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Review article

Systemic sclerosis and interstitial lung disease: From pathogenesis, to screening, diagnosis, and classification

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ABSTRACT

Interstitial lung disease (ILD) is a common and potentially devastating complication of systemic sclerosis (SSc), a chronic autoimmune disorder characterized by fibrosis and vascular abnormalities. The association between SSc and ILD underscores the intricate interplay between immune dysregulation, vasculopathy, and tissue fibrosis. This review provides a comprehensive overview of the immunological, clinical, and radiological features of ILD in the context of SSc. It highlights the diverse spectrum of ILD patterns observed in SSc patients, ranging from non-specific interstitial pneumonia to usual interstitial pneumonia. The intricate pathogenic mechanisms linking SSc and ILD involve aberrant immune responses, endothelial dysfunction, profibrotic cytokine signaling, and genetic factors. Immunological alterations, diagnostic challenges, and prognostic implications are discussed, underscoring the need for multidisciplinary management strategies. By elucidating the complex relationship between SSc and ILD, this review aims to contribute to a deeper understanding of the underlying mechanisms and facilitate the development of interdisciplinary interventions for improved patient outcomes.

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Esclerosis sistémica y enfermedad pulmonar intersticial: de la patogenia al cribado, el diagnóstico y la clasificación

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RESUMEN

La enfermedad pulmonar intersticial (EPI) es una complicación frecuente y potencialmente devastadora de la esclerosis sistémica (SSc), un trastorno autoinmune crónico caracterizado por fibrosis y anomalías vasculares. La asociación entre la SSc y la EPI subraya la difícil interacción entre la desregulación inmunitaria, la vasculopatía y la fibrosis tisular. Esta revisión proporciona una visión global de las características inmunológicas, clínicas y radiológicas de la EPI en el contexto de la SSc; de igual manera, se destaca el diverso espectro de patrones de EPI observados en pacientes con SSc, que van desde la neumonía intersticial inespecífica a la habitual. Los intrincados mecanismos patogénicos que relacionan la SSc y la EPI implican respuestas inmunitarias aberrantes, disfunción endotelial, señalización profibrótica de citoquinas y factores genéticos. Se discuten las alteraciones inmunológicas, los retos diagnósticos y las repercusiones pronósticas, subrayando la necesidad de estrategias de gestión multidisciplinares. Al elucidar la compleja relación entre la SSc y la EPI, esta revisión pretende contribuir a una comprensión más profunda de los mecanismos subyacentes y facilitar el desarrollo de intervenciones interdisciplinarias para mejorar los resultados de los pacientes.

Systemic sclerosis (SSc) is an autoimmune connective tissue disorder which can progress with multiple life-threatening organ involvement including interstitial lung disease (ILD). To date, three pathogenic pathways for the development of SSc have been implicated, including immune dysregulation, vasculopathy, and progressive fibrosis. ILD is one of the most common manifestations of SSc and a primary contributor to SSc-related deaths, followed by pulmonary arterial hypertension and cardiac causes.[1–3] The clinical presentations of SSc-related ILD (SSc-ILD) vary from asymptomatic with stable lung function to severe dyspnea and cough with progressive lung involvement.[4] Considering the complex nature and heterogenous clinical presentation of SSc-ILD, both proper assessment of patients for early diagnosis and management and better understanding of the disease pathogenesis are crucial for mitigating the detrimental consequences of SSc-ILD and development of better, and someday, curative treatments.

The pathogenesis of SSc-related ILD

Results of clinical and preclinical animal-based studies have revealed that SSc-ILD proceeds from various complex pathways which might be summarized in endothelial and epithelial lung injury. There is dysregulation of the immune system including innate and adaptive immune cells with an increase in pro-inflammatory and pro-fibrotic cytokines, eventually resulting in fibrosis with exaggerated deposition of extracellular matrix (ECM).[5] However, there are still major areas of uncertainty regarding the pathogenesis of SSc-ILD.

The role of lung/tissue injury in SSc-ILD

Repetitive and sustained injury of alveolar endothelial and epithelial cells is believed to be the initial step for the development of ILD-SSc.[6,7] Thrombin, a procoagulant factor, is released after tissue and vascular injury. Bronchoalveolar fluid (BAL) from patients with SSc who have pulmonary fibrosis demonstrates a remarkable increase in thrombin activity with associated mitogenic activity of thrombin on lung fibroblasts that may be related to pulmonary fibrosis.[8] As well, thrombin promotes the differentiation of lung fibroblasts into myofibroblasts, which is the cornerstone of the fibrotic process.[9] The preclinical studies assessing the inhibition of thrombin have demonstrated that dabigatran, a direct thrombin inhibitor, reduces the myofibroblast differentiation of lung fibroblasts and pulmonary fibrosis.[10,11] However, at the clinical level, a study evaluating the tolerability and safety of dabigatran in patients with SSc-ILD failed to show an effect of dabigatran on pulmonary function tests (PFTs).[12]

Another possible mediator released after lung injury is endothelin-1 (ET-1) which is a strong vasoconstrictor and is secreted by endothelial cells, epithelial cells, and alveolar macrophages. ET-1 has pro-inflammatory and pro-fibrotic effects by activating the neutrophil aggregations, cytokine production and inducing fibroblasts, and promoting endothelial-mesenchymal transition (EndoMT).[13–15] The pathologic assessment of lung tissue from patients with SSc-ILD has revealed a marked increase in expression of ET-1 and its receptors.[16] Furthermore, serum ET-1 level has been found to be significantly increased in serum and BAL from patients with SSc-ILD in previous studies.[17–19] Moreover, the evaluation of patients with SSc with nailfold video capillaroscopy has elu-

cidated that peripheric microvascular abnormalities reflecting the endothelial damage are related to ILD, supporting the role of microvascular injury in the pathogenesis of SSc-ILD.[20]

Alveolar epithelial cells (AECs) divide into two cell subsets. Type I AECs comprise the majority of the alveolar epithelial line, and type II AECs, which are proliferating cells with a high regeneration capacity and are responsible for production of surfactants.[21,22] Apart from surfactants, type II AECs produce a mucin-like glycoprotein, called Krebs von den Lungen-6 (KL-6). The level of KL-6 increases with alveolar epithelial damage or cellular regeneration.[23] KL-6 induces lung fibroblast proliferation while inhibiting the apoptosis of fibroblasts.[24] The serum level of KL-6 is found to be markedly elevated in SSc-ILD and related to the severity of lung involvement.[25,26] After epithelial alveolar injury, type II AECs start to proliferate and some undergo apoptosis while the remaining cells differentiate into type I AECs in normal repair. However, in pathologic conditions such as idiopathic pulmonary fibrosis or SSc-ILD, type II AECs have been implicated in fibrosis due to their capacity for endothelial-mesenchymal transition (EMT) through transforming-growth factor beta (TGF-β) signaling.[22,27] Furthermore, alveolar macrophages and type II AECs are considered as a TGF-β secreting cells in SSc with fibrosing alveolitis.[28] Similar to AECs, lung endothelial cells can differentiate into fibroblasts in bleomycin-induced lung injury and fibrosis.[29] The immunohistopathological investigation of lung tissue has demonstrated the occurrence of EndoMT in SSc-ILD.[30]

The role of inflammation and alteration of immune cells in SSc-ILD

Alveolitis-inflammation

Alveolitis, the infiltration of alveoli with inflammatory and immune cells, is reflected in an increased percentage of neutrophils, lymphocytes or eosinophils in BAL.[31] The results of numerous studies revealed a prominent granulocytosis (neutrophilia and eosinophilia) in BAL from patients with SSc-ILD.[32] Moreover, significant neutrophilia on BAL is found in patients with SSc even with normal findings on computed tomography (CT) of the chest compared to healthy participants.[33] Histopathologic examination of the lung in patients with SSc at an early stage has shown interalveolar inflammation with a higher number of macrophages and infiltration of the interstitium with lymphocytes and plasma cells. As well, inflammation and fibrosis are found together which may support the role of inflammation in the fibrosis of SSc-ILD. Interestingly, occasional polymorphonuclear cells in alveolar space are detected in contrast to BAL findings.[34] In BAL or sera of patients with SSc-ILD, the levels of pro-inflammatory markers such as interleukin (IL)-6, IL-8, IL-4, monocyte chemoattractant protein-1 (MCP-1), leukotriene B4, and leukotriene E4 are increased.[35–39] All these results strongly suggest that inflammation may play a pivotal role in the pathogenesis of SSc-ILD.

T cells

Activated specific adaptive immune cells including T helper (Th)2 cells, Th22 cells, Th17 cells, and B cells participate in the pathogenesis of SSc-ILD.[22] The differentiation toward Th2 cells, which have a profibrotic phenotype, has been observed in SSc. IL-4 and IL-13, mainly produced by Th2 cells, have profibrotic effects through the activation of fibroblast and promoting collagen synthesis via the TGF-β pathway.[40] Another important role of these cytokines is the activation of macrophages with the profibrotic phenotype (M2 polarization) which has been suggested to play a role in the fibrotic process in SSc.[41] The level of IL-4 is significantly higher in BAL and sera of patients with SSc-ILD.[36,39] A recent study has demonstrated a significant association between IL-13 level and severity of ILD in SSc.[42] Moreover, the frequency of $CD4^+$ T cells producing IL-22 is shown to be elevated in patients with SSc-ILD, and the level of serum IL-22 is positively correlated with the presence of ILD in SSc.[43,44]

Several studies have evaluated the role of regulatory T (Treg) cells in SSc. These cells are responsible for maintaining immune homeostasis and suppressing effector immune cells. Several studies have demonstrated a remarkable decline in circulating Treg cells in SSc, although a few studies have shown a significant increase in Treg cells.[45] A study with a small number of patients with SSc reported a significant increase in the ratio of Treg cells and Th17 cells in SSc compared to healthy controls.[46] This study also reported an elevated percentage of Treg cells in patients with high ILD scores on CT and in patients with decreased carbon monoxide diffusing capacity (DLCO).[46] Another recent study reported that patients with SSc-ILD have a higher number of Treg cells than healthy controls.[47] Moreover, the level of IL-35, secreted mainly by Treg cells, is found to be increased in patients with SSc who have 94% of the lung involved. The level of IL-35 is positively associated with Treg cells and high-resolution computerized tomography (HRCT) PFT lung scores.[48] These results might be explained by the diminished suppressive effect of Treg cells in SSc.[49,50]

IL-33 is released from stromal cells such as epithelial cells, endothelial cells, and fibroblasts after tissue injury or cell damage.[51] IL-33 promotes polarization of M2 macrophages and differentiation of Treg cells into Th2 cells and thus attenuates dermal and pulmonary fibrosis through IL-13-dependent fibrotic pathways.[51,52] The serum level of IL-33 is significantly increased in patients with SSc, especially those with microvascular involvement and skin and pulmonary fibrosis, and is correlated with the severity of pulmonary and skin fibrosis.[53,54]

B cells

The dysregulation of B cell immunity including hyperactivation of B cells with production of autoantibodies, alteration of B cell homeostasis, and imbalance between B cell subsets, plays a fundamental role in the pathogenesis of SSc.[55] The investigation of lung tissue samples from patients with SSc-ILD has indicated that there are prominent B cell infiltrations in most of the lung specimens in addition to T cell infiltrations.[56]

B regulatory (Breg) cells secrete IL-10, which has potent anti-inflammatory and anti-fibrotic effects, and inhibit $CD4^+$ T cell proliferation and differentiation of Th1 and Th17 cells.[57] Recent reports have revealed that patients with SSc-ILD have a markedly decreased count of Breg cells compared to patients with SSc but without ILD.[58,59] Effector B (Beff) cells or activated B cells are responsible for the production of autoantibodies,

inducing collagen synthesis of fibroblasts and promoting fibrosis through secretion of IL-6 and TGF-β.[55] A significantly higher level of IL-6-producing Beff cells and decreased level of IL-10-producing Breg cells is observed in patients with SSc compared to healthy controls. There is also a positive correlation between effector B (Beff)/Breg cells ratio and extent of ILD in SSc.[60] In patients with SSc-ILD, a significant increase in serum IL-6 level is detected compared to patients with SSc without ILD, and the level of IL-6 is predictive for deterioration of lung function tests.[61,62] Another important effect of B cells on SSc is to produce disease-specific autoantibodies such as anti-topoisomerase I autoantibody (ATA) and anti-centromere autoantibody believed to be a contributor to SSc pathogenesis[63] ATA positivity is a strong predictor for the development of ILD in SSc.[64]

Fibroblasts–myofibroblasts

Myofibroblasts and fibroblasts are the main driving cells leading to fibrosis through excessive ECM deposition in ILD. Myofibroblasts are derived from various cell types including fibroblasts activated by profibrotic mediators and stimuli, circulating fibrocytes, and mesenchymal transition of epithelial and endothelial cells (EMT and EndoMT).[41] In SSc, cultured fibroblasts derived from BAL have overexpression of myofibroblast phenotype markers such as alpha-smooth muscle cell actin (α-SMA), vimentin, and desmin with increased collagen production.[65]

Screening

Given the devastating consequences of SSc-ILD including its higher mortality rate and negative effects on quality of life, the screening for ILD in SSc has become crucial to early diagnosis and appropriate management.[1,66] Notwithstanding this imperative, there are still no formal, universally acknowledged screening guidelines for SSc-ILD. Patients with SSc who should be considered for ILD screening are especially those with risk factors for the development of ILD. These risk factors are considered to be dcSSc, presence of anti-topoisomerase I antibody, male sex, African American ethnicity, presence of respiratory symptoms, and history of smoking.[67] Screening for ILD in SSc usually involves careful evaluation of pulmonary symptoms, physical examination, PFTs, and HRCT. All patients with SSc should be examined with lung auscultation, especially for velcro-like crackles, and also respiratory symptoms such as cough and dyspnea should be reviewed to assess the lung involvement at every visit. However, a Canadian research group has shown that the diagnosis of ILD based upon physical examination (presence of basilar velcro-like crackles) and/or chest imaging with radiography has lower sensitivity compared to forced vital capacity (FVC) % predicted in patients with SSc, but higher specificity.

According to expert consensus, PFTs should be ordered in all patients with SSc and repeated regularly.[67] Screening PFTs are usually performed and repeated within six to twelve months. The most commonly assessed PFT parameters are FVC and diffusion capacity of carbon monoxide (DLCO). However, some patients with SSc, particularly those with anti-topoisomerase antibodies, have normal FVC and DLCO values despite the presence of fibrosis on HRCT.[68]

Results of several studies have revealed that these PFT parameters have low sensitivity and specificity for diagnosing ILD in patients with SSc.[68,69] PFTs also have poor sensitivity for detecting ILD in patients with early diffuse cutaneous systemic sclerosis (dcSSc).[70] However, an EUSTAR report on a very large number of patients has shown that DLCO is the earliest functional parameter to be reduced in SSc-ILD[71] and that it correlated very well with HRCT changes.[72] Taken together, this evidence suggests that the PFTs may raise the suspicion of an ongoing interstitial process but are not sufficient to diagnose ILD in patients with SSc.

HRCT is considered as the gold standard tool for the detection of ILD in SSc.[73,74] HRCT provides valuable findings including the pattern of ILD and the severity or extent of fibrosis, findings that correlate with disease prognosis.[75] The reports of a survey evaluating the approach of rheumatologists for screening SSc-ILD have revealed that HRCT is used in newly diagnosed patients with SSc by 66% of SSc experts and 51% of general rheumatologists.[73] Another survey analysis has shown that 65% of responders routinely use HRCT as a screening tool for ILD in patients newly diagnosed SSc, and 30.7% of responders perform HRCT when clinical indicators of ILD such as a decline in PFTs (FVC < 80% predicted), crackles on auscultation or dyspnea are present.[76] A recent prospective study has reported that the majority of patients with SSc undergo HRCT.[77] Use of HRCT is related to the presence of anti-centromere autoantibody and missing FVC values in patients followed at SSc-expert centers.[77]

Expert consensus guidelines recommend that HRCT should be performed in all patients with SSc to screen for ILD.[67,78] However, there is no consistency in the recommended screening interval with HRCT. Generally, the frequency of obtaining HRCT should be based on the clinician's decision taking into account risk factors for the development of ILD.[67]

Recent evidence has suggested that lung ultrasound may be a promising imaging tool for ILD screening because of its high sensitivity to detect parenchymal modifications in SSc.[79–81] The results of an assessment of ILD in SSc with lung ultrasound have shown an inverse relationship between B-lines and pulmonary function tests and a significant correlation between B-lines and HRCT scores. While currently not widely studied or used for ILD screening, lung ultrasound may emerge as a possible modality for identifying ILD in SSc.[82]

ILD diagnosis in SSc

The clinical course of systemic sclerosis (SSc) is variable. ILD in SSc may be asymptomatic, or present as exertional dyspnea or persistent dry cough.[83] However, dyspnea in SSc may be multifactorial and caused also by vascular disease, musculoskeletal involvement, anemia or cardiac disease.[84]

Pulmonary complications are the leading cause of disease-related mortality in SSc.[85] ILD was the leading cause of death in a EUSTAR reported cohort of over 5800 patients; 35% of all SSc-related deaths were related to pulmonary fibrosis.[86]

ILD is present in up to 80% of patients with SSc[87] and frequently appears during the first 4–6 years after the disease onset. It is noteworthy that most patients with ILD will develop

severe restrictive lung disease in the first 5 years after the onset of symptoms.[88] PFT are neither sensitive nor specific enough to detect early ILD. HRCT is the standard test for confirming the diagnosis.[89–91] Histological study of the lung is not considered as a routine tool to diagnosis ILD in SSc and is reserved for cases of diagnostic uncertainty.[92,93]

Lung parenchyma involvement in SSc can be due to causes other than ILD and. Patients with SSc-ILD may also have other forms of lung disease as well. Immunosuppressive treatment predisposes to lung infections including COVID19. Carcinoma and pulmonary lymphangitic carcinomatosis can simulate ILD, so that neoplastic processes must be considered in the differential diagnosis of ILD. Other conditions that should be considered in the differential diagnosis of ILD are exposure-related lung disease such as asbestosis, and chronic hypersensitivity pneumonitis.[94]

Primary heart involvement or arrhythmia due to SSc can cause left heart dysfunction (LDH) and can also mimic symptoms of ILD. Pulmonary veno-occlusive disease (PVOD) shares some radiological findings with ILD. Transthoracic echocardiography is a useful tool to screen for pulmonary arterial hypertension (PAH) and can help in cases where PAH or left heart disease is suspected.[95]

Other pulmonary complications of SSc include the underlying connective tissue disease of the chest wall skin that may directly restrict respiratory movement, and muscle involvement with inflammation or fibrosis that impairs ventilation of the lungs.[84,85] Pleural disease can occur with pleural effusions, although it is less common than in other CTDs (connective tissue diseases) and may be a clinical indication of an overlap syndrome.

Finally, it is always important to exclude, even if uncommon, the possibility of iatrogenesis caused by immunosuppressive therapy such as acute methotrexate toxicity[96] or amiodarone toxicity.[97]

ILD classification in SSc

Systemic sclerosis-associated interstitial lung disease (SSc-ILD) can be classified by different ways. It can be categorized by lung-tissue histology, high-resolution computerized tomography (HRCT) imaging-pattern, radiographic extent of disease and likelihood of progression.

The main histological features of SSc-ILD are based on parenchymal infiltration of inflammatory cells and subsequent fibrosis of the lung tissue.[98,99] The cellular composition of the infiltrates and the disorganization and dysregulation of the lung parenchyma define the different patterns that can be identified. Due to usually good radiologic–histologic pattern correlation, lung biopsy is not usually required.[93] HRCT is usually sufficient confirming ILD and characterizing the type of interstitial changes with a high degree of reliability. Lung biopsy is usually done in cases where malignancy, infection, or other conditions such as hypersensitivity pneumonitis are suspected.

The histological ILD subsets seen in SSc-ILD include non-specific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), organizing pneumonia (OP) and lymphoid interstitial pneumonia (LIP). In SSc-ILD, NSIP is the most common ILD histological pattern, present in up to 77% of cases, although UIP can also be seen in 25–40% of cases.[93,100]

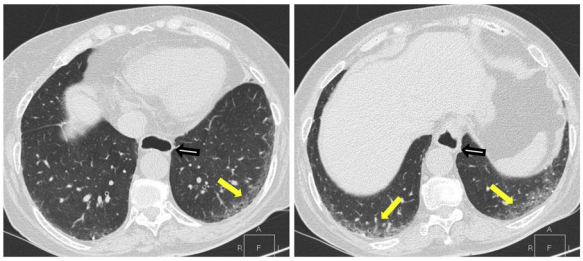

Fig. 1 – (A, B) High resolution computed tomography demonstrating NSIP with subpleural ground-glass opacities (short arrows) with traction bronchiectasis (arrows) and sparing of the subpleural lung.

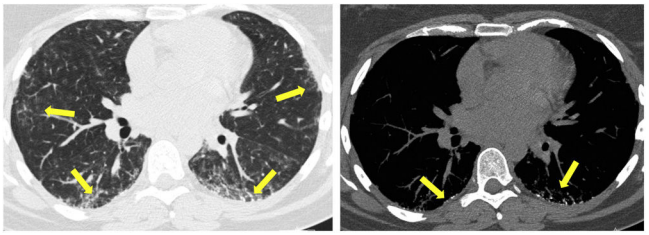

Fig. 2 – (A) NSIP with subpleural multifocal patchy ground-glass opacities (arrows); (B) subpleural dendriform ossification is also observed (arrows).

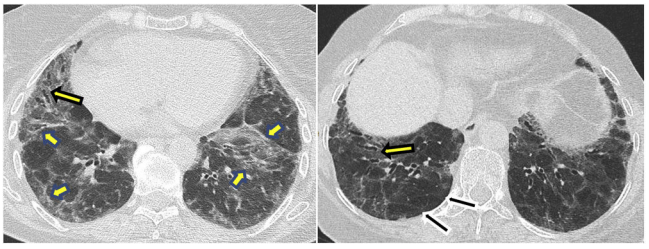

Fig. 3 – (A, B) Fibrotic NSIP with subpleural sparing. HRCT shows multifocal patchy ground-glass opacities (short arrows) with traction bronchiectasis (arrows) and sparing of the subpleural lung (black arrows).

Typically SSc-ILD manifests on HRCT as predominantly ground-class opacities (GGO) with a combination of pulmonary fibrosis, consistent with the NSIP pattern, which can be subcategorized as cellular NSIP or fibrotic NSIP.[101] Fibrotic NSIP is more prevalent than the cellular subtype and has higher risk of progression.[102] However, honeycombing cystic change is reported between 11 and 37% of patients with SSc-ILD.[99,103] Since the honeycombing pattern is typically a marker for UIP and pulmonary fibrosis and is rarely present in NSIP pattern, it is suggested that patients with SSc-ILD may have an overlap of different patterns. Table 1 shows the radiological patterns and signs of fibrosis on chest HRCT.[104]

Chest HRCT is the main tool to detect and to characterize ILD in SSc. Examples of the NSIP pattern with different radiological signs in patients with SSc are shown in Figs. 1–4. As previously noted, it is highly recommended that HRCT be performed in all patients with SSc at the beginning of the

Table 1 – Radiological patterns and signs of fibrosis on chest high resolution computed tomography.

Radiological patterns	Radiological signs
NSIP	• Peripheral distribution; occasionally central • Preference in inferior lobes • Patchy GGO with linear, reticular, and micronodular images • Traction bronchiectasis/bronchiolectasis when NSIP fibrotic • Infrequent honeycombing cystic pattern
UIP	• Subpleural, basal and symmetrical; occasionally diffuse • Apico-basal progression • Honeycombing pattern with reticulation, bronchiectasis, and traction bronchiectasis • Minimal ground-glass opacities
LIP	• Bilateral involvement • Preference in inferior lobes • Patchy areas of GGO with small centrilobular unclearly defined nodules • Multiple thin-walled cysts
OP	• Peripheral and often frankly subpleural • Patchy areas of consolidation (increased lung attenuation with architectural distortion) • Coalescence progression to diffuse alveolar damage and fibrosis signs with GGO and traction bronchiectasis

Definition of abbreviations: NSIP = non-specific interstitial pneumonia; GGO = ground glass opacities; UIP = usual interstitial pneumonia; LIP = lymphoid interstitial pneumonia; OP = organizing pneumonia.

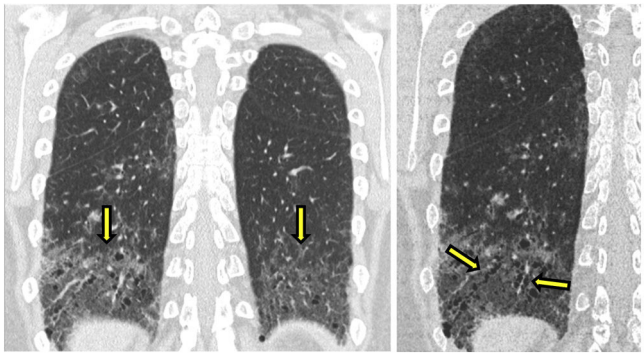

Fig. 4 – (A) Fibrotic NSIP with lower bilateral ground-glass opacities (arrows) and (B) multiple traction bronchiectasis (arrows).

disease.[105] HRCT is also useful for the assessment of disease progression. Several studies demonstrated that patients with UIP pattern tend to have worst survival in comparison with patients with NSIP pattern.[98]

Prognosis and risk factors

While the ILD pattern on HRCT is useful for diagnosis, and there is a trend for shorter survival in patients with UIP pattern compared to those with an NSIP pattern,[98] the utility of assessing SSc-ILD prognosis on the basis of pattern alone is limited. In contrast, to HRCT patterns, fibrotic findings have been correlated with mortality in SSc. A recent study of the Norwegian nationwide SSc cohort found an association between the presence of fibrosis and mortality.[90] We can find fibrotic features in 55–65% of all patients with SSc and in up to 96% of those with abnormal pulmonary function test (PFT) results.[99]

The extent of parenchymal involvement on HRCT is an important outcome measure. Several studies analyzed the visual scoring of lung fibrosis extent and demonstrated that more extensive ILD (>20% of lung tissue involved) was associated with decreased survival.[83,106] Subsequently, numerous studies have demonstrated a significant correlation between the progression of ILD extent on HRCT scan over time and the decline of predicted DLCO, but only a trend for FVC.[107–109] However, there is a low degree of agreement on the quantification of the ILD extent among expert radiologists.

Recently, the use of quantitative CT (QCT) methods have been evaluated to improve diagnostic accuracy, and several studies have shown them to be a powerful tool in the evaluation of connective tissue-related ILD and specifically scleroderma-related ILD.[110] Different quantitative analysis tools have shown to produce objective, quantifiable and reproducible assessments of disease progression and stratification. The CALIPER (Computer-Aided Lung Informatics for Pathology Evaluation and Rating) platform is a useful tool not only to quantify lung damage but also to evaluate the worsening of PFTs, as it showed that a value of ground glass $\geq$ 4.5% is predictive of DLCO worsening of 10%.[111]

The combination of pulmonary fibrosis and emphysema (CPFE syndrome) has been reported in patients with CTD-ILD.[112,113] A study including a cohort of >300 patients found a significant prevalence of emphysema in patients with SSc-ILD in both smokers and nonsmokers.[112] Emphysema was associated, for a given extent of fibrosis, with a reduction in DLCO of >10%.[112]

In SSc-ILD, the clinical course of disease varies widely from slowly progressive, or even stable disease, to severe and rapidly progressing.[114] The prognosis for patients is more closely linked to a combination of severity indicators including progressive functional decline and disease extent of lung fibrosis by HRCT, together with other clinical and laboratory variables.[84,115–117]

Careful prognostic evaluation is essential to the formulation of a management plan, including the staging of disease severity and the definition of longitudinal disease behavior (by serial imaging and PFT).[85]

Pulmonary function tests (PFTs) have been associated with an increased risk of mortality [118–120] in SSc-ILD. A *post hoc* Cox regression analysis of patients from SLS I and II showed that significant declines in FVC (≥10% predicted) or DLCO (≥15% predicted) over 24 months were strong prognosis factors as predictors of mortality, even when adjusting for treatment arm and baseline disease severity.[121] PFT was added to the to the Outcome Measures in Rheumatology (OMERACT) definition of progression of CTD-ILD. A clinically meaningful progression was defined as: ≥10% relative decline in %FVC predicted or 5–10% relative decline in %FVC and ≥15% relative decline in %DLCO predicted.[122]

Additional risk factors for worse prognosis of SSc-ILD include demographic (male sex, older age, African American race, smoking habits) and clinical involvements (absence or presence of respiratory symptoms, arthritis, diffuse SSc subtype with elevated Rodnan skin score, gastro-esophageal reflux disease, pulmonary hypertension), specific antibodies (anti-Scl70 and RNA-polIII) and circulating biomarkers such as elevated C-reactive protein.[93,121–124] The skin is almost always involved in systemic sclerosis, and several studies have shown that there is an increased risk of ILD and progression of ILD-SSc in presence of diffuse skin involvement.[93,120,125–127] On the other hand, the presence of anti-centromere antibodies decreases the likelihood to develop ILD.[105,128]

Gastro-esophageal reflux (GERD) is another clinical manifestation recognized as a potential risk impairing lung function in SSc-ILD.[129,130]

Circulating biomarkers have long been associated with the presence and development of SSc-ILD, but their potential to classify ILD and to predict the clinical course of the disease is to date conflicting and their use is not yet validated for management of SSc-ILD in clinical practice.[93,105] Currently, Krebs von der Lungen-6 serum level (sKL-6) is considered to be one of the most reliable biomarkers for diagnosis, prognosis and prediction of therapeutic responsiveness of SSc-ILD. In SSc-ILD, sKL-6 has been found to be negatively correlated with pulmonary function and positively correlated with radiological extent of lung fibrosis.[131] Furthermore, sKL-6 > 1000 U/mL was associated with increased mortality at 5 years of follow-up.[132] The serum values for surfactant protein-A (SP-A) and D (SP-D) have been associated with the extent of damage to the capillary/alveolar barrier, but their diagnostic and prognostic value in SSc-ILD is still controversial.[133] SP-A is known to have lower sensitivity and specificity than SP-D. SP-D appeared to be a strong biomarker for diagnosis.[131] It also is associated with severity of SSc-ILD,[134] correlating significantly with fibrosis scores on HRCT but not with ground-glass opacities.[131] Another promising biomarker for activity and severity of SSc-ILD is the serum level of CCL18 (Pulmonary and Activation Regulated Chemokine (PARC)), which was found to be a predictor of mortality and progression.[135,136] A large prospective trial with 427 patients with SSc-ILD showed that sCCL18 > 85 pg/mL and male sex were the best predictors of functional decline,[131] although the association with mortality was unclear.

Unmet needs and prediction models

Personalized medicine and a multidisciplinary approach are essential to stage the severity of the disease and to determine the likelihood of progression. The current evidence from observational cohorts suggest that only 20–30% of patients with SSc-ILD will develop a progressive disease course.[137–139] Accurately assessing and defining progression in SSc-ILD could help identify patients at risk. Accordingly, different composite grading systems for screening and prognosis of ILD in SSc have been proposed. Goh et al. developed an algorithm in order to classify patients based on the extent of disease[83] integrating HRCT observations and FVC values from PFTs. Extensive disease was defined as: >20% lung involvement on HRCT or 10–20% lung involvement on HRCT and FVC < 70% predicted. On the other hand, limited disease was defined as: ≤10% lung involvement on HRCT, or 10–20% lung involvement on HRCT and FVC ≥ 70% predicted. This prognostic algorithm has been validated as a predictor of mortality. There is an approximately a three-fold increased risk of death and clinical decline (defined as need for supplemental oxygen or lung transplantation) in patients with SSc-ILD how have extensive disease compared to those with limited disease.[118–120]

The SPAR model was suggested in 2018 as a useful composite staging system to predict ILD progression by combining SpO_2 after 6MWT (6-minute walk test) and the presence of arthritis (defined as one or more tender and swollen joints as judged by the treating physician).[140] Wu et al. developed this model by using two independent prospective cohorts of patients who met 2013 ACR/EULAR Classification Criteria for SSc and had mild ILD (<20% lung involvement) assessed by HRCT at baseline. It defined ILD progression as a decrease in FVC ≥ 15% or ≥10% combined with a decrease in DLCO ≥ 15% at 1-year follow-up. In their multivariate analysis, declines in SpO_2 after 6MWT and arthritis were identified in both cohorts as independent predictors of ILD progression, with an optimal SpO_2 cut-off value of 94% by receiver–operator characteristic analysis. A latter observational study demonstrated that the SPAR model increased the prediction success rate for ILD progression to 91.7% among patients who fulfilled criteria for both the $SpO_2 \leq 94\%$ after 6MWT and arthritis.

Another validated prediction model for mortality risk in SSc-ILD is the smoking history, age, and DLCO (SADL) model, which was developed by using two independent prospective cohorts of patients meeting 2013 ACR/EULAR Criteria for ILD. The three abovementioned variables were included in the final risk prediction model to create a point scoring system used to identify a classification with low, moderate or high mortality risk at Three years from ILD diagnosis.[141]

Including simple commonly used variables facilitates the use of these composite-staging systems, which can be useful tools in clinical practice, even though further validation is required.

Progressive pulmonary fibrosis

Recently, progressive pulmonary fibrosis (PPF), also referred to as progressive fibrosing ILDs (PF-ILD), was recognized as a

Table 2 – Definition of progressive pulmonary fibrosis.

In a patient with ILD of known or unknown etiology other than IPF who has radiological evidence of pulmonary fibrosis, PFF is defined as at least two of the following three criteria occurring within the past year with no alternative explanation[a]:

1. Worsening respiratory symptoms
2. Physiological evidence of disease progression (either of the following):
   a. Absolute decline in FVC ≥ 5% predicted within 1 year of follow-up
   b. Absolute decline in DLCO (corrected for Hb) ≥ 10% predicted within 1 year of follow-up
3. Radiological evidence of disease progression (one or more of the following):
   a. Increased extent or severity of traction bronchiectasis and bronchiolectasis
   b. New ground-glass opacity with traction bronchiectasis
   c. New fine reticulation
   d. Increased extent or increased coarseness of reticular abnormality
   e. New or increased honeycombing
   f. Increased lobar volume loss

Definition of abbreviations: ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; PPF = progressive pulmonary fibrosis; Hb = hemoglobin.

[a] Although it is critical to exclude alternative explanations of worsening features for all patients with suspected progression, that is particularly important in patients with worsening respiratory symptoms and/or decline in DLCO given the lower specificity of these features for PPF compared with FVC and chest computed tomography.

distinct clinical entity[101,142] by the American Thoracic Society and European Respiratory Society/ATS/ERS) in collaboration with the American College of Chest Physicians (ACCP). The established definition of PPF is shown in Table 2.[101]

Accordingly, PPF is characterized by a disease course like that of idiopathic pulmonary fibrosis (IPF), the prototype of fibrosing ILD, with rapid decline in lung function, respiratory failure, and higher infection risk due to an increased distal alveolar bacterial burden, leading to early mortality. Therefore, it is crucial to monitor the evolution of SSc-ILD, and should rely on multicompartmental assessment (physiological, clinical, and radiological assessment, together with validated biomarkers).

In addition, non-lethal complications of SSc could often be of greater importance to patients than the risk of developing a life-threatening lung manifestation and so a comprehensive, multidisciplinary long-term care plan must provide the context for management of organ-based disease. The recent European consensus statement[105] showed support for a multidimensional model of care and proposed an algorithm to provide clinical guidance for the identification and management of SSc-ILD, assessing ILD severity by using multiple methods (HRCT, FVC and DLCO, exercise-induced blood oxygen desaturation, clinical symptoms, and quality of life).

Conclusions

In SSc, the early identification of ILD is of paramount importance for prompt initiation of disease management strategies and therapies to slow and hopefully arrest disease evolution. Screening is pivotal and should be regularly conducted early in the SSc disease course in all patients. The gold standard for ILD diagnosis is HRCT, a technique that is associated with radiation exposure and can be burdensome to organize as well as costs. For this reason, the combination of PFTs and lung ultrasound may emerge as a viable approach that can be repeated on multiple occasions without radiation concern. Currently, conclusive diagnosis relies on HRCT with characterization of the architectural features of the lung that also point at the possible pathological pattern. In follow-up, clinical signs and symptoms as well as PFTs and HRCT are instrumental to define disease progression and shape tailored treatment for each SSc patient.

Conflict of interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary material

The Spanish translation of this article is available as supplementary material at doi:10.1016/j.rcreu.2023.09.001.

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