²⁷ In a patient with ILD

who develops increasing dyspnea during MTX treatment, and in whom a reduction in DLCO is detected with respect to the previous measurement, or ground glass opacities appear, MTX should be discontinued.^{4,28}

The anti-TNF-alphas (infliximab, etanercept and adalimumab) have demonstrated their effectiveness in the treatment of RA. In most cases, their side effects are related with their immunosuppressive effect, which manifests with infections, among which tuberculosis merits a special mention. TNF-alpha is a cytokine involved in the early immune response of a wide variety of inflammatory mediators, and is a critical mediator in the pathogenesis of pulmonary fibrosis.²⁹ Isolated cases of improvement in symptoms, stabilization of lung function and radiological images have been reported with these drugs.^{29,30} However, cases of ILD onset^{31,32} and major clinical exacerbation have also been reported after commencing each of these drugs.^{33–35} ILDs related with anti-TNF treatment are more aggressive and have higher mortality compared with ILD in patients who receive MTX alone, and most cases occur shortly after receiving treatment. In prescription guidelines for anti-TNF treatment, caution is advised when exposing RA patients with pulmonary fibrosis and close monitoring of lung function is recommended.³⁶

Leflunomide has been used as an alternative to MTX in patients with underlying lung disease. However, in 2001, at the British Society of Rheumatology meeting, the first adverse effects of leflunomide on the lung in patients with RA were reported.³⁷ In Japan, an incidence of 0.5% of ILD in patients treated with leflunomide has been described.³⁸ Until now, a few cases of ILD associated with tocilizumab have been identified: one case in the series of Smolen et al.³⁹ and one isolated case described by Kawashiri et al.⁴⁰ Several cases of ILD associated with rituximab treatment have also been noted in patients with lymphoma³⁹ and some cases of organizing pneumonia have been reported in patients diagnosed with RA after commencing rituximab treatment.^{41,42}

Pulmonary complications could be responsible for 10%–20% of the mortality in patients with RA. The survival of patients with ILD is lower than that expected in patients with RA without ILD. In general, the evolution and prognosis of patients with ILD associated with collagen disease are better than those of patients with idiopathic pulmonary fibrosis (IPF).^{43,44} The prognosis for ILD associated with RA is better than for IPF.⁴⁵ However, the survival of patients with RA who have an ILD with a UIP pattern is the same as that of IPF.⁴³ In general, the mean 5-year survival of patients with ILD and RA is less than 40%. Various clinical factors have been described that may predict lower survival: progressive dyspnea measured on standardized scales; reduction in lung size on the chest X-ray; degree of extension of the disease on the HRCT scan; decrease in FVC and decrease in the gas transfer capacity.⁴⁶

ILD has traditionally been treated with corticoids, combined or not with other immunosuppressants, without taking the underlying histopathology into consideration. ILD with a UIP pattern has a poor response to corticoids, while OP usually has a very favorable evolution,²⁰ so it seems logical to base treatment on the underlying interstitial pneumonia pattern.

In general, aggressive treatment is justified in patients in whom there is evidence of inflammation on the HRCT scan, lymphocytosis in the BAL and who do not have a UIP pattern, especially if they are young patients with progressive deterioration in lung function. Other treatments that should be considered are pulmonary rehabilitation and oxygen therapy if there is respiratory failure. When the disease is very advanced, lung transplantation must be considered.

Pulmonary Rheumatoid Nodules

These appear in fewer than 1% of chest X-rays in patients with RA. Up to 22% of cases can be detected on the chest HRCT scan; this prevalence increases in autopsies of patients with RA.⁴⁷

They are more common in chronic patients, but in some cases may be the first manifestation of RA. They are generally asymptomatic and rarely cause coughing or hemoptysis. They are more common in patients with subcutaneous nodules, smokers and high RF.⁴⁸ They are round, well-defined opacities and can be single or multiple, unilateral or bilateral. Their size is also variable, from millimeters to several centimeters, and they are most often found in the upper lobes in a subpleural position. Histologically they have the same characteristics as subcutaneous rheumatoid nodules, with a central area of fibrinoid necrosis enveloped by a layer of histiocytes with a typical palisade arrangement, surrounded peripherally by granulation tissue and chronic inflammation. In 50% of cases, they cavitate. Differential diagnosis must be made with primary pulmonary neoplasia if it is a single nodule, or with metastases if there are multiple nodules, and with granulomas, mycosis, pulmonary vasculitis and histiocytosis X. The clinical evolution is variable, and they can increase in number or size, cavitate, decrease or remain stable. The prognosis is good, and very rarely becomes complicated resulting in pneumothorax, pyopneumothorax or bronchopleural fistula. The only definitive diagnosis is the histological study.

Caplan's Syndrome

This was first described in 1953 by Caplan in coal miners with pneumoconiosis and RA.⁴⁹ It is characterized by the onset, in patients with RA, of rounded nodular images in both lung fields, with predominantly peripheral location and which may cavitate, together with typical pneumoconiosis abnormalities. The pathogenesis of the nodules in Caplan's syndrome is not well known, and it is believed that the inorganic material could be the trigger for immunological phenomena that favor (in the context of RA) the formation of nodules.⁵⁰

Pleural Involvement

Its prevalence has been estimated at 5%, but up to 20% of patients may have related symptoms at some time during the course of their disease.⁵¹ Pleural effusion may appear at any time during its course, and may even precede the diagnosis of RA. It can present as an incidental finding on chest X-ray, and in some cases it is detected due to the presence of pleuritic-type pain, fever and dyspnea on exertion. Occasionally, the pleural involvement coincides with exacerbation of the joint symptomatology, and may coincide with the onset of another pulmonary pathology, such as the presence of rheumatoid nodules or the development of ILD. The effusion is generally unilateral and most often affects the right side, but in 25% of cases it may be bilateral. The pleural fluid varies between a serofibrous exudate and a turbid liquid. It is usually an exudate, and occasionally may be pseudo-chylous due to the accumulation of cholesterol, especially in chronic effusions. Sanguineous fluid requires other etiology of the effusion to be ruled out. It generally has low or normal glucose, low pH and proteins and high lactate dehydrogenase (LDH).⁵² RF in the pleural fluid is often positive. In the acute forms, there is predominance of polymorphonuclear leukocytes, and in the chronic, lymphocytes. The presence of multinucleated cells and histiocytes is more specific to RA, as they are cells that come from sub-pleural rheumatoid nodules. In cases where the pleural fluid study is not sufficient to make the etiological diagnosis, a pleural biopsy should be performed in order to discard tuberculosis or neoplasm. The clinical course is highly variable: it may disappear in 4 weeks to 3 months, but can occasionally last for

years. It usually does not require specific treatment. Non-specific anti-inflammatory drugs (NSAID) are used in the case of pain, and if it does not respond, treatment with oral corticoids may be prescribed.

Vascular Involvement

Pulmonary vasculitis in RA as a primary abnormality is uncommon, and is usually associated with lung parenchyma pathology. Diffuse alveolar hemorrhage in RA may be secondary to small vessel vasculitis and not due to the existence of systemic vasculitis. The diagnosis is based on the presence of iron-laden macrophages in the BAL, which usually suggests subclinical pulmonary hemorrhage.

Airways Involvement

Bronchiectases

A quite significant prevalence of bronchiectasis has been observed in patients with RA, but is very variable depending on the series consulted (0%–30%).⁵³ CT scanning is the most sensitive test for its diagnosis. The colonization of these bronchiectases by different microorganisms is the cause of repeated respiratory infections, which is very important to take into account in these patients who receive immunosuppressive treatment for their underlying disease.

Obliterating Bronchiolitis

This is a very rare but very serious complication. It is characterized by acute or sub-acute obstruction of the small airways, causing dry cough and rapidly progressive dyspnea. It produces an obstructive pattern that is refractory to bronchodilator treatment, secondary to obstruction of the bronchioles due to inflammation and fibrosis of the bronchial walls. The chest X-ray may be normal or show signs of air trapping. Bronchial wall thickening, areas of centrilobular emphysema and bronchiectases can be observed on the HRCT scan. There is constrictive bronchiolitis with lymphocytic infiltrate in the lung biopsy. It is a very severe clinical condition with a very poor response to treatment and a high mortality rate.

Systemic Sclerosis

Systemic sclerosis is a generalized connective tissue disorder characterized clinically by skin thickening and fibrosis and internal organ involvement. Pulmonary involvement is the second most common manifestation. The prevalence of pulmonary involvement varies between 25% and 90% of patients with sclerosis. Sixty percent (60%) of patients have respiratory symptoms throughout the course of their disease, and there are findings of involvement in 80% of autopsies of patients with scleroderma. The two most common forms of pulmonary involvement are ILD and PH, which are the two leading causes of death. Occurring with less frequency are bronchiectases (which can appear in up to 68% of patients if HRCT is used as a diagnostic method⁵⁴), pleural effusion (<10%), spontaneous pneumothorax, drug-associated pneumonitis and lung cancer.

Parenchymal Involvement

Interstitial Lung Disease

ILD appears more often in patients with diffuse systemic sclerosis than in those who have limited systemic sclerosis. The prevalence of ILD depends on the population selected for the studies and the definition of ILD applied, but can be observed in up to 74% of patients. It is associated mainly with the presence of severe

Raynaud's phenomenon, digital ulcers and tendon involvement. ILD can be the first clinical manifestation of systemic sclerosis.⁵⁵ African-American ethnicity, degree of skin involvement, hypothyroidism, cardiac involvement, creatine phosphokinase (CPK) and creatinine levels have been associated with the development of early pulmonary involvement.⁵⁶

The presence of certain antibodies is related with an increased likelihood of developing ILD. However, their sensitivity and predictive values are low. A large proportion of patients with systemic sclerosis have positive anti-nuclear antibodies (ANA), and anti-topoisomerase I antibodies are found in up to 40% of patients with lung involvement. On the other hand, it has been observed that the presence of anti-centromere antibodies could be a protective factor against the development of ILD. The presence of anti-topoisomerase type I antibodies is associated with lower baseline FVC levels ($P < .001$) and accelerated decline in FVC.⁵⁷ In another study, a prevalence of ILD of 79% was observed in patients with antibodies against U11/U12 ribonucleoprotein (RNP).⁵⁸ In recent years, major studies have been conducted in order to find biomarkers that are capable of predicting the development of pulmonary fibrosis, and which correlate with its clinical course and clinical response to different therapeutic agents.^{59,60} Krebs von den Lungen 6 antigen (KL-6) and pulmonary surfactants A and D (PS-A and -D) have been related with the onset of ILD.^{61,62} In a cohort of Japanese patients, elevated PS-A and -D levels were found in patients with ILD, and it was observed that the PS-D isoform was more sensitive for the diagnosis and identification of pulmonary fibrosis than the A isoform.⁶³ A correlation was also observed between the PS-D, FVC and DLCO levels.⁶⁰ Another study found that patients with systemic sclerosis had higher levels of both proteins than healthy individuals, and that patients with alveolitis had higher levels than those who did not.⁶⁴ These results were later confirmed, and it was observed that the KL-6 and SP-D levels correlated positively with the degree of fibrosis in the CT scan, with KL-6 more strongly correlated.⁶⁵ Another marker, CC chemokine ligand (CCL) 18 has also been observed to be higher in systemic sclerosis than in systemic lupus erythematosus (SLE) and healthy individuals, and its increase in systemic sclerosis is associated with pulmonary fibrosis and decreased DLCO and FVC. It was observed that the levels were lower in patients with inactive ILD than in those with active fibrosis.⁶⁶ A glycoprotein, YKL-40, may be a marker for evaluating pulmonary involvement in patients with systemic sclerosis,⁶⁷ although it is not specific, since it is also elevated in other conditions, such as hepatic fibrosis and numerous malignant tumors.

Clinical onset is insidious and the manifestations appear at a late stage, perhaps due to the relative physical inactivity of patients with systemic sclerosis, so screening with non-invasive tests is recommended when there is clinical suspicion of systemic sclerosis. At disease onset, chest X-rays, PFTs, DLCO and even the 6-min walk test and HRCT scans should be performed. The most typical symptoms are dry cough, limited exercise tolerance and progressive dyspnea, although there is not usually a good clinical correlation between the dyspnea and radiological findings. There is a good correlation between the symptoms, DLCO and histological findings. Cough is rare, and occasionally there may be hemoptysis secondary to the presence of bronchial telangiectases. Bibasilar "Velcro"-like crackles at the end of inspiration, and in some cases cyanosis, acropachy and signs of right heart failure, can be observed on the physical examination.

Chest X-ray is of little use for early diagnosis; HRCT scanning is the most sensitive imaging test at this stage. In established ILD, a bilateral reticular pattern which is generally more pronounced in the bases can be observed, thin-walled cysts in bases known as honeycomb lung. HRCT scanning enables the type of lung lesions and their degree of extension to be determined, and

detects involvement in up to 44% of patients with a normal chest X-ray. It has been seen that 85% of patients who present a normal HRCT scan at diagnosis do not develop ILD after 5 years of follow-up.⁶⁸ For this reason, it is proposed that a CT scan be performed at diagnosis, and if there is no involvement, repeat after 2 and 5 years.⁶⁹ In systemic sclerosis, we can find images with NSIP, UIP, DAD and COP patterns. Seventy-six percent (76%) of cases are NSIP, while UIP is only found in 11% of cases.⁷⁰ At present, it is accepted that lung biopsy is not necessary in patients with scleroderma-associated ILD, except in cases in which there is a discrepancy between the clinical manifestations and the findings on the HRCT scan.¹⁹ It is considered that there is limited disease if there is involvement $< 20\%$ on the HRCT scan and extensive disease if it is $> 20\%$.⁷¹

In all patients with systemic sclerosis, even in the absence of symptoms, PFTs should be carried out as screening. Most often there is evidence of a restrictive disorder with a reduction in the FVC below 80% and/or a decline in the DLCO below 75. The decrease in DLCO is the most sensitive static parameter and the first to be affected. It has been observed that up to 50% of patients with ILD may have abnormal PFTs at disease onset, even when asymptomatic, although only 16% have a reduction in FVC below 55%.⁷² An isolated reduction in the diffusion capacity confers an unfavorable prognosis for some authors.⁷³ A DLCO $< 40\%$ is correlated with a 5-year survival of 5%, while with a DLCO $> 40\%$, the 5-year survival is greater than 75%. The 6-min walk test may be altered in patients with systemic sclerosis, even in some cases with other normal PFTs and HRCT scans. However, this test has several limitations in these patients: measuring the saturation presents difficulties due to the presence of severe Raynaud's phenomenon, and musculoskeletal abnormalities in these patients mean that the results are not always a reflection of the pulmonary involvement.⁷⁴

There are different opinions on the usefulness and clinical significance of BAL in patients diagnosed with scleroderma. BAL is not specific, but may reveal the presence of inflammatory alveolitis with neutrophils above 3% and the presence of more than 2% of eosinophils. The presence of alveolitis in the BAL is correlated with the severity, and has been related with a progressive deterioration in lung function.⁷⁵

ILD associated with connective tissue disease has a better prognosis than idiopathic ILD.⁷⁶ Black and Asian ethnicity, males, cardiac involvement and early onset of the disease are associated with more severe interstitial involvement.⁷⁷ The prognosis worsens with FVC and DLCO less than 70%, extensive involvement on the HRCT scan and rapid deterioration, defined as a 10% reduction in the FVC and 15% reduction in DLCO in 1 year. Monitoring every 6 months with PFTs is recommended, or earlier if there is clinical deterioration in the absence of a valid cause.

On one hand, basic support treatment is required which includes oxygen therapy in cases where there is respiratory failure, rehabilitating treatment and treatment of gastro-esophageal reflux, since it is one of the factors that has been related with ILD, both idiopathic and associated with connective tissue disease. On the other hand, pharmacological treatment aimed directly at ILD includes treatment with corticosteroids and immunosuppressants. The use of corticoids is recommended in cases with NSIP-type radiological pulmonary involvement, although the increased risk that these patients have for presenting renal crises in connection with the administration of high glucocorticoid doses should be remembered, so the use of doses of under 15 mg/day is recommended. In the recommendations established by the European League Against Rheumatism (EULAR), cyclophosphamide is recommended for the treatment of lung involvement.⁷⁸ Cyclophosphamide treatment has been shown to improve PFTs, CT findings

and quality of life measured using the Health Assessment (HAQ) and Short Form 36 Health Survey (SF36) questionnaires.^{79–82} The improvement may be more pronounced in patients with greater pulmonary involvement, with FVC <70%.⁸² It has been observed that some of the side effects of oral cyclophosphamide treatment may be reduced with the use of intravenous cyclophosphamide.⁸² Some results have been published on the use of mycophenolate in patients with scleroderma, in whom an improvement in FVC was shown after 12 months of treatment.^{82,83} Rituximab has demonstrated an improvement in interstitial disease in some isolated cases. Recently the 1-year results of a randomized study conducted with 14 patients with scleroderma were published, and it was observed that the group who received treatment showed an improvement in FVC and DLCO.⁸⁴ Lung transplant is an option in patients with scleroderma and ILD whose involvement progresses despite having received cyclophosphamide treatment.

Vascular Involvement

Pulmonary Hypertension

Systemic sclerosis is the connective tissue disease that is most often associated with PH, and is one of the most common causes of morbidity and mortality. It is the most common manifestation of pulmonary vascular disease in systemic sclerosis, and its prevalence varies depending on the series consulted, from 7% to 50%. It can appear alone or associated with ILD. It is more common in women, and the older the patient is at the time of diagnosis. Approximately one third of patients are asymptomatic; the most common symptom is dyspnea on exertion, which is usually late onset and progressive. Another symptom, although less common, is syncope during exercise. The clinical presentation, diagnostic procedure and treatments used do not differ from those used in idiopathic PH.⁸⁵ Its onset causes a decrease in the survival rate from 88% to 40% 2 years after diagnosis. An annual echocardiogram is therefore recommended in all patients diagnosed with scleroderma. It has been observed that N-terminal pro-brain natriuretic peptide (NT-proBNP) and active BNP levels in these patients have high sensitivity and specificity for its diagnosis, and that decrease in the DLCO of below 60% is a predictive factor for developing PH.⁸⁶

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease that causes generalized inflammation with very variable clinical expression, as it can affect any organ. Its incidence varies between 3 and 8 cases per 100 000 persons, depending on the origin of the population. It is more common in women, with a female/male ratio of 9/1, and its mean age of onset is 30 years.

Its etiology is unknown, and there is a genetic component with polygenic participation upon which other factors act, both endogenous (hormones) and exogenous (chemical substances, drugs, ultraviolet radiation, infections).

Respiratory tract manifestations are common in SLE, and include involvement of the pleura, lung parenchyma, airways and pulmonary vasculature (Table 2).

Pleural Involvement

Pleural involvement is the most common respiratory manifestation of SLE. Pleuritic pain occurs in 40%–50% of patients during the course of their disease,⁸⁷ even with no abnormalities on the chest X-ray.^{88,89} In 5%–10% of patients, it may be the first clinical manifestation.⁹⁰ In some autopsy series, pleural involvement has been found in 93% of patients with SLE.⁸⁹

Table 2
Pulmonary Manifestations of Systemic Lupus Erythematosus.

Pleural involvement	Pleuritis Pleural effusion
Parenchymal involvement	Acute pneumonitis Chronic pneumonitis
Vascular involvement	Acute reversible hypoxemia Pulmonary thromboembolism Alveolar hemorrhage
Respiratory muscle involvement	Shrinking lung syndrome
Airways involvement	Cancer Limited air flow

Pleural effusion usually presents with dyspnea, pleuritic pain, cough and fever. It is generally small or moderate, and predominantly bilateral. It may be recurrent. It has characteristics of exudate, with normal or slightly low glucose levels, generally higher than in RA. The LDH is increased and complement is decreased. ANA, anti-DNA and lupus erythematosus (LE) cells can be found in the pleural fluid.

Differential diagnosis should be made with pleural effusion caused by infection, heart failure, pulmonary embolism and neoplasms. Pleural fluid analysis is generally diagnostic and pleural biopsy rarely needs to be performed; it will be indicated in cases of clinically suspected tuberculosis or neoplasm.

The pleuritic pain usually subsides with NSAID. The effusion usually responds to moderate doses of corticoids, although the use of high doses may occasionally be necessary. If an adequate response is not achieved with corticoids, anti-malarials or other immunosuppressants such as azathioprine and cyclophosphamide can be added. On rare occasions, drainage of the effusion and even pleurodesis in the case of recurring effusions may be necessary.⁹⁰

Parenchymal Involvement

Acute Pneumonitis

This is an uncommon manifestation in SLE, and occurs in 1%–5% of these patients.⁹¹ In some cases it may be the presenting form of SLE.⁹² It is characterized clinically by fever, dyspnea, cough and occasionally hemoptysis. Bilateral infiltrates can be found on the chest X-ray, predominantly in the bases. Ground-glass infiltrates and areas of reticular thickening with a honeycomb pattern can be seen on the HRCT scan. Histopathological examination of the lesion is not specific, and shows alveolar wall damage with necrosis, edema and alveolar hemorrhage and formation of hyaline membranes; capillaritis can also appear. Granular deposits of immunoglobulin G and complement can be found in the alveolar septa.⁸⁹

The frequency of this complication is higher in patients with anti-SSA antibodies.⁹³ The prognosis is poor, with mortality close to 50%. It has a worse prognosis if there are predominantly neutrophils or eosinophils in the BAL, and if it appears in the post-partum period. In survivors, it may progress to chronic interstitial pneumonitis with severe restrictive ventilatory impairment.

It is essential to make the differential diagnosis with infections, so it is usually necessary to perform a BAL to look for potential pathogens. Empirical antibiotic treatment should be administered until infection has been discarded. The treatment of acute pneumonitis is based on corticoids at high doses of 1–2 mg/kg/day and, in very critically ill patients, pulses of 1 mg/day for 3 days. If there is a lack of response, other immunosuppressants such as cyclophosphamide, intravenous immunoglobulins and plasmapheresis can be added.⁸⁹

Chronic Interstitial Pneumonitis

This is a rare complication in SLE, with a prevalence of around 3%–9%.⁹⁴ It may exist in sub-clinical form in one third of patients, in whom abnormalities can be observed on the HRCT scan, despite being asymptomatic.⁹⁵

The symptomatology is similar to idiopathic pneumonitis, with progressive dyspnea on exertion, dry cough and onset of dry “Velcro” crackles in the auscultation, predominantly in the bases. The radiological findings do not differ from those produced by idiopathic pneumonitis either. Ground glass infiltrates, a reticular pattern and honeycombing may also appear. The radiological findings are related and are predictive of the histopathological pattern. The ground glass infiltrates are related with the NSIP pattern, and the honeycombing with UIP. The histological patterns found in lung disease secondary to SLE are similar to those in idiopathic pneumonitis; the most common is the NSIP pattern, followed by the UIP pattern; LIP and COP patterns have also been observed.⁹⁶

Treatment should be individualized, as in general this pneumonitis is less aggressive than idiopathic pneumonitis. Infection should be ruled out by BAL or lung biopsy. Treatment is based on high-dose corticoids, and it is sometimes necessary to add another immunosuppressant, such as cyclophosphamide, azathioprine or mycophenolate.⁹⁷

COP is characterized histologically by the formation of fibrous tissue in the bronchioles and alveolar ducts. It causes dry cough, dyspnea, chest pain, fever and respiratory failure. Peripheral patchy alveolar infiltrates (which may be bilateral) can be found on the radiological studies, with thickening of the bronchi. It can be diagnosed with transbronchial biopsy or, occasionally, with a lung biopsy. It usually progresses favorably when treated with corticoids, although it is sometimes necessary to add another immunosuppressant.

Diffuse Alveolar Hemorrhage

This is a rare, although potentially fatal, complication of SLE. Its prevalence varies between less than 2% and 5.4% of patients with SLE, and it may be the first manifestation of this disease.⁹⁸ The symptoms usually develop in hours or a few days, with fever, cough, dyspnea and hemoptysis. It usually occurs in patients with active SLE. Radiologically, bilateral alveolar infiltrates can be observed; magnetic resonance imaging may be useful for demonstrating the presence of blood.⁹⁰ The DLCO is usually elevated, which differentiates it from acute pneumonitis. BAL is useful for discarding infection and enables the diagnosis to be confirmed, as macroscopically it shows a hemorrhagic fluid and microscopically, abundant hemosiderin-laden macrophages.

It is important to make a differential diagnosis with infection, pulmonary embolism and vasculitis, and to discard coagulopathies. The definitive diagnosis is lung biopsy, in which two patterns can be found: capillaritis with immune complex deposits or hemorrhage.⁹⁰

Treatment is based on the use of high-dose corticoids together with cyclophosphamide. Plasmapheresis is also useful. Rituximab could also be useful, but further studies are required.⁹⁹

Vascular Involvement

Pulmonary Hypertension

This is not a common complication of SLE. Its prevalence varies between 3% and 4% in SLE patients, according to the series.^{100,101} It is not related with either the duration or severity of the lupus, and may be a presenting form of SLE. It has a worse prognosis and poorer survival than primary PH.¹⁰²

The diagnostic test is Doppler ultrasound, which enables the pulmonary arterial pressure to be estimated and helps to discard other causes of PH. The diagnosis should be confirmed with right cardiac catheterization, which will show pulmonary artery pressure >25 mmHg and capillary wedge pressure <15 mmHg, with decreased cardiac output.

Treatment is similar to PH, although calcium channel antagonists have not proven as effective. They include anti-coagulants, calcium antagonists, endothelin receptor antagonists (bosentan, ambrisentan), sildenafil and prostacyclins.^{103,104} Treatment with immunosuppressants such as cyclophosphamide may bring some additional benefit.¹⁰⁴

Acute Reversible Hypoxemia

This refers to an episode of respiratory failure without clear evidence of pulmonary disease in patients hospitalized for SLE. Its pathogenesis is unclear, although it is postulated that it is due to leukoagglutination and activation of complement in the pulmonary capillaries. It usually responds favorably to treatment with corticoids alone or in combination with aspirin.¹⁰⁵

Muscle Involvement

Shrinking Lung Syndrome

This consists of the onset of dyspnea, weakness of the respiratory muscles and a decrease in the lung volumes on the chest X-ray, with elevation of the diaphragm and a restrictive pattern in the functional tests in the absence of parenchymal involvement that justifies it. The prevalence is around 0.9% of patients with SLE.⁹⁹

Clinically, patients report dyspnea on exertion, which sometimes remains even at rest and worsens when supine. Cough is rare. In the auscultation, there may be diminished breath sounds at the bases, and sometimes crackles. Radiologically, it manifests with elevation of the diaphragm and laminar atelectasis at the bases. A restrictive pattern will be observed in the PFTs.

It has a good prognosis and an acceptable response to treatment, which consists of corticoids, to which bronchodilators and theophylline can be added.

Airways Involvement

Involvement of the upper airways occurs in 0.3%–3% of patients with SLE, in the form of inflammation of the laryngeal mucosa, cricoarytenoiditis and vocal cord paralysis.^{89,99} It generally has a good response to corticoid treatment.

Symptomatic involvement of the lower airways is also rare in SLE. Bronchiectasis and bronchial wall thickening can be found in 20% of lupus, but are usually silent. The appearance of obliterating bronchiolitis has also been described in some cases in which cyclophosphamide treatment may be beneficial.¹⁰⁶

Sjögren's Syndrome

Sjögren's syndrome (SS) is a slowly progressive autoimmune inflammatory disease characterized by lymphocytic infiltration of the exocrine glands that diminishes glandular function and causes mucosal dryness. It may be primary, if it is not associated with other collagen diseases, or secondary, if it is associated with other connective tissue diseases. Its prevalence is 0.5%–1.0%, and increases to 10%–30% in patients with other collagen diseases.^{107–109} Prevalence of pulmonary disease varying between 9% and 75% have been described in SS patients, depending on the criteria and methods used for diagnosis.^{110,111} In Spain, a prevalence of 11% of

Table 3
Pulmonary Manifestations in Sjögren's Syndrome.

<i>Diffuse interstitial lung disease</i>
Nonspecific interstitial pneumonia
Lymphoid interstitial pneumonia
Usual interstitial pneumonia
Organizing pneumonia
<i>Airway disease</i>
Dry rhinitis
Xerostomia
Xerotrachea
Bronchitis/lymphocytic bronchiolitis
Bronchiectases
Follicular bronchiolitis
<i>Lymphoma</i>
<i>Pseudolymphoma</i>
<i>Amyloidosis</i>
<i>Pleural involvement</i>
Pleural effusion
Pleural thickening
<i>Vascular disease</i>
Vasculitis
Pulmonary hypertension

pulmonary disease has been described in patients with primary SS.¹¹²

It can affect the respiratory system in various ways (Table 3). Pleuropulmonary disease is more common in the secondary form and ILD in primary SS.¹¹³ Parenchyma and airways involvement can coexist in the same patient.¹¹⁴

Diffuse Pulmonary Disease

ILD is the most common form of pulmonary involvement in SS; although clinically significant, it only occurs in a minority of patients. However, PFTs can be affected in up to 20%.⁹¹

Within the interstitial pneumonias, NSIP is the form that is most often associated with SS.^{115,116} It manifests clinically with dyspnea and dry cough. It causes a restrictive ventilatory pattern and diminished DLCO. A reticular pattern, traction bronchiectases and ground glass pattern can be observed on the HRCT scan.

Lymphocytic interstitial pneumonia is a benign lymphoproliferative disease. Although it has been classically associated with SS, it can appear in other conditions such as HIV infection, common variable immunodeficiency syndrome and other autoimmune diseases. Its prevalence in SS is 0.9%.¹¹⁰ Histologically it is characterized by a polyclonal infiltrate of mature lymphocytes, plasma cells and histiocytes, both in the interstitium and in the alveoli. It is sometimes associated with follicular bronchiolitis. Although some patients are asymptomatic, it can cause dyspnea and dry cough, while other symptoms such as fever, weight loss and sweating are rare. Ground glass infiltrates, thin-walled cysts, different sized nodules, centrilobular nodules and septal thickening can be found on the HRCT scan. PFTs are characterized by a restrictive pattern with reduced CO transfer capacity. Definitive diagnosis is by lung biopsy. Treatment is based on corticoids and other immunosuppressants. Some cases have been described that progress favorably with rituximab.^{116,117}

UIP is not common in patients with SS, and its clinical, radiological and histological manifestations do not differ from idiopathic UIP.¹¹⁵ Only a few cases of OP have been described in patients with SS.^{118,119}

Airway Disease

The upper airway is often affected in SS, and a sensation of dryness of the nasal mucosa, mouth (xeristomy) trachea (xerotrachea), and even the large bronchi (xerobronchitis) are common.¹²⁰

The lower airway is also often affected in SS, and usually manifests with cough and dyspnea. Up to 46% of patients with SS may have a positive bronchial hyper-reactivity test.¹²¹ Small airway involvement and air trapping can be observed in the PFTs.¹¹⁰ Signs of air trapping can also be observed in the HRCT scan which correlate with the PFT results. Histologically, lymphocyte infiltration and peribronchiolar fibrosis occur. In some cases, bronchiectases may also appear, especially in the lower lobes; it occurs more often in older patients and patients with anti-smooth muscle antibodies (anti-SMA), which usually predisposes them to more respiratory infections and pneumonias.¹²²

Lymphoproliferative Diseases

Follicular Bronchiolitis

This is a type of lymphoproliferative disease that usually coexists with LIP and lymphocytic bronchitis. Histologically, it is characterized by nodules of lymphocytic infiltrates with germinal center hyperplasia around the bronchioles. It responds well to corticoid treatment.^{107,108}

Lymphomatoid Granulomatosis

This is a rare disease, in which there is angiodescriptive, granulomatous and lymphoreticular proliferation. It can affect the lungs, skin and central nervous system.

Lymphoma

The prevalence of primary pulmonary lymphoma in patients with SS is estimated to be between 1% and 2%.¹¹² They are generally B-cell MALT lymphomas. Its radiological presentation is very varied, and it can appear as masses, single or multiple nodules that may be cavitated and diffuse infiltrates. It is sometimes indistinguishable radiologically from other types of benign diseases. Diagnosis should be made with lung biopsy.

Pleural Disease

Pleura effusion is rare in primary SS, and in general appears associated with RA. In primary SS, when it appears, the effusion is usually bilateral, with biochemical characteristics of exudates, with normal pH and glucose levels and predominantly lymphocytes in the cell count.

Idiopathic Inflammatory Myopathies

Idiopathic inflammatory myopathies are a heterogeneous group of diseases of autoimmune origin that cause muscle weakness due to inflammation of the skeletal muscles. Lung complications are the most common cause of morbidity and mortality in these patients.¹²³ They appear in more than 40% of patients.¹²⁴ The most common are aspiration pneumonia, hypoventilation and diffuse ILD.

Pneumonias

Infectious complications are common in these patients. Up to 50% have dysphagia, and aspiration pneumonia can appear in

17% of cases. Opportunistic infections are also common; *Pneumocystis jiroveci* and *Candida albicans* are the most common microorganisms.^{125,126}

Hypoventilation

Ventilatory failure due to weakness of the respiratory muscles is a rare process in patients with polymyositis, and occurs in less than 5%.¹²³ However, it is more common in dermatomyositis. It occurs as a result of a restrictive defect due to a decrease in the lung volumes, with a reduction in the total lung capacity (TLC) and decrease in the maximal inspiratory (MIP) and expiratory pressures (MEP). The values that can predict this ventilatory failure are MIP and MEP <30% of their theoretical value and FVC <55%.¹²³

Diffuse Interstitial Disease

This is a frequent complication in these patients, with a prevalence that varies between 5% and 65% in different series, depending on the diagnostic method.¹²⁷ One study demonstrated an incidence of 65% by abnormalities in the CT scan or PFTs, in patients recently diagnosed with polymyositis or dermatomyositis.¹²⁸

Interstitial disease adopts three patterns of evolution in these patients^{91,127}: (i) one form with acute onset of symptoms, which can lead rapidly to severe respiratory failure. It usually corresponds histologically with DAD, and extensive consolidation and a ground glass pattern appear on the radiology; (ii) one form with chronic progression, with a more insidious course, which is the most common and in general correlates with a NSIP histological pattern and is characterized radiologically by a reticular pattern with ground glass opacities, without honeycombing; and (iii) a minor form, with no symptoms but with radiological or functional abnormalities.

There is evidence that certain autoantibody profiles are related with particular clinical development subgroups. Thus, aminoacyl-tRNA-synthetase antibodies (antisyntetase Ab) are a predictive factor for development of interstitial disease.¹²⁹ The most common is antihistidyl-tRNA-synthetase (anti-Jo-1 Ab), which is found in 20% of patients with myositis.¹³⁰ Carriers of these antibodies develop a disease called anti-synthetase syndrome, which is characterized by ILD, arthritis, myositis, Raynaud's phenomenon and "mechanic's hands".¹³¹ Furthermore, these antibodies can appear in patients with ILD with no myopathy symptoms, and it has been postulated that they should be investigated in all patients with interstitial disease.¹³² Most have histology compatible with NSIP and in general progress favorably with treatment, although some may have a rapidly progressive course, especially those with a NSIP pattern.¹³³

Treatment of these patients is based on corticoids, although they generally require a combination of other immunosuppressants¹³⁴ such as cyclosporine and azathioprine. Cyclophosphamide has been used in cases of disease refractory to other treatments.¹³⁴ Tacrolimus and mycophenolate have also been beneficial in some cases, although further studies are required to find the optimal treatment for these patients.¹³⁵

Mixed Connective Tissue Disease/Undifferentiated Connective Tissue Disease

Mixed connective tissue disease is a systemic inflammatory disorder in which patients have a combination of clinical findings of SS, SLE, systemic sclerosis and inflammatory myopathy, and frequently have high titers of anti-RNP antibodies.

They may have the pulmonary manifestations of these diseases. The incidence of pulmonary disease is unknown; although it can reach 67%, it is generally asymptomatic.⁹¹ ILD can often appear with a NSIP pattern, pleural effusion and even PH.

Some patients have symptoms suggestive of collagen disease but do not meet criteria for any defined disease and are classified as undifferentiated connective tissue disease. The interstitial disease associated with this condition characteristically meets NSIP criteria. Furthermore, NSIP may be the initial manifestation of an undifferentiated connective tissue disease.^{136,137}

Biological Treatments and Interstitial Lung Disease

New biological drugs used in the treatment of autoimmune diseases have meant a major advance in the treatment of these conditions. However, various cases of onset of ILD or exacerbation (even severe) of a pre-existing disease have been described with the use of anti-TNF (infliximab, etanercept, adalimumab) as well as anti-CD20 (rituximab) and anti-IL (tocilizumab) agents.⁶ Abatacept could be a safe drug in these patients, although further studies are still required that enable this to be confirmed.¹³⁸

Conflict of Interests

The authors declare that they have no conflict of interests.

References

1. Tureson C, Jacobsson L, Crowson CS, Gabriel SE, Matteson EL. Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factor over 46 year. *Ann Rheum Dis.* 2003;62:722–7.
2. Lynch DA. Lung disease related to collagen vascular disease. *J Thorac Imaging.* 2009;24:299–309.
3. Grutters JC, Wells AU, Wuyts W, Schenk P, Leroy S, Dawson JK, et al. Evaluation and treatment of interstitial lung involvement in connective tissue diseases: a clinical up date. *Eur Respir Mon.* 2006;34:27–49.
4. Saravanan V, Kelly C. Drug-related pulmonary problems in patients with rheumatoid arthritis. *Rheumatology.* 2006;45:787–9 [editorial].
5. Searles G, Mckendry RJ. Methotrexate pneumonitis in rheumatoid arthritis: potential risk factors. Four case report and review of the literature. *J Rheumatol.* 1987;14:1164–71.
6. Panopoulos ST, Sfikakis PP. Biological treatment and connective tissue disease associated interstitial lung disease. *Curr Opin Pulm Med.* 2011;17:362–7.
7. Tureson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Extra-articular disease manifestation in rheumatoid arthritis: incident trends and risk factors over 46 years. *Ann Rheum Dis.* 2003;62:722–7.
8. Ancochea J, Gómez J, Vilar J, Xaubet A. Consenso para el diagnóstico de las neumonías intersticiales idiopáticas. *Arch Bronconeumol.* 2010;46 Suppl. 5:1–21.
9. Meyer KC, Decker C, Baughman R. Toxicity and monitoring of immunosuppressive therapy used in systemic autoimmune diseases. *Clin Chest Med.* 2010;556–88.
10. Carmona L, Villaverde V, Hernández-García C, Ballina J, Gabriel R, Laffon A, et al. The prevalence of rheumatoid arthritis in the general population of Spain. *Rheumatology (Oxford).* 2002;41:88–95.
11. Nannini C, Ryu JH, Matteson EL. Lung disease in rheumatoid arthritis. *Curr Opin Rheumatol.* 2008;20:340–6.
12. American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med.* 2002;165:277–304.
13. Suzuki A, Ohosone Y, Obama M, Mita S, Matsuoka Y, Irimajiri S, et al. Cause of death in rheumatoid arthritis: a population-based study. *Arthritis Rheum.* 2005;52:722–32.
14. Dawson JK, Fewins HE, Lynch MP, Graham DR. Fibrosing alveolitis in patients with rheumatoid arthritis as assessed by high resolution computed tomography, chest radiography and pulmonary function test. *Thorax.* 2001;56:622–7.
15. Carmona L, González-Alvaro I, Balsa A, Belmonte M, Tena X, Sanmarti R. Rheumatoid arthritis in Spain: occurrence of extra-articular manifestation and estimates of disease severity. *Ann Rheum Dis.* 2003;62:897–900.
16. Gochoico BR, Avila NL, Chow CK, Novero LJ, Wu HP, Ren P, et al. Progressive preclinical interstitial lung disease in rheumatoid arthritis. *Arch Intern Med.* 2008;168:159–66.

17. Luukkainen R, Saltyshev M, Pakkasela R, Nordqvist E, Huhtala H, Hakla M. Relationship of rheumatoid factor to lung diffusion capacity in smoking and non-smoking patients with rheumatoid arthritis. *Scand J Rheumatol.* 1995;24:119-20.
18. Bongartz T, Nannini C, Medina-Velasquez YF, Achenbach SJ, Crowson CS, Ryu JH, et al. Incidence and mortality of interstitial lung disease in rheumatoid arthritis. *Arthritis Rheum.* 2010;62:1583-91.
19. Dawson JK, Fewins HE, Desmond J, Lynch MP, Graham DR. Predictors of progression of HRCT diagnosed fibrosing alveolitis in patients with rheumatoid arthritis. *Ann Rheum Dis.* 2002;61:517-21.
20. Tanaka N, Kim JS, Newell JD, Brown KK, Cool CD, Meehan R, et al. Rheumatoid arthritis-related lung disease: CT findings. *Radiology.* 2004;232:81-91.
21. Gilligan DM, O'Connor CM, Ward K, Bresnihan B, FitzGerald MX. Bronchoalveolar lavage in patients with mild and severe rheumatoid lung disease. *Thorax.* 1990;45:592-6.
22. Kolarz G, Scherak O, Popp W, Ritschka L, Thumb N, Wottawa A, et al. Bronchoalveolar lavage in rheumatoid arthritis. *Br J Rheumatol.* 1993;32:556-62.
23. Lee HK, Kim DS, Yoo B, Seo JB, Rho JY, Colby TV, et al. Histopathology pattern and clinical features of rheumatoid arthritis-associated interstitial lung disease. *Chest.* 2005;127:2019-27.
24. Flaherty KR, Colby TV, Travis WD, Toews GB, Mumford J, Murray S, et al. Fibroblastic foci in usual interstitial pneumonia. *Am J Respir Crit Care Med.* 2003;167:1410-5.
25. Dawson JK, Gram DR, Desmond J, Fewins HE, Lynch MO. Investigation of the chronic pulmonary effects of low-dose oral methotrexate in patients with rheumatoid arthritis: a prospective study incorporating HDCT scanning and pulmonary function tests. *Rheumatology.* 2002;41:262-7.
26. Carson CW, Cannon GW, Egger MJ, Ward JR, Clegg DO. Pulmonary disease during the treatment of rheumatoid arthritis with low dose pulse methotrexate. *Semin Arthritis Rheum.* 1987;16:186-95.
27. Kremer JM, Alarcón GS, Weinblatt ME, Kaymakçian MV, Macaluso M, Cannon GW, et al. Clinical, laboratory, radiographic, and histopathology features of methotrexate-associated lung injury in patients with rheumatoid arthritis. A multicenter study with literature review. *Arthritis Rheum.* 1997;40:1829-37.
28. Saravanan V, Kelly C. Reducing the risk of methotrexate pneumonitis in rheumatoid arthritis. *Rheumatology.* 2004;43:143-7.
29. Vasallo R, Matteson E, Thomas CF. Clinical response of rheumatoid arthritis-associated pulmonary fibrosis to tumour necrosis factor- α inhibition. *Chest.* 2001;122:1093-6.
30. Dellapira PF, Fry THA, Willoghby J. The treatment of interstitial lung disease associated with rheumatoid arthritis with infliximab. *Chest.* 2003;124:109S.
31. Peno-Grenn L, Lluberas G, Kingsley T, Brantley S. Lung injury linked to etanercept therapy. *Chest.* 2002;122:1858-60.
32. Shoe A, van der Lann-Baalbergen NE, Huizinga TW, Braalbergen FC, van Laar JM. Pulmonary fibrosis in patient with rheumatoid arthritis treated with adalimumab. *Arthritis Rheum.* 2006;55:157-9.
33. Ostor AJ, Crisp AJ, Somerville ME, Scott DGI. Fatal exacerbation of rheumatoid arthritis associated fibrosing alveolitis in patients given infliximab. *BMJ.* 2004;329:1266.
34. Hagiwara K, Sato T, Takagi-Kobayashi S, Hasegawa S, Shigihara N, Akiyama O. Acute exacerbation of preexisting interstitial lung disease after administration of etanercept for rheumatoid arthritis. *J Rheumatol.* 2007;34:1151-4.
35. Allanore Y, Devos-Fraçois G, Caramella C, Bourmier P, Jounieaux V, Kahan A. Fatal exacerbation of fibrosing alveolitis associated with systemic sclerosis in a patient treated with adalimumab. *Ann Rheum Dis.* 2006;65:834-5.
36. Ledingham J, Deighton C, British Society for Rheumatology Standards, Guidelines and Audit Working Group (SGAWG). Update on the British Society for Rheumatology guidelines for prescribing TNF α blockers in adults with rheumatoid arthritis (update of previous guidelines of April 2001). *Rheumatology.* 2005;44:157-63.
37. Balakrishnan C, Fernando M, Kaki S, Rae AM, Dasgupta B. Serious pulmonary complications in patients treated with leflunomide. *Rheumatology.* 2001;40 Suppl. 1:83-4.
38. Ito S, Sumida T. Interstitial lung disease associated with leflunomide. *Intern Med.* 2004;43:1103-4.
39. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, et al. Effect of interleukin-6 receptors inhibition with tocilizumab in patients with rheumatoid arthritis: a double-blind, placebo-controlled, randomized trial. *Lancet.* 2008;371:987-97.
40. Kawasshiri S, Kawakami A, Sakamoto N, Ishimatsu Y, Eguchi K. A fatal case of acute exacerbation of interstitial lung disease in a patient with rheumatoid arthritis during treatment with tocilizumab. *Rheumatol Int.* 2010;32:4023-6.
41. Soubrier M, Jeannin G, Kemeny JL, Tournadre A, Caillot N, Caillaud D, et al. Organizing pneumonia after rituximab therapy: two cases. *Joint Bone Spine.* 2008;75:362-5.
42. Wagner SA, Mehta AC, Laber DA. Rituximab-induced interstitial lung disease. *Am J Hematol.* 2007;82:916-9.
43. Agustí C, Xaubet A, Roca J, Agustí AGN, Rodrigues-Roisin R. Interstitial pulmonary fibrosis with and without associated collagen vascular disease: results of a two year follow up. *Thorax.* 1992;47:1035-40.
44. Park JH, Kim DS, Park IN, Jang SJ, Kitaichi M, Nicholson AG, et al. Prognosis of fibrotic interstitial pneumonia: idiopathic versus collagen vascular disease-related subtypes. *Am J Respir Crit Care Med.* 2007;175:705-11.
45. Rajasekaran A, Shovlin D, Saravanan V, Lord P, Kelly C. Interstitial lung disease in patients with rheumatoid arthritis: comparison with cryptogenic fibrosing alveolitis over 5 years. *J Rheumatol.* 2006;33:1250-3.
46. Brown KK. Rheumatoid lung disease. *Proc Am Thorac Soc.* 2007;4:443-8.
47. Espinoza-Poblano E, Betancourt-Hernández L, Canizales-Cobos M, Careaga-Reyna G, Esparza-Pantoja J. Nódulos pulmonares necrobióticos en ausencia de artritis reumatoide. Reporte de un caso. *Neumol Cir Torax.* 2000;59:109-11.
48. Gómez Herrero H, Arraza Sarasa M, Rubio Marco I, García de Eulate Martín-Moro I. Nódulos pulmonares reumatoides: forma de presentación, métodos diagnósticos y evolución a propósito de 5 casos. *Reumatol Clin.* 2011;8:212-5.
49. Caplan A. Certain unusual radiological appearances in the chest of coal-miners suffering from rheumatoid arthritis. *Thorax.* 1953;8:29-37.
50. Mial WE, Caplan A, Cochrane AL, Kilpatrick GS, Oldham MA. An epidemiological study of rheumatoid arthritis associated with characteristic chest X-ray appearances in coal-workers. *Br Med J.* 1953;2:1231-6.
51. Mateo Soria L, Valverde García J. Manifestaciones cardiopulmonares. Madrid: Artritis Reumatoide Drug Farma; 2003.
52. Light RW. Pleural diseases. Philadelphia: Lea and Febinger; 1983.
53. Skare TL, Nakano I, Escuissati DL, Batistetti R, Rodrigues Tde O, Silva MB. Pulmonary changes on high-resolution computed tomography of patients with rheumatoid arthritis and their association with clinical, demographic, serological and therapeutic variables. *Rev Bras Reumatol.* 2011;51:325-30, 336-337.
54. Andonopoulos AP, Yarmenitis S, Georgiou P, Bounas A, Vlahanastasi C. Bronchiectasis in systemic sclerosis. A study using high resolution computed tomography. *Clin Exp Rheumatol.* 2001;19:187-90.
55. Van der Kamp R, Tak PP, Jansen HM, Bresser P. Interstitial lung disease as the first manifestation of systemic sclerosis. *Neth J Med.* 2007;65:390-4.
56. McNearney TA, Reveille JD, Fischbach M, Friedman AW, Lisse JR, Goel N, et al. Pulmonary involvement in systemic sclerosis: associations with genetic, serologic, sociodemographic, and behavioral factors. *Arthritis Rheum (Arthritis Care Res).* 2007;57:318-26.
57. Assassi S, Sharif R, Lasky RE, McNearney TA, Estrada-Y-Martin RM, Draeger H, et al. Predictors of interstitial lung disease in early systemic sclerosis: a prospective longitudinal study of the GENISOS cohort. *Arthritis Res Ther.* 2010;12:R166.
58. Fertig N, Domsic RT, Rodriguez-Reyna T, Kuwana M, Lucas M, Medsger Jr TA, et al. Anti-anti-U11/U12 RNP antibodies in systemic sclerosis: a new serologic marker associated with pulmonary fibrosis. *Arthritis Rheum.* 2009;61:958-65.
59. Prasse A, Müller-Ouernheim J. Non-invasive biomarkers in pulmonary fibrosis. *Respirology.* 2009;14:788-95.
60. Kumánovics G, Minier T, Radics J, Pálincás L, Berki T, Czirják L. Comprehensive investigation of novel serum markers of pulmonary fibrosis associated with systemic sclerosis and dermatomyositis. *Clin Exp Rheumatol.* 2008;26:414-20.
61. Castro SV, Jimenez SA. Biomarkers in systemic sclerosis. *Biomarkers Med.* 2010;4:133-47.
62. Yanaba K, Hasegawa M, Hamaguchi Y, Fujimoto M, Takehara K, Sato S. Longitudinal analysis of serum KL-6 levels in patients with systemic sclerosis: association with the activity of pulmonary fibrosis. *Clin Exp Rheumatol.* 2003;21:429-36.
63. Takahashi H, Kuroki Y, Tanaka H, Saito T, Kurokawa K, Chiba H, et al. Serum levels of surfactant proteins A and D are useful biomarkers for interstitial lung disease in patients with progressive systemic sclerosis. *Am J Respir Crit Care Med.* 2000;162:258-63.
64. Hant FN, Ludwicka-Bradley A, Wang HJ, Li N, Elashoff R, Tashkin DP, et al. Surfactant protein D and KL-6 as serum biomarkers of interstitial lung disease in patients with scleroderma. *J Rheumatol.* 2009;36:773-80.
65. Bonella F, Volpe A, Caramaschi P, Nava C, Ferrari P, Schenk K, et al. Surfactant protein D and KL-6 serum levels in systemic sclerosis: correlation with lung and systemic involvement. *Sarcoidosis Vasc Diffuse Lung Dis.* 2011;28:27-33.
66. Koderá M, Hasegawa M, Komura K, Yanaba K, Takehara K, Sato S. Serum pulmonary and activation-regulated chemokine/CCL18 levels in patients with systemic sclerosis: a sensitive indicator of active pulmonary fibrosis. *Arthritis Rheum.* 2005;52:2889-96.
67. Nordenbaek C, Johansen JS, Hallberg P, Wilk A, Garbarsch C, Ullman S, et al. High serum levels of YKL-40 in patients with systemic sclerosis are associated with pulmonary involvement. *Scand J Rheumatol.* 2005;34:293-7.
68. Launay D, Remy-Jardin M, Michon-Pasturel U, Mastora I, Hachulla E, Lambert M, et al. High resolution computed tomography in fibrosing alveolitis associated with systemic sclerosis. *J Rheumatol.* 2006;33:1789-801.
69. Bussone G, Mouthon L. Interstitial lung disease in systemic sclerosis. *Autoimmunity Rev.* 2011;10:248-55.
70. Bouros D, Wells AU, Nicholson AG, Colby TV, Polychronopoulos V, Pantelidis P, et al. Histopathology subsets of fibrosing alveolitis in patients with systemic sclerosis and their relationship to outcome. *Am J Respir Crit Care Med.* 2002;165:1581-6.
71. Goh NS, Desai SR, Veeraraghavan S, Hansell DM, Copley SJ, Maher TM, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. *Am J Respir Crit Care Med.* 2008;177:1248-54.
72. Steen VD, Medsger Jr TA. Severe organ involvement in systemic sclerosis with diffuse scleroderma. *Arthritis Rheum.* 2000;43:2437-44.
73. Steen VD, Conte C, Owens GR, Medsger TA. Severe restrictive lung disease in systemic sclerosis. *Arthritis Rheum.* 1994;37:1283-9.
74. Garin MC, Highland KB, Silver RM, Strange C. Limitations to the 6-minute walk test in interstitial lung disease and pulmonary hypertension in scleroderma. *J Rheumatol.* 2009;36:330-6.
75. Varga J. Systemic sclerosis: an update. *Bull NYU Hosp Jt Dis.* 2008;66:198-202.

76. Wells AU, Cullinan P, Hansell DM, Rubens MB, Black CM, Newman-Taylor AJ, et al. Fibrosing alveolitis associated with systemic sclerosis has a better prognosis than lone cryptogenic fibrosing alveolitis. *Am J Respir Crit Care Med.* 1994;149:1583-90.
77. Jacobsen S, Halberg P, Ullman S, Hoier-Madsen M, Petersen J, Mortensen J, et al. A longitudinal study of pulmonary function in Danish patients with systemic sclerosis. *Clin Rheumatol.* 1997;16:384-90.
78. Kowal-Bielecka O, Landewé R, Avouac J, Chwiesko S, Miniati I, Czirjak L, et al. EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR). *Ann Rheum Dis.* 2009;68:620-8.
79. Berezne A, Valeyre D, Ranque B, Guillevin L, Mouthon L. Interstitial lung disease associated with systemic sclerosis: what is the evidence for efficacy of cyclophosphamide? *Ann N Y Acad Sci.* 2007;1110:271-84.
80. Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD, Furst DE, et al. Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med.* 2006;354:2655-66.
81. Nadashkevich O, Davis P, Fritzer M, Kovalenko W. A randomized unblinded trial of cyclophosphamide versus azathioprine in the treatment of systemic sclerosis. *Clin Rheumatol.* 2006;25:205-12.
82. Espinos G, Simeon CP, Plasín MA, Xaubet A, Muñoz X, Fonollosa V, et al. Eficacia de la ciclofosfamida en el tratamiento de la enfermedad pulmonar intersticial asociada a la esclerosis sistémica. *Arch Bronconeumol.* 2011;47:239-45.
83. Gerbino AJ, Goss CH, Molitor JA. Effect of mycophenolate mofetil on pulmonary function in scleroderma-associated interstitial lung disease. *Chest.* 2008;133:455-60.
84. Daoussis D, Lioussis S-NC, Tsamandas AC, Kalogeropoulou C, Kazantzis A, Sirinian C, et al. Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study. *Rheumatology.* 2010;49:271-80.
85. Mathai SC, Hassoun PM. Therapy for pulmonary arterial hypertension associated with systemic sclerosis. *Curr Opin Rheumatol.* 2009;21:642-8.
86. Allanore Y, Borderie D, Avouac J, Zerkak D, Meune C, Hachulla E, et al. High N-terminal pro-brain natriuretic peptide levels and low diffusing capacity for carbon monoxide as independent predictors of the occurrence of precapillary pulmonary arterial hypertension in patients with systemic sclerosis. *Arthritis Rheum.* 2008;58:284-91.
87. Keane MP, Lynch JP. Pleuropulmonary manifestation of systemic lupus erythematosus. *Thorax.* 2000;55:159-66.
88. Bourou D, Pneumatikos I, Tzouveleki A. Pleural involvement in systemic autoimmune disorders. *Respiration.* 2008;75:361-71.
89. Menet B, Ginzler EM. Pulmonary manifestations of systemic lupus erythematosus. *Semin Respir Crit Care Med.* 2007;28:441-50.
90. Kamen DL, Strange CS. Pulmonary manifestations of systemic lupus erythematosus. *Clin Chest Med.* 2010;31:479-88.
91. Laurentis A, Veerarahavan A, Renzoni E. Connective tissue-associated interstitial lung disease: how does it differ from IPF? How should the clinical approach differ? *Cron Respir Dis.* 2011;8:53-82.
92. Crestani B. The respiratory system in connective tissue disorders. *Allergy.* 2005;60:715-35.
93. Mochizuki T, Aotsuka S, Satoh T. Clinical and laboratory features of lupus patients with pulmonary disease. *Respir Med.* 1999;93:95-101.
94. Weinrib L, Sharma OP, Quismorio Jr FP. A long-term study of interstitial lung disease in systemic lupus erythematosus. *Semin Arthritis Rheum.* 1990;20:48-56.
95. Sant SM, Doran M, Fenelon HM, Breatnach ES. Pleuropulmonary abnormalities in patients with lupus erythematosus: assessment with high resolution computed tomography, chest radiography and pulmonary function tests. *Clin Exp Rheumatol.* 1997;15:507-13.
96. Tansey D, Wells AU, Colby TV, Ip S, Nikolakoupolou A, du Bois RM, et al. Variations in histological patterns of interstitial pneumonia between connective tissue disorders and their relationship to prognosis. *Histopathology.* 2004;44:585-96.
97. Pego-Reigosa JM, Medeiros DA, Isenberg DA. Respiratory manifestations of systemic lupus erythematosus: old and new concepts. *Best Pract Res Clin Rheumatol.* 2009;23:469-80.
98. Nellessen CM, Pöge U, Brensing KA, Sauerbruch T, Klehr H, Rabe C. Diffuse alveolar hemorrhage in a systemic lupus erythematosus patient successfully treated with rituximab. A case report. *Nephrol Dial Transplant.* 2008;23:385-6.
99. Prabu A, Patel K, Yee CS, Nitgtingale P, Situnavake RD, Thickett DR, et al. Prevalence and risk factors for pulmonary arterial hypertension in patients with lupus. *Rheumatology (Oxford).* 2009;48:1506-11.
100. Pan TL, Thumboo J, Boey ML. Primary and secondary pulmonary hypertension in systemic lupus erythematosus. *Lupus.* 2000;9:338-40.
101. Chung SM, Lee CK, Lee EY, Yoo B, Lee SD, Moon HB. Clinical aspects of pulmonary hypertension in patients with idiopathic pulmonary arterial hypertension. *Clin Rheumatol.* 2006;25:866-72.
102. Robbins IM, Gaine SP, Schilz R, Tapson VF, Rubin LJ, Loyd JE. Epoprostenol for treatment of pulmonary hypertension in patients with systemic lupus erythematosus. *Chest.* 2000;117:14-8.
103. Rubin LJ, Badesch DB, Barst RJ, Galie N, Black CM, Keogha A, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med.* 2002;346:896-903.
104. González-López L, Cardona-Muñoz EG, Celis A, García-De la Torre I, Orozco-Barocio G, Salazar-Páramo M, et al. Therapy with intermittent pulse cyclophosphamide for pulmonary hypertension associated with systemic lupus erythematosus. *Lupus.* 2004;13:105-12.
105. Martínez-Taboada VM, Blanco R, Armona J, Fernández-Sueiro JL, Rodríguez-Valverde V. Acute reversible hypoxemia in systemic lupus erythematosus: a new syndrome or an index of disease activity? *Lupus.* 1995;4:259-62.
106. Gondeau B, Cormier C, Menkes CJ. Bronchiolitis obliterans in systemic lupus erythematosus: beneficial effect of intra venous cyclophosphamide. *Ann Rheum Dis.* 1991;50:956-8.
107. Papiiris SA, Tsonis IA, Moutsopoulos HM. Sjögren syndrome. *Semin Crit Care Med.* 2007;28:459-72.
108. Gardiner P, Ward C, Allison A, Ashcroft T, Simpson W, Walter H, et al. Pleuropulmonary abnormalities in primary Sjögren syndrome. *Clin Rheumatol.* 1993;205:831-7.
109. Kokoski M, Riemer EC, Highland KB. Pulmonary Involvement in Sjögren syndrome. *Clin Chest Med.* 2010;31:489-500.
110. Constantopoulos SH, Papadimitriou CS, Moutsopoulos HM. Respiratory manifestations in primary Sjögren syndrome. A clinical, functional and histologist study. *Chest.* 1985;88:226-9.
111. Parke AL. Pulmonary manifestations of primary Sjögren syndrome. *Rheum Dis Clin North Am.* 2008;34:459-71.
112. Ramos-Casal M, Solans R, Rosas J, Camps MT, Gil A, Pino-Montes J, et al. Clinical and immunologic expression in 1010 patients. *Medicine (Baltimore).* 2008;87:210-9.
113. Shi JH, Liu HR, Xu WB, Feng RE, Zhag ZH, Tian XL, et al. Pulmonary manifestations of Sjögren syndrome. *Respiration.* 2009;78:377-86.
114. Parambil JG, Myers JL, Lindell RM, Matteson EL, Ryu JH. Interstitial lung disease in primary Sjögren syndrome. *Chest.* 2006;130:1489-95.
115. Ito I, Nagai S, Kitaichi M, Nicholson AG, Johkon T, Noma S, et al. Pulmonary manifestation of primary Sjögren syndrome: a clinical, radiological and pathologic study. *Am J Respir Crit Care Med.* 2005;171:632-8.
116. Isaksen K, Jonsson R, Omdal R. Anti CD20 treatment in primary Sjögren syndrome. *Scand J Immunol.* 2008;68:554-64.
117. Seror R, Sordet C, Guillevin L, Hachulla E, Masson C, Ittah M, et al. Tolerance and efficacy of rituximab and changes in serum B cell biomarkers in patients with systemic complications of primary Sjögren syndrome. *Ann Rheum Dis.* 2007;66:351-7.
118. Matteson EL, Ike RW. Bronchiolitis obliterans organizing pneumonia and Sjögren syndrome. *J Rheumatol.* 1990;17:676-9.
119. Ionone S, Toya SP, Tomos P, Tzelepis GE. Cryptogenic organizing pneumonia associated with primary Sjögren syndrome. *Rheumatol Int.* 2008;28:1053-5.
120. Bellido-Casado J, Plaza V, Díaz C, Geli C, Domínguez J, Margarit G, et al. Inflamación bronquial, clínica respiratoria y función pulmonar en el síndrome de Sjögren primario. *Arch Bronconeumol.* 2011;47:330-4.
121. Nakanishi M, Fukuoka J, Tanaka T, Demura Y, Umeda Y, Ameshima S, et al. Small airway disease associated with Sjögren syndrome: clinico-pathological correlations. *Respir Med.* 2011;105:1931-8.
122. Soto-Cardenas MJ, Pérez-de-Lis M, Bove A, Navarro C, Brito-Zeron P, Diaz-Lagares C, et al. Bronchiectasis in primary Sjögren syndrome: prevalence and clinical significance. *Clin Exp Rheumatol.* 2010;28:47-653.
123. Torres C, Belmonte R, Carmona L, Gómez-Reino FJ, Galindo M, Ramos B, et al. Survival mortality and causes of death in inflammatory myopathies. *Autoimmunity.* 2006;39:205-15.
124. Fathi M, Lundberg IE, Tornling G. Pulmonary complications of polymyositis and dermatomyositis. *Semin Respir Crit Care Med.* 2007;28:451-8.
125. Marie I, Hachulla E, Cherin P, Hellot MF, Herson S, Levesque H, et al. Opportunistic infections in polymyositis and dermatomyositis. *Arthritis Rheum.* 2005;53:155-6.
126. Kalluri M, Oddis C. Pulmonary manifestations of the idiopathic inflammatory myopathies. *Clin Chest Med.* 2010;31:501-12.
127. Fathi M, Dastmalchi M, Rasmussen E, Lundberg IE, Tornling G. Interstitial lung disease, a common manifestation of newly diagnosed polymyositis and dermatomyositis. *Ann Rheum Dis.* 2004;63:297-301.
128. Labirua A, Lundberg IE. Interstitial lung disease and idiopathic inflammatory myopathies: progress and pitfalls. *Curr Opin Rheumatol.* 2010;22:633-8.
129. Fathi M, Lundberg IE. Interstitial lung disease in polymyositis and dermatomyositis. *Curr Opin Rheumatol.* 2005;17:701-8.
130. Marguerie C, Bunn CC, Beynonn HLC, Berstein RM, Hughes JM, So AK, et al. Polymyositis, pulmonary fibrosis and autoantibodies to aminoacyl-tRNA synthetase enzymes. *Q J Med.* 1990;77:1019-38.
131. Watanabe K, Handa T, Tanizawa K, Hosono Y, Taguchi Y, Noma S, et al. Detection of antisynthetase syndrome in patients with idiopathic interstitial pneumonias. *Respir Med.* 2011;105:1238-47.
132. Koreeda Y, Higashimoto I, Yamamoto M, Takahashi M, Kaji K, Fujimoto M, et al. Clinical and pathological findings of interstitial lung disease patients with anti-aminoacyl-tRNA synthetase autoantibodies. *Intern Med.* 2010:361-9.
133. Saketkoo LA, Ascherman DP, Cottin V, Cristopher-Stine L, Danoff SK, Oddis CV. Interstitial lung disease in idiopathic inflammatory myopathy. *Curr Rheumatol Rev.* 2010;6:108-9.
134. Kameda H, Nagasawa H, Ogawa H, Sekiguchi N, Takei H, Tokuhira M, et al. Combination therapy with corticosteroids, cyclosporine A and intravenous pulse

- cyclophosphamide for acute/subacute interstitial pneumonia in patients with dermatomyositis. *J Rheumatol.* 2005;32:1719-26.
135. Morganroth PA, Kreider ME, Werth VP. Mycophenolate mofetil for interstitial lung disease in dermatomyositis. *Arthritis Care Res.* 2010;62:1496-501.
136. Kinder BW, Collard HP, Koth L, Daikh DI, Wolters PJ, Elicker B, et al. Idiopathic nonspecific interstitial pneumonia: lung manifestation of undifferentiated connective tissue disease? *Am J Respir Crit Care Med.* 2007;176:691-7.
137. Romagnoli M, Nannini C, Picucchi S, Girelli F, Gurioli C, Casoni G, et al. Idiopathic NSIP: an interstitial lung disease associated with autoimmune disorders? *Eur Respir.* 2011;38:384-91.
138. Perez-Alvarez R, Perez-de-Lis M, Diaz-Lagares C, Pego-Reigosa JM, Retamozo S, Bove A, et al. Interstitial lung disease induced or exacerbated by TNF-targeted therapies: analysis of 122 cases. *Semin Arthritis Rheum.* 2011;41:256-64.