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Case Report

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# Systemic sclerosis-associated interstitial lung disease complicated by precapillary pulmonary hypertension: a real-world case

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## ABSTRACT

Systemic sclerosis (SSc) is a rare autoimmune disease characterized by widespread vasculopathy and progressive fibrosis. Pulmonary involvement, particularly interstitial lung disease (ILD) and pulmonary hypertension (PH), is among the leading causes of morbidity and mortality in these patients. Herein, we present a case of precapillary PH that developed following interstitial lung disease (SSc-ILD) in a patient with SSc. A 60-year-old female diagnosed with SSc in 2019 based on positive antinuclear antibody (ANA) and anti-Scl-70 antibody findings was referred to our outpatient clinic with progressively worsening exertional dyspnea. Initial evaluation revealed a marked reduction in diffusing capacity for carbon monoxide (DLCO, 24% predicted) and a cellular nonspecific interstitial pneumonia (NSIP) pattern on high-resolution computed tomography (HRCT). Over the following years, the NSIP pattern progressed from a cellular to a fibrotic phenotype, accompanied by significant clinical deterioration by 2022. As the disease progressed to the fibrotic stage and the patient was diagnosed with progressive pulmonary fibrosis, nintedanib therapy was initiated. Right heart catheterization revealed a mean pulmonary artery pressure of 39 mmHg, confirming precapillary PH and leading to a diagnosis of group 1 pulmonary arterial hypertension (PAH). Macitentan was initiated for PAH, while nintedanib, administered for ILD, had to be discontinued because of gastrointestinal intolerance. Despite partial improvement in pulmonary artery pressures, pulmonary function continued to deteriorate, with DLCO declining to 13% predicted. The patient died of cardiopulmonary arrest in 2024. The coexistence of SSc-ILD and PH represents a severe clinical phenotype associated with a poor prognosis. A progressive decline in DLCO may serve as a sensitive functional marker of the development of pulmonary vascular disease, while right heart catheterization remains the gold standard for definitive diagnosis. Early recognition and individualized management are crucial for optimizing outcomes in these complex patients.

**Keywords**: Scleroderma; systemic, lung diseases; interstitial, hypertension; pulmonary, cardiac catheterization, pulmonary diffusing capacity

## INTRODUCTION

Systemic sclerosis (SSc) is a rare chronic autoimmune connective tissue disease characterized by immune dysregulation, widespread vasculopathy, and progressive fibrosis. The disease is classified into localized and systemic forms, and in the systemic form, structural and functional abnormalities may develop in various organ systems, including the lungs, gastrointestinal system, heart, and kidneys, in addition to skin involvement. SSc most commonly occurs between 25 and 55 years of age and is approximately four times more frequent in females than in males.[1]

Pulmonary involvement is one of the most important causes of morbidity and mortality in SSc. In particular, interstitial lung disease (ILD) and pulmonary hypertension (PH), whether occurring alone or concomitantly, significantly worsen the prognosis of the disease. The pathogenesis of SSc-associated pulmonary disease involves excessive extracellular matrix deposition resulting from endothelial injury, immune activation, chronic inflammation, and fibroblast proliferation. This process leads to progressive parenchymal fibrosis, impaired diffusion in the interstitial space, and pulmonary vascular remodeling.

SSc-associated interstitial lung disease (SSc-ILD) has been reported with prevalence rates ranging from 26% to 60% in different series. The disease may develop concurrently with the diagnosis of SSc or may emerge several years after the initial diagnosis. Clinically, it most commonly manifests as progressive exertional dyspnea, dry cough, and reduced exercise capacity.

High-resolution computed tomography (HRCT) is the primary imaging modality for the diagnosis of SSc-ILD and assessment of disease extent. The most frequently observed radiological pattern is nonspecific interstitial pneumonia (NSIP), followed by the usual interstitial pneumonia (UIP) pattern. In the early stages, ground-glass opacities and increasing reticular attenuation are predominant, whereas as the disease progresses, traction bronchiectasis, volume loss, subpleural fibrosis, and honeycombing may develop.[2]

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Pulmonary function tests, particularly the diffusing capacity for carbon monoxide (DLCO), are important prognostic indicators in the assessment of the disease. A restrictive ventilatory defect is the most commonly observed functional abnormality in SSc-ILD and is characterized by reductions in FVC and DLCO. In particular, a marked decline in DLCO may be an early indicator not only of interstitial involvement but also of concomitant pulmonary vascular disease and the development of PH. From another perspective, an FVC/DLCO ratio >1.6 may represent a risk factor for PH.[3]

PH is one of the most severe and potentially fatal complications of SSc and may present as connective tissue disease-associated pulmonary arterial hypertension (group 1 PAH) or PH secondary to interstitial lung disease (group 3 PH-ILD). Differentiating these two phenotypes is critical for both treatment and prognosis. The coexistence of SSc-ILD and PH is associated with a marked reduction in exercise capacity, severe impairment in gas exchange, and decreased survival.

In this case report, we present the clinical course, diagnostic evaluation process, and long-term follow-up outcomes of precapillary PH developing in the setting of SSc-associated ILD.

## CASE REPORT

A 60-year-old woman was evaluated at the rheumatology clinic in 2019 because of Raynaud's phenomenon. Following clinical evaluation and serological investigations, she was diagnosed with SSc. On the autoimmune panel, antinuclear antibody (ANA) was positive, and the anti-Scl-70 level was >200 U/ml, whereas anti-SSA, anti-SSB, anti-Jo-1, anti-CCP, p-ANCA, and c-ANCA were negative. The serum angiotensin-converting enzyme level was within the normal range.

The patient was referred to the pulmonary diseases outpatient clinic because of exertional dyspnea. At the initial evaluation, physical examination revealed digital clubbing, tachypnea following exertion, and fine inspiratory crackles at the left lung base. Pulmonary function tests showed an $FEV_1$ of 1.54 L (67%), an $FEV_1$/FVC ratio of 86.6%, and a DLCO of 24%. The DLCO/VA value was 51%. During the six-minute walk test (6MWT), the patient was able to walk 240 meters; oxygen saturation decreased from 92% to 82%, while the Borg dyspnea score increased from 2 to 6 (**Figure 1**).

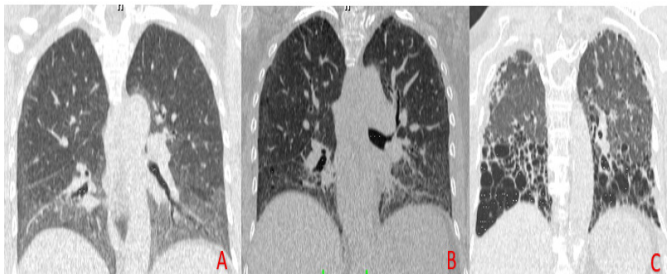



**Figure 1.** Serial coronal high-resolution computed tomography (HRCT) images showing the progression of systemic sclerosis-associated interstitial lung disease. (A) Early NSIP in 2019. (B) Progressive reticulation and traction bronchiectasis in 2022. (C) Advanced pulmonary fibrosis in 2024

HRCT: High-resolution computed tomography, NSIP: Nonspecific interstitial pneumonia

HRCT revealed a cellular NSIP pattern. Because there were no prominent fibrotic changes radiologically and the patient did not accept antifibrotic therapy, close clinical follow-up was planned. In addition to oral prednisolone and nifedipine treatments initiated by the rheumatology department, an inhaled corticosteroid/long-acting $\beta_2$-agonist combination was prescribed at the pulmonary diseases outpatient clinic.

The patient was followed at another center until 2022 and presented to our clinic again in the same year. Retrospective review of the patient's medical history and healthcare system records revealed that she had not been using her inhalers regularly, had been prescribed prednisolone frequently, and had been using colchicine. At presentation after a prolonged interval, her resting oxygen saturation was measured at 85%, and fine inspiratory crackles were now detected at both lung bases. A marked deterioration was observed in pulmonary function tests; $FEV_1$ was 1.02 L (49%), DLCO was 17%, and DLCO/VA was 42%. During the six-minute walk test, the distance she was able to walk had decreased to 185 meters, oxygen saturation decreased from 87% to 75%, and the Borg dyspnea score increased from 3 to 9. She was classified as World Health Organization (WHO) Functional Class III.

Because of the clinical and functional deterioration, the patient was hospitalized for further investigation, treatment, and evaluation. Transthoracic echocardiography revealed a systolic pulmonary artery pressure (sPAP) of 52 mmHg. Considering that the underlying connective tissue disease represented a significant risk factor for PH, right heart catheterization was performed. Hemodynamic assessment revealed a mean pulmonary artery pressure of 39 mmHg, a pulmonary capillary wedge pressure of 5 mmHg, a pulmonary vascular resistance of 6 Wood units, and a cardiac output of 4.3 L/min. A vasoreactivity test with adenosine (the agent available at our hospital) was negative. Based on these findings, the patient was diagnosed with SSc-associated precapillary PAH (group 1 PAH).

On the basis of her clinical status, the patient was classified as high risk according to the PAH risk assessment, and macitentan was initiated for the treatment of PH. In addition, because of clinical, functional, and radiological progression, the patient agreed to antifibrotic therapy, and nintedanib 150 mg twice daily was added to the treatment regimen. Although antifibrotic therapies are currently reimbursed (in Turkiye) for SSc-ILD patients with a diagnosis of progressive pulmonary fibrosis, our patient did not meet the criteria of FVC >50% and DLCO >30%, which were among the main application criteria at the time of presentation. An application was therefore submitted for off-label use of antifibrotic therapy, and treatment could be initiated after approval was obtained. In addition, following a rheumatology consultation requested during hospitalization, mycophenolate mofetil was added to the treatment, and prednisolone and nifedipine were continued.

At the three-month follow-up, the patient was found to have developed significant gastrointestinal adverse effects and dyspeptic symptoms. During the same period, pulmonary function tests continued to deteriorate ($FEV_1$ 37%, DLCO 16%, DLCO/VA 38%), and antifibrotic therapy was discontinued because the patient did not wish to continue treatment. Nevertheless, partial improvement in the severity of dyspnea was reported, and follow-up echocardiography

showed that the sPAP had decreased to 28 mmHg. On the 6-minute walk test, she walked 200 meters, with oxygen saturation decreasing from 86% at baseline to 77% at the end of the test. The Borg dyspnea score was 4 at baseline and 7 at the end of the test (**Figure 2**).

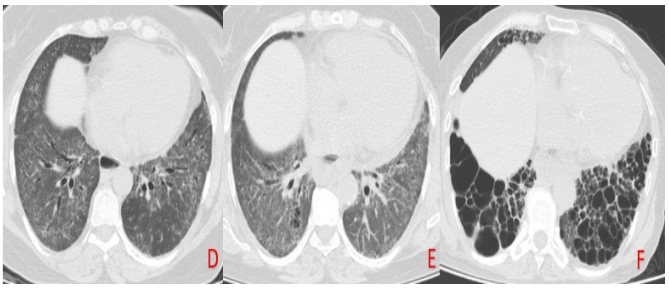



**Figure 2.** Serial axial HRCT images demonstrating disease progression. (D) Ground-glass opacities in 2019. (E) Increasing reticulation and traction bronchiectasis in 2022. (F) Extensive fibrotic changes and honeycombing in 2024

HRCT: High-resolution computed tomography

During the COVID-19 pandemic, the patient's regular follow-up was disrupted, and she was reassessed approximately two years later, in 2024. At presentation, she was using a wheelchair and receiving oxygen support. Oxygen saturation measured on room air was 72%. Physical examination revealed bilateral diffuse inspiratory crackles, decreased breath sounds in the upper lung zones, and a prominent scleroderma facies with marked skin involvement. Pulmonary function tests demonstrated severe restrictive ventilatory impairment and severe diffusion impairment; $FEV_1$ was 0.57 L (31%), DLCO was 13%, and DLCO/VA was 24%. Follow-up echocardiography revealed an sPAP of 22 mmHg.

The patient was scheduled for another follow-up visit three months later; however, she did not attend the appointment. Information later obtained from another medical center indicated that she had died of cardiopulmonary arrest.

## DISCUSSION

SSc is a connective tissue disease characterized by widespread vasculopathy and systemic involvement, with a higher prevalence among women. Pulmonary involvement, particularly ILD and PH, is the major cause of morbidity and mortality in these patients. Despite advances in current treatment options, SSc-ILD remains one of the most important organ manifestations determining survival. The prevalence of SSc-ILD has been reported to range from 26% to 60% in the literature, reflecting the clinical and radiological heterogeneity of the disease.[4]

The present case is noteworthy in demonstrating the progressive nature of SSc-associated ILD over time and the accompanying pulmonary vascular involvement. In our patient, radiological findings initially consistent with a cellular NSIP pattern were observed, while the presence of traction bronchiectasis, one of the important findings indicating progression to the fibrotic stage, also suggested a progressive disease course. During follow-up, both functional and clinical deterioration occurred. The radiological progression observed in our case supports the transition of the disease from an inflammatory phase to a fibrotic phase.[5] Antifibrotic therapy was planned at the time of initial diagnosis based on the pulmonary function tests, DLCO, and radiological findings; however, the patient did not accept the treatment.

The most striking feature of this case was the development of PH accompanied by a marked and progressive decline in diffusion capacity. In patients with SSc, a reduced DLCO may reflect not only interstitial lung involvement but also pulmonary vascular disease. In particular, disproportionately reduced DLCO values relative to the decline in FVC are considered suggestive of concomitant PH. In a study conducted by Sakayori et al.,[3] an FVC/DLCO ratio >1.6 was reported to be an early predictive marker for PH. In our patient, an FVC of 66%, a DLCO of 24%, and an FVC/DLCO ratio of 2.75 at the time of diagnosis, together with a low DLCO and a high DLCO/VA, may be considered important markers of PH. The decline in DLCO from 24% at the time of diagnosis to 13% during follow-up demonstrates the progressive nature of pulmonary vascular disease. Indeed, right heart catheterization performed following the echocardiographic findings revealed a mean pulmonary artery pressure of 39 mmHg, a pulmonary capillary wedge pressure of 5 mmHg, and a pulmonary vascular resistance of 6 Wood units; these findings confirmed the diagnosis of SSc-associated precapillary PH.[6]

In SSc, PH may present as connective tissue disease-associated PAH (group 1 PAH) or PH secondary to ILD (group 3 PH-ILD).[7,8] Differentiation between these two clinical phenotypes is of great prognostic and therapeutic importance. Current guidelines and reviews emphasize that right heart catheterization is the diagnostic gold standard in patients with SSc when PH is suspected.[6] The hemodynamic findings obtained in our case indicated that the patient could be classified as having a group 1 precapillary PH phenotype.

From a therapeutic perspective, immunomodulatory and antifibrotic therapies constitute the main treatment approaches for SSc-ILD. The Scleroderma Lung Study II reported that mycophenolate mofetil demonstrated similar efficacy to cyclophosphamide but was better tolerated. In addition, the SENSCIS study demonstrated that nintedanib significantly reduced the annual rate of decline in FVC.[9,10] Although nintedanib therapy was initiated in our patient because of progressive functional loss, treatment could not be maintained due to gastrointestinal adverse effects, treatment non-adherence, and continued progression in pulmonary function tests. Antifibrotic therapy, which had been planned to be initiated in 2019 when early findings of fibrotic NSIP were already present, could only be initiated in 2022 because of patient non-adherence. The advanced degree of fibrosis at the time treatment was initiated, together with the increased loss in pulmonary function and DLCO, probably contributed to the lack of response to treatment. From this perspective, when criteria for progressive pulmonary fibrosis are present in patients with SSc-ILD, initiating antifibrotic therapy without delay is important to slow the progression of the disease. Although improvement in echocardiographic parameters was observed following the initiation of macitentan for the treatment of PH, the overall course of the disease remained progressive.[11]

This case demonstrates the importance of regular functional monitoring in SSc-associated ILD and, in particular, careful

assessment of changes in DLCO. It also emphasizes that echocardiographic evaluation and, when necessary, right heart catheterization should be performed without delay to enable early recognition of PH. Factors such as treatment non-adherence, interruptions in follow-up, and presentation at an advanced stage may also adversely affect the prognosis of the disease.[12]

## CONCLUSION

PH accompanying SSc-associated ILD represents a severe clinical phenotype associated with significant functional limitation and increased mortality. This case demonstrates that a progressive decline in DLCO may be an important warning marker for pulmonary vascular disease and that right heart catheterization plays a critical role in the diagnostic process. Early diagnosis, regular functional follow-up, close monitoring for PH, and individualized treatment strategies are of fundamental importance for improving clinical outcomes in this patient population.

## ETHICAL DECLARATIONS

### Informed Consent

Written informed consent was obtained from the patient included in this report. Signed consent forms are retained by the author and are available upon request.

### Peer Review Process

This report underwent external peer review.

### Conflict of Interest

The author declares no conflicts of interest.

### Financial Disclosure

This case report did not receive any financial support.

### Author Contributions

The author is solely responsible for the entirety of conception, execution, analysis, and writing of the manuscript.

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