

INTERSTITIAL LUNG DISEASE IN SYSTEMIC SCLEROSISPuji Astuti Tri K¹, Anak Agung Arie¹, Cleopas Martin Rumende², Zulkifli Amin²¹Internal Medicine Department, Cipto Mangunkusumo National General Hospital-Faculty of Medicine, Universitas Indonesia²Division of Respiriology and Critical Care, Internal Medicine Department, Cipto Mangunkusumo National General Hospital-Faculty of Medicine, Universitas Indonesia**ABSTRACT**

Systemic sclerosis (SSc) atau sklerosis sistemik adalah kelainan jaringan ikat yang ditandai dengan disfungsi sistem imun, kerusakan mikrovaskular dan fibrosis. Systemic sclerosis melibatkan multiorgan, terutama paru, yaitu sebesar 90% pasien dengan SSc. Interstitial lung disease (ILD) atau penyakit paru intersisial merupakan komplikasi tersering pada SSc dan menyebabkan angka kematian yang tinggi. Penanganan kasus ILD pada SSc pada dasarnya sesuai dengan perjalanan skleroderma. Kami melaporkan sebuah kasus dari pasien perempuan 59 tahun, dengan keluhan luka menghitam pada ujung jari manis kirinya yang disertai dengan hilangnya segmen distal jari tersebut, serta batuk berdahak putih dengan sesak nafas yang memberat bila beraktivitas. Pemeriksaan fisik menunjukkan manifestasi skleroderma disertai dengan penyakit paru intersisial. Dalam perjalanannya, keluhan semakin memberat sehingga pasien mendapatkan terapi immunosupresan dan terapi suportif.

Kata kunci: sklerosis sistemik, penyakit paru intersisial

ABSTRACT

Systemic sclerosis (SSc) is a chronic tissue disorder characterized by immune dysfunction, microvascular injury, and fibrosis. Many organs involved in patients with SSc; especially, pulmonary involvement occurs in up to 90% of patients with SSc. Interstitial lung disease (ILD) is a major complication in SSc and causing high mortality rate. The SSc-ILD therapy is basically consistent with the progress of scleroderma pathophysiology. We reported a case of 59-years-old female patient with a blackened ulcer on her left hand ring finger with disappearing of her distal finger segment, and also a chronic white phlegm cough followed by dyspnea in exertion. Clinical examination and evaluation showed that she had a scleroderm, accompanied with ILD. Her complaint did not improve, so she got an immunosuppressant and supportive therapy to control her worsening disease.

Keywords: systemic sclerosis, interstitial lung disease

manifest in SSC are Interstitial Lung Disease (ILD) and pulmonary hypertension. Both of them cause high mortality rates in SSC, 33% and 28% of death respectively.^{2,3} Prevalence of SSc in the US is 50-300 cases per 1 million inhabitants, with 90% of cases diagnosed with ILD. The 5 years survival rate was 84,1% and 74,9% in 10 years.⁴ The incidence of SSc-associated ILD (SSc-ILD) mostly occurs in women aged 30 to 55 years.⁵

The clinical manifestations of SSc-ILD are difficult to distinguish from idiopathic pulmonary High Resolution CT (HRCT) scan fibrosis or other lung diseases.⁵ The most sensitive investigation to detect ILD is by means of High Resolution CT (HRCT) scan, with a ground glass appearance as primary feature. The SSc-ILD therapy is basically consistent with the progress of scleroderma pathophysiology.

INTRODUCTION

Systemic Sclerosis (SSc) is a chronic connective tissue disorder involving many organs, with a variety of manifestations and often leads to disability and mortality. SSc is also characterized by an inflammatory process, followed by functional and structural impairment of the blood vessels to the visceral organ, then continued with fibrosis.¹

Lung disease is the most common complication of SSc. About 80% of patients with SSc have lung disease, especially fibrotic lung disease, and is the most common cause of death in SSc patients (33%). Fibrotic lung diseases that

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Systemic sclerosis (SSc) is a chronic tissue disorder characterized by immune dysfunction, microvascular injury, and fibrosis. Many organs involved in patients with SSc; especially, pulmonary involvement occurs in up to 90% of patients with SSc. Interstitial lung disease (ILD) is a major complication in SSc and causing high mortality rate. The SSc-ILD therapy is basically consistent with the progress of scleroderma pathophysiology. We reported a case of 59-years-old female patient with a blackened ulcer on her left hand ring finger with disappearing of her distal finger segment, and also a chronic white phlegm cough followed by dyspnea in exertion. Clinical examination and evaluation showed that she had a scleroderm, accompanied with ILD. Her complaint did not improve, so she got an immunosuppressant and supportive therapy to control her worsening disease.

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INTRODUCTION

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Lung disease is the most common complication of SSc. About 80% of patients with SSc have lung disease, especially fibrotic lung disease, and is the most common cause of death in SSc patients (33%). Fibrotic lung diseases that manifest in SSC are Interstitial Lung Disease (ILD) and pulmonary hypertension. Both of them cause high mortality rates in SSC, 33% and 28% of death respectively.^{2,3}

Prevalence of SSc in the US is 50-300 cases per 1 million inhabitants, with

90% of cases diagnosed with ILD. The 5 years survival rate was 84,1% and 74,9% in 10 years.⁴ The incidence of SSc-associated ILD (SSc-ILD) mostly occurs in women aged 30 to 55 years.⁵

The clinical manifestations of SSc-ILD are difficult to distinguish from idiopathic pulmonary High Resolution CT (HRCT) scan fibrosis or other lung diseases.⁵ The most sensitive investigation to detect ILD is by means of High Resolution CT (HRCT) scan, with a ground glass appearance as primary feature. The SSc-ILD therapy is basically consistent with the progress of scleroderma pathophysiology.

CASE ILLUSTRATION

A 59-years-old female patient admitted to the hospital with a blackened ulcer on her left hand ring finger since 3

weeks before arrival to hospital, accompanied with swelling, redness, pain (visual analog scale: 6), and disappearing of her distal finger segment. Patient also complained a chronic white phlegm cough followed by shortness of breath which was getting more cumbersome. The patient felt nauseated and bloated. There was no fever complained. Such complaints often recur since 3 years ago, accompanied by tightness on the forehead and around the mouth. There were no other diseases histories. She was hemodynamically stable with peripheral oxygen saturation 98% on room air.

Physical examination showed fibrosis in the forehead and around the mouth. From chest auscultation, a basilar

crackle was obtained. There were also atrophy, gangrene, and auto amputation the tip of the thumb of both hands.

From the laboratories, there was a mild leucocytosis ($12.800/\text{mm}^3$). ANA test resulted a positive, 1/1000 homogenous titer with rough speckled pattern. Chest radiography showed a cardiomegaly with aortic calcification and reticular infiltrates in both lungs (Fig.1). Spirometry test showed restrictive results, and failure peripheral airway with FVC 44,1%, FEV1 42,9%. The chest CT scan showed ground glass appearance, with aortic calcification and dilatation along the thoracic esophagus to the esophagogastric junction (Fig.2).

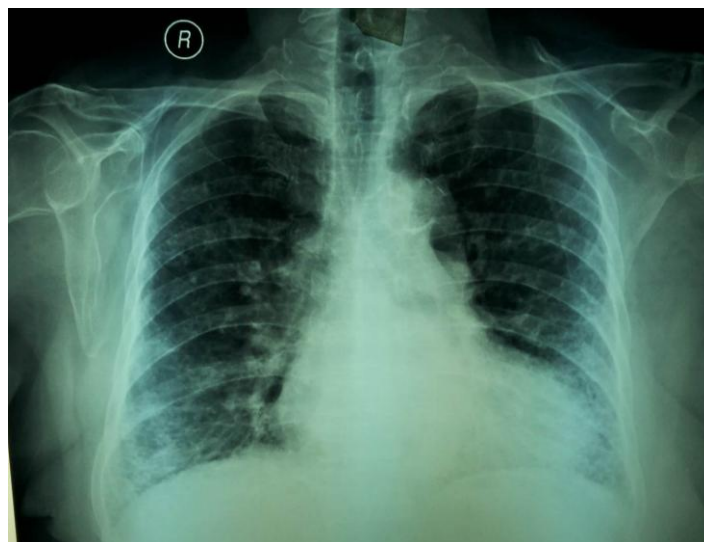


Figure 1. Chest radiography showing with aortic calcification and reticular infiltrates in both lungs

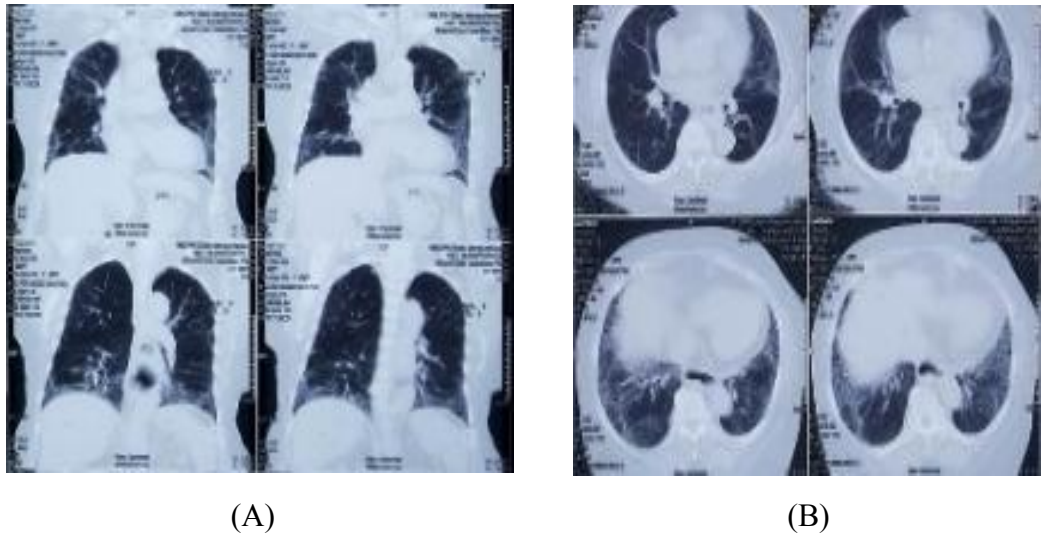


Figure 2. High resolution computed tomography (HRCT) scan of the chest showed ground glass appearance in (A). Coronal view, (B). Axial view

During treatment, the complaints of cough and dyspnea worsened. She then treated with targeted dose of unfractionated heparin, antiplatelet, nifedipin, and beraprost for her digital ulcer. For the SSc-ILD, she got mycophenolate mofetil, and morphine sulphate for her pain treatment.

DISCUSSION

SSc is characterized by three mechanisms, such as vasculopathy of small blood vessels, autoantibody formation, and fibroblast dysfunction that increase the deposit of extracellular matrix.⁶ The initial stage is inflammation, then it involves the blood vessel tissue's structure and function, and progressively lead to visceral organ dysfunction due to fibrosis.¹

Table 1. The American College of Rheumatology / European League Against Rheumatism Collaborative Initiative 2013 Criteria for the classification of systemic sclerosis⁶

Item	Sub-item(s)	Weight/score
Skin thickening of the fingers of both hands - extending proximal to the metacarpophalangeal joints (<i>sufficient criterion</i>)		9
Skin thickening of the fingers (<i>only count the</i>	Puffy finger	2

<i>higher score)</i>	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions (<i>only count the higher score</i>)	Digital tip ulcers	2
	Fingertip pitting scras	3
Telangiectasia	-	2
Abnormal nailfold capillaries	-	2
Pulmonary arterial hypertension and/or interstitial lung disease (<i>max score: 2</i>)	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon	-	3
SSc-related autoantibodies (anticentromere, anti-topoisomerase I (anti Scl-70), anti RNA polymerase III) (<i>maximum score:3</i>)	Anticentromere	3
	Anti-topoisomerase I	
	Anti-RNA polymerase III	

In this case, there was a thickening of the skin of the fingers of both hands up to the metacarpophalangeal joint (9 points), finger swelling (4 points), fingertip ulcers (2 points), nail abnormalities (2 points), interstitial lung disease (2 points) and Raynaud's phenomenon (3 points). With a total of 22 points, the diagnosis of SSc in this patient was upright.

ILD is very common (90% of cases in SSC) and is the leading cause of death in SSc. It occurs interstitial tissue abnormalities of the lung parenchyma. Early ILD enforcement helps to improve the prognosis of SSc.^{1,3} The pathogenesis of SSc-ILD is not yet fully understood. There are three mechanisms of SSc-ILD; 1. Repeated and persistent endothelial cell damage, 2. Activation of the natural and adaptive immune system, 3. Activation of fibroblasts, resulting from injury and accumulation of extracellular matrix.⁷

The epithelial or endothelial cell death is known to be a major cause of SSc-ILD. It causes necrosis, apoptosis,

pyroptosis, activation of the coagulation pathway, and inducing the expression of $\alpha v \beta 6$ epithelial integrins, then activating TGF β , which ultimately activates the response immune to fibrosis. Another mechanism is immune system dysregulation, imbalance and dysfunction of T cell in the circulation and bronchoalveolar fluid. Increased T cells (Th17 and Th22) in the circulation cause pulmonary fibrosis. Activation of myofibroblasts also play a role in pulmonary fibrosis.^{8,9,10}

The SSc-ILD manifestations are characterized by dyspnea on exertion and may be accompanied with a non-productive cough and inspiratory fine crackles at the bilateral basilar area on auscultation, supported by typical SSc symptoms. However, crackles usually can not be detected at the beginning of symptoms. A SSc-ILD patients have positive antinuclear antibody (ANA) results, anti-Scl 70, anti-topoisomerase I (anti-Topo I) and anti-Th / To, and anti-centromere antibodies.¹¹

Chest X-rays showed reticular marking, but the sensitivity and

specificity are low in detecting parenchymal abnormalities. High Resolution CT (HRCT) scan was a major radiological examination for this case, with non-specific interstitial pneumonia (NSIP) appearance. At the beginning of the disease, there was a 'ground glass opacities' in the peripheral region of the lung, then progress into a reticular and honeycomb feature on the pulmonary basal. High Resolution CT (HRCT) scan also could determine ILD prognosis. Pulmonary involvement increases more than 20% of mortality rate.¹²

Pulmonary function tests also very important in determining the severity SSc-ILD. On spirometry test showed restrictive pattern with decreased forced expiratory volume in 1 sec (FEV1) and forced vital capacity (FVC), as well as a normal or slightly increased FEV1/FVC ratio, due to parenchymal damage.¹³

Inflammatory cells and other inflammation mediators (neutrophil and eosinophil, and may be lymphocytes and mast cells) were present in the bronchoalveolar lavage (BAL) fluid of patients with SSc-ILD, reflecting ongoing inflammation in the lungs. In histopathology, a nonspecific interstitial pneumonitis (NSIP) is the most common histological finding. Fewer than 20% of patients with SSc-ILD showed inflammation-dominant lesions at lung biopsy.^{2,12}

Inflammation and fibrosis are the main mechanisms of ILD in SSC. Inflammation is a reversible phase, so the treatment could be given in this

phase. But, in the event of pulmonary fibrosis, which most patients had, there is no specific treatment to overcome it. Therefore, the prevention of disease progression becomes the main goal of therapy.¹⁴

Cyclophosphamide is used as an induction regimen. Oral administration of 2 mg/kg/day for 12 months, and 600 mg/m²/month, intravenous for 6 months, coupled with oral prednisolone 20 mg alternate, followed by azathioprine 2,5 mg/kg/day could reduce or prevent the progresivity. Cyclophosphamide is indicated for severe fibrosis for slowing the process.¹⁵ During the treatment, the short-term side effects such as leukopenia and infection, and a long-term side effects such as infertility, carcinogenesis, and toxic to bone marrow could be happen. The intermittent intravenous administration could reduce the risk of side-effects. It is recommended the use of intravenous cyclophosphamide pulse dose (1g / m² for 6-12 months). The dosage and duration of therapy may be adjusted by age and comorbid factors.¹⁴

Mycophenolate mofetil (MMF) is a lymphocyte proliferation inhibitor. The performance of MMF versus cyclophosphamide is still under study by SLS II (Scleroderma Lung Study II). In a prospective observational one-year study of 14 patients who took MMF (720 mg bid for 12 months, except for the first week of treatment [360 mg bid]) plus 5 mg/day PSL), six patients experienced at least a 10% improvement in their FVC and five patients' pulmonary function remained stable. MMF is commonly used as

maintenance therapy after cyclophosphamide.¹⁶

The use of azathioprine is not recommended as an induction therapy, but rather as a maintenance therapy after cyclophosphamide.¹⁴ Corticosteroids are not suggested as monotherapy, but in combination with cyclophosphamide (initial dose 500 mg/m² followed by 750 mg/m² for 1 month later, monthly for 6 months, then every 2 months until 12 months, combined with high doses (prednisolone) 1 mg/kgBB/day for 4 weeks then decreased 5 mg/day, alternate for 2 weeks).¹⁷

Rituximab is a monoclonal antibody that works directly against CD20 antigen on the surface of B lymphocytes. *Daoussis et al.* randomly piloted studies of 14 diffuse type cutaneous scleroderma patients with rituximab plus standard therapy and standard single therapy. Rituximab is given in 2 cycles (as a baseline and repeated 24 weeks later). One cycle consists of administering intravenous every week for 4 weeks (375 mg/m²/week). After one year, patients given rituximab showed improvement in FVC, DLCO, and Rodnan skin scores on scleroderma.¹⁸

Tyrosine kinase inhibitor, imatinib mesilate, works by blocking the pro-fibrotic agent c-Abl kinase (as a TGF- β inhibitor). In the few existing studies, patients who received imatinib 200 mg/day provided good results,

while the dose of 600 mg/day did not provide lung function improvement.¹⁴

A study by *Levy, et al.* in 3 cases, obtained one of the three patients had mild restrictive lung disease and then recovered after getting a dose immunoglobulin therapy a total of 56 g. Gived intravenous immunoglobulin (2 g / kg for 5 days, 1 cycle per month) also provide efficacy against percutaneous deployment in case of SSC. However, the benefits of the process of lung fibrosis in ILD until now have not obtain enough data.¹⁹

According to a randomized, multicentre study conducted by the *Autologus Stem Cell Transplantation International Scleroderma Trial (ASTIS)*, which compared hematopoetic stem cell transplantation (HSCT) with cyclophosphamide (monthly administration) in 156 dcSSc patients, showed an increase in FVC and total lung capacity at 1 year of HSCT use.¹³

Lung transplantation is the last therapeutic option in case of SSc-ILD who did not respond to medical, or in severe ILD. However, SSC is a poor candidate for transplantation due to its numerous comorbidities, such as gastrointestinal reflux, dysmotility, decreased renal function (creatinine clearance <50 mL/min/1,73 m²), ulceration of the skin, and arrhythmia. Transplant contraindications include untreated organ failure, extrapulmonary infections, malignancy (less than 2 years), active smokers, psychological disorders, chest and

spine deformities, neuromuscular degenerative disease, and body mass index less than $<15\text{kg/m}^2$. A one year mortality rate in SSc bilateral lung transplantation patient was 6,6% and 13,6% in patients with lung fibrosis.²⁰

CONCLUSION

Systemic sclerosis (SSc) involves multiple organs and has many clinical manifestations. The most frequent organ involvement in SSc is the lung, manifesting as interstitial lung disease, which leads to lung fibrosis. The mechanism of SSc-ILD has been known as a result of immune-mediated epithelial and or endothelial cell death.

The enforcement of ILD diagnosis as early as possible provides a better prognosis and could prevent the disease get worsening. It is not only necessary to get an early diagnosis, but also to define the severity of the disease and to predict prognosis. The risk factors of every patients should be checked. The earlier we know the severity, the earlier we start the treatment, so that the better prognosis we might get.

An easy way to diagnose SSc-ILD is by chest high resolution computed tomography (HRCT) scan. Patients should be re-evaluated regularly in order to define if remission has been reached and therapy should be modified if needed. Cyclophosphamide is the initial choice of therapy for the induction phase in SSc-ILD. However, other therapeutic agents options may be used, although

the effectiveness of each drug remains in the continuous evaluation.

REFERENCES

1. King TE. In: Longo D.L, Kasper D.L, Jameson J.L et al. Harrison's principles of internal medicine volume 1. 19th Ed. New York: The McGraw-Hill Companies, Inc; 2015. p 1708-715.
2. Scholand MB, Carr E, Frech T, et al. Interstitial lung disease in systemic sclerosis: diagnosis and management: review article. *Rheumatology* 2012: 1-5.
3. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. *Ann Rheum Dis* 2007; 66:940-944.
4. Walker UA, Tyndall A, Czirják L, et al. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database.

- Ann Rheum Dis 2007; 66: 754–763.
5. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al, on behalf of the ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement : idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011;183:788–824.
 6. Hoogen FV, Khanna D, Fransen J, et. Al. 2013 classification criteria for systemic sclerosis. *Am Col Rheum* 2013: 1-10.
 7. Massagué J, Gomis RR. The logic of TGF- β signaling. *FEBS Lett* 2006; 508: 2811–2820.
 8. Blackwell TS, Tager AM, Borok Z, Moore BB, Schwartz DA, Anstrom KJ, et al. Future directions in idiopathic pulmonary fibrosis research: an NHLBI workshop report. *Am J Respir Crit Care Med* 2014;189:214–22.
 9. Radstake TR, van Bon L, Broen J, Wenink M, Santegoets K, Deng Y, et al. Increased frequency and compromised function of Tregulatory cells in systemic sclerosis (SSc) is related to a diminished CD69 and TGF- β expression. *PLoS One* 2009;4:e5981.
 10. Hamaguchi Y. Autoantibody profiles in systemic sclerosis: predictive value for clinical evaluation and prognosis. *J Dermatol* 2010; 37: 42–53.
 11. Goh NS, Desai SR, Veeraraghavan S, Hansell DM, Copley SJ, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. *Am J Respir Crit Care Med* 2008; 177: 1248-1254.
 12. Herzog EL, Mathur A, Tager AM, et. al. Interstitial lung disease associated with systemic sclerosis and idiopathic pulmonary fibrosis. 2014; 66:1967-75.

13. Yasuoka H. Recent Treatments of Interstitial Lung Disease with Systemic Sclerosis. *Clinical Medicine Insights: Circulatory, Respiratory and Pulmonary Medicine* 2015;9(S1) 97–110.
14. Tashkin DP, Elashoff R, Clements PJ, et al; Scleroderma Lung Study Research Group. Effects of 1-year treatment with cyclophosphamide on outcomes at 2 years in scleroderma lung disease. *Am J Respir Crit Care Med*. 2007;176:1026–34.
15. Theodore AC, Tseng CH, Li N, Elashoff RM, Tashkin DP. Correlation of Cough with Disease Activity and Treatment with Cyclophosphamide in Scleroderma Interstitial Lung Disease: Findings from the Scleroderma Lung Study. *Chest*. 2011.
16. Simeón-Aznar CP, Fonollosa-Plá V, Tolosa-Vilella C, Selva-O'Callaghan A, Solans-Laqué R, Vilardell-Tarrés M. Effect of mycophenolate sodium in scleroderma-related interstitial lung disease. *Clin Rheumatol*. 2011;30:1393–8.
17. Campos DP, Del Toro ME, Casanovas AP, et al. Are high dose of prednisone necessary for treatment of interstitial lung disease in systemic sclerosis? *Reumatol Clin*. 2012;8:58–62.
18. Daoussis D, Lioussis SN, Tsamandas AC, et al. Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study. *Rheumatology* 2010; 49: 271–280.
19. Levy Y, Sherer Y, Langevitz P, et al. Skin score decrease in systemic sclerosis patients treated with intravenous immunoglobulin – a preliminary report. *Clin Rheumatol*. 2000;19:207–11.
20. Saggarr R, Khanna D, Furst DE, et al. Systemic sclerosis and bilateral lung transplantation: a single centre experience. *Eur Respir J* 2010; 36: 893–900.