

Diffuse Systemic Sclerosis with Interstitial Lung Disease and Severe Pulmonary Arterial Hypertension: A Case Report

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ABSTRACT

Systemic sclerosis is a rare connective tissue disease categorized by extensive lung fibrosis, vascular and immunologic abnormalities. Autoimmune antibodies like anticentromere, anti-Scl-70 (anti-topoisomerase I), and anti-RNA polymerase II are commonly involved in progressive disease. Clinical presentations consist of Raynaud's phenomenon, digital ulcers; pericardial effusion, and telangiectasia and are mostly associated with pulmonary complications like interstitial lung disease and pulmonary arterial hypertension. Disease-specific therapy is unavailable instead; symptomatic management is only the line of treatment. We report here a case of diffuse systemic sclerosis with interstitial lung disease and pulmonary arterial hypertension.

Keywords: Diffuse systemic sclerosis, Interstitial lung disease, Pulmonary arterial hypertension, Raynaud's phenomenon.

INTRODUCTION

Systemic sclerosis (SSc) is a systemic connective tissue disease characterized by fibrosis, vasculopathy, and immunologic abnormalities. The term sclerosis originates from the Greek word "skleros" meaning hard. Systemic sclerosis is 'scleroderma' that extends beyond the skin i.e. systemic spread of the disease. It can be classified into four types: limited cutaneous (lcSSc), diffuse cutaneous (dcSSc), systemic sclerosis sine scleroderma, and systemic sclerosis overlap. The limited cutaneous SSc involves skin thickening distal to elbows and knees, feet, and face whereas dcSSc extends proximal to elbows and knees, trunk. The primary confirmatory diagnostic feature involves skin thickening of fingers proximal to metacarpophalangeal joints. Other clinical features include fingertip lesions, telangiectasia, abnormal nail fold capillaroscopy, pulmonary arterial

hypertension (PAH), and/or interstitial lung disease (ILD), Raynaud's phenomenon (RP).

The pooled prevalence estimate in Asia is 6.8 per 100,000. Based on a study by Steen VD and Medsger TA, the incidence rate of disease ranges from 50-300 per million with female predominance, especially in the age group of 30-50 years. The leading cause of mortality associated with SSc is pulmonary complications like pulmonary fibrosis or ILD and PAH.¹ PAH and ILD both exhibit similar symptoms like fatigue, dyspnea, and exertional syncope. Various anti-fibrotic and immunosuppressive agents have been explored in randomized controlled trials, but none of the agents exhibited proven benefits in combating symptoms of PAH-SSc. Dubious management of SSc-related pulmonary manifestations has drastically increased the mortality rate by 6% to 33%.¹⁻⁴ PAH and PF are now the most commonly reported causes of death in SSc patients. ILD

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appears to be one of the major causes of death in dsSSc, whereas PAH in lcSSc.

CASE REPORT

A 34-year-old female patient was hospitalized with complaints of breathlessness and cough for 15 days. The patient was apparently alright fifteen days back, then she developed breathlessness which was insidious in onset and progressive in nature, initially aggravated on exertion, relieved on taking rest, and eventually developed dyspnoea even at rest. The cough was dry and associated with chest pain while coughing. She also had a history of bilateral cold sensations in her hands and feet. The patient was a known case of progressive systemic sclerosis for 9 years without any other comorbidities and received regular oral therapy consisting of Pentoxifylline 400 mg, Sildenafil 50 mg, and aspirin 150 mg for 3 years. The patient had no familial history. During the examination, oxygen saturation was 63% at room air, followed by blood pressure (140/90 mmHg), respiratory rate (28 cycles per minute), and heart rate (120 beats per minute). Physical examination exhibited tightness around eyelids, pallor conjunctiva, beak-like nose (Figure 1), microstomia, sclerodactyly over fingers and toes (Figure 2), secondary Raynaud's phenomenon, digital ulcers, resorption of the mandibular condyle, decreased oral aperture, rhytides, telangiectasia on the right hand, bilateral pedal edema, and acroosteolysis. Loud p2 and tachycardia were heard in the cardiovascular examination along with 2D echocardiography suggesting severe



Figure 1: Beak-like nose and microstomia.



Figure 2: Sclerodactyly over fingers.

pulmonary arterial hypertension, congested inferior vena cava, and moderate pericardial effusion. A previous report of a pulmonary function test revealed severe restrictive breathing. Currently, the High-resolution computed tomography (HRCT) report indicated non-specific interstitial pneumonia. The pathological findings included decreased hemoglobin (7 g/dL), increased erythrocytes (6.13 million/mm³), and leukocytes (11.23 K/uL) count as well as peripheral blood smear analysis concluding microcytic hypochromic anemia with neutrophilic leukocytosis. The symptomatic management was mainly focused on alleviating breathlessness which included oxygen supplementation (8-10 L/min), Budesonide nebulization (1.5 mg/day), and intravenous Dexamethasone (4 mg/day), later changed to oral Prednisolone (40 mg/day) when saturation reached stability. Intravenous iron sucrose supplementation was given and packed cell volume blood was transfused to manage iron deficiency anemia. Sildenafil (100 mg/day) was orally administered to treat severe pulmonary arterial hypertension (PAH) and Raynaud's phenomenon. Oral Pentoxifylline (1200 mg/day) along with aspirin (150 mg/day) was considered to improve digital ulcers and intermittent claudication. Intravenous Cyclophosphamide (500 mg/day) and oral Nintedanib (150 mg/day) were administered to manage interstitial lung disease with progressive skin thickening.

The patient was receiving therapy for 7 years and was non-adherent for five years. The treatment focused on relieving RP and localized scleroderma for which she received oral Nifedipine (10 mg/day) for two years, and seven cycles of Dexamethasone Pulse therapy. The patient did not turn up for four years; therefore follow-up of the disease was unavailable. Later, the patient visited the outpatient



Figure 3: Skin thickening distal elbows.

department with complaints of discoloration of fingers aggravated due to cold, thickening of the skin (Figure 3), and exertional dyspnea, suggesting progressive disease. The pulmonary function test revealed a severely restrictive breathing pattern. Drugs like Sildenafil, Aspirin, and Pentoxifylline were advised for the management, which she continued to the present. After completing ten days of hospitalization, the patient's quality of life and perception of dyspnoea was improved.

DISCUSSION

Diffuse systemic sclerosis (dcSSc) unlike linear SSc extends beyond the skin with pulmonary, gastrointestinal, and renal complications. ILD and PAH are considered to be the most common causes of mortality and present similar clinical symptoms that include dyspnea on exertion, cough, lethargy, tachycardia, and physical limitations. These symptoms were similar in this patient with grade 2 dyspnea (modified medical research council) and a 2D echocardiography report suggesting severe PAH. SSc-related antibodies like anticentromere, anti-Scl-70 (anti-topoisomerase I), and anti-RNA polymerase II are the indicators of progressive disease. Among these, the presenting case was Anti-Scl-70 positive and it is present in diffuse systemic sclerosis with interstitial lung disease.¹ HRCT analysis typically shows non-specific interstitial pneumonia (NSIP) with velcro-tearing-like crepitations followed by forced vital capacity (FVC) value <70% predicted in extensive disease, identical in our case and honeycombing was seen in bilateral

lung fields, indicative of progressive disease and cardiomegaly with pericardial effusion was also observed.¹ Gastrointestinal complication includes impaired upper GI motility followed by dysphagia, eventually leading to gastrointestinal reflux disease (GERD). The patient had complaints of dysphagia and no signs of GERD.

RP typically occurs in both localized and generalized systemic sclerosis. It is manifested by episodic pallor followed by cyanosis in distal portions of digits, triggered by cold.¹ It is distinguished into primary and secondary phenomena. The primary phenomenon is characterized by onset at a younger age, positive family history, and normal nail fold capillaroscopy whereas the secondary phenomenon occurs at an older age (except juvenile systemic sclerosis) with asymmetric finger pits and digital ulcers, positive antinuclear antibody, and abnormal nail fold capillaroscopy. The patient lived in a tropical area and manifestations like skin tightening, hyperpigmentation, puckering face, sclerodactyly, and telangiectasia were usually triggered during winters.

Clinical Pharmacist Assessment

Pharmacotherapy of dcSSc is challenging as disease-specific therapy is unavailable, therefore symptomatic clinical management is the only alternative. The revised guidelines of the European League against Rheumatism (EULAR, 2016) comprehensively discussed the treatment of systemic sclerosis. Immunosuppressive agents like methotrexate, mycophenolate mofetil (MMF), and cyclophosphamide (CYC) are employed in dcSSc. MMF (2-3g /day) is a commonly preferred drug in dcSSc-ILD whereas CYC (15 mg/kg/month or 0.6 g/m² /month) is recommended in progressive disease. Albeit, reports of CYC-induced adverse drug effects are frequent such as thrombocytopenia, haematuria, leukopenia, anemia, and pneumonia. Endothelial receptor antagonists (ERA) like Bosentan and Ambrisentan are beneficial in improving exercise capacity in PAH. Selective PDE-5 inhibitors like Sildenafil and Tadalafil or Riociguat showed similar efficacy, specifically in SSc-related PAH. The treatment of RP with dihydropyridine calcium channel antagonists like Nifedipine is proven beneficial and other drugs including Sildenafil, intravenous Iloprost, and Fluoxetine are reserved in severe RP attacks. CYC (500mg/month) was considered in the therapy over MMF due to progressive ILD. Nifedipine was discontinued due to severe dizziness; instead, Pentoxifylline was employed to treat RP.^{5,6} As ERA may complicate anemia, Sildenafil was utilized in PAH management. Alongside clinical management, pulmonary rehabilitation would aid in the improvement of health-related quality of life and exercise tolerance.⁷

CONCLUSION

There is no definitive therapy to manage systemic sclerosis effectively. A targeted organ-specific approach must be the line of treatment to avert advancement of the disease and associated complications. Pulmonary rehabilitation should be considered as a part of management to improve quality of life. Early diagnosis with HRCT and frequent pulmonary function tests are necessary to alleviate ILD manifestations. Extensive research is imperative to reduce the rates of morbidity and mortality.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

EULAR: European League against Rheumatism; **SSc:** Systemic Sclerosis; **lcSSc:** Limited Cutaneous Systemic Sclerosis; **dcSSc:** Diffuse Cutaneous Systemic Sclerosis; **ILD:** Interstitial Lung Disease; **PAH:** Pulmonary Arterial Hypertension; **RP:** Raynaud's phenomenon; **FVC:** Forced Vital Capacity; **GERD:** Gastroesophageal Reflux Disease; **HRCT:** High-Resolution Computed Tomography; **MMF:** Mycophenolate Mofetil; **CYC:** Cyclophosphamide; **ERA:** Endothelial Receptor Antagonist; **PDE-5:** Phosphodiesterase type-5.

SUMMARY

Systemic sclerosis is a rare connective disease characterized by extensive lung fibrosis, vascular and immunologic

abnormalities. Clinical presentations include Raynaud's phenomenon, digital ulcers, telangiectasia, and are most commonly associated with interstitial lung disease and pulmonary arterial hypertension. We report a case of diffuse systemic sclerosis with interstitial lung disease and pulmonary arterial hypertension in a 34-year-old female. She was admitted with complaints of breathlessness and cough with 63% saturation at room air along with digital ulcers, skin thickening distal to elbows and knees. She was a known case of progressive systemic sclerosis for 9 years and received oral therapy for the same. The treatment was approached based on European League against Rheumatism (EULAR) guidelines that included oral sildenafil, Pentoxifylline, and Cyclophosphamide. After completing ten days of hospitalization, the patient's quality of life and perception of dyspnea was improved.

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