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Case report

Scleroderma-related interstitial lung disease

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ABSTRACT

Scleroderma-related interstitial lung disease (SSc-ILD) is a pulmonary fibrosing disorder characterized by systemic inflammation and progressive scarring of the lungs that leads to respiratory failure. Although certain immunosuppressive therapies may slow disease progression, current treatment strategies are not curative; consequently, SSc-ILD continues to be a major cause of morbidity and mortality. We present four cases of SSc-ILD that emphasize the importance of early screening and detection, close follow-up, and aggressive management. We also highlight the need for well-conducted clinical trials designed to identify new and effective treatments.

1. Introduction

Progressive Systemic Sclerosis or scleroderma is a systemic inflammatory disorder characterized by vascular damage, inflammation, and fibrosis of the skin and internal organs [1]. It was first described in 1752 by Dr Carlo Curzio in Italy as a disease that "turned the skin to wood" [2]. Since then, the prevalence and incidence of the disease has continued to rise with current literature estimating the prevalence of scleroderma at 18.4 per 100,000 [3]. In addition to its involvement of the skin and joints, scleroderma can also affect several organs including the lungs, kidneys and gastrointestinal system. Pulmonary hypertension and interstitial lung disease (ILD) are the most widely reported pulmonary complications that arise in scleroderma patients with a third of patients having pulmonary fibrosis [4]. The 5-year mortality for patients with progressive systemic sclerosis and ILD have a survival of 82–90% in 5 years, with ILD or pulmonary hypertension being responsible for 60% of the mortality observed in such cases [5]. Since the 1980's, successful treatment of scleroderma renal crisis has rendered pulmonary complications (e.g., pulmonary hypertension) the most common cause of death in these patients [6], with severe restrictive lung disease being present in 13% of patients with SSc [7].

Herein, we present four cases of SSc-ILD that emphasize the need for early screening and detection, close follow-up and aggressive management, and the desperate need for the development of safe and effective treatments capable of improving outcomes.

2. Case reports

2.1. Case 1

A 64-year-old African-American female carrying a diagnosis of scleroderma since 2007 was referred to our clinic in 2011 after she began to exhibit dyspnea on exertion and decreased exercise capacity. She denied cough and fevers, and had no significant weight loss. Her physical examination revealed a prominent P2 heart sound and coarse crackles at the left base. Initial pulmonary function tests (PFTs) showed a FEV1 of 2.18L (97% of predicted), FVC 2.53L (88% of predicted), TLC of 3.69L (71% of predicted), and a DLCOHb 37% of predicted. She underwent a high-resolution chest computer tomogram that showed reticulation, ground-glass opacifications, and traction bronchiectasis consistent with non-specific interstitial pneumonitis (Fig. 1A). She also had a transthoracic echocardiogram showing changes consistent with moderate pulmonary hypertension and tricuspid regurgitation, but preserved left heart function. Given her symptoms and objective findings of lung involvement, she was started on cyclophosphamide therapy

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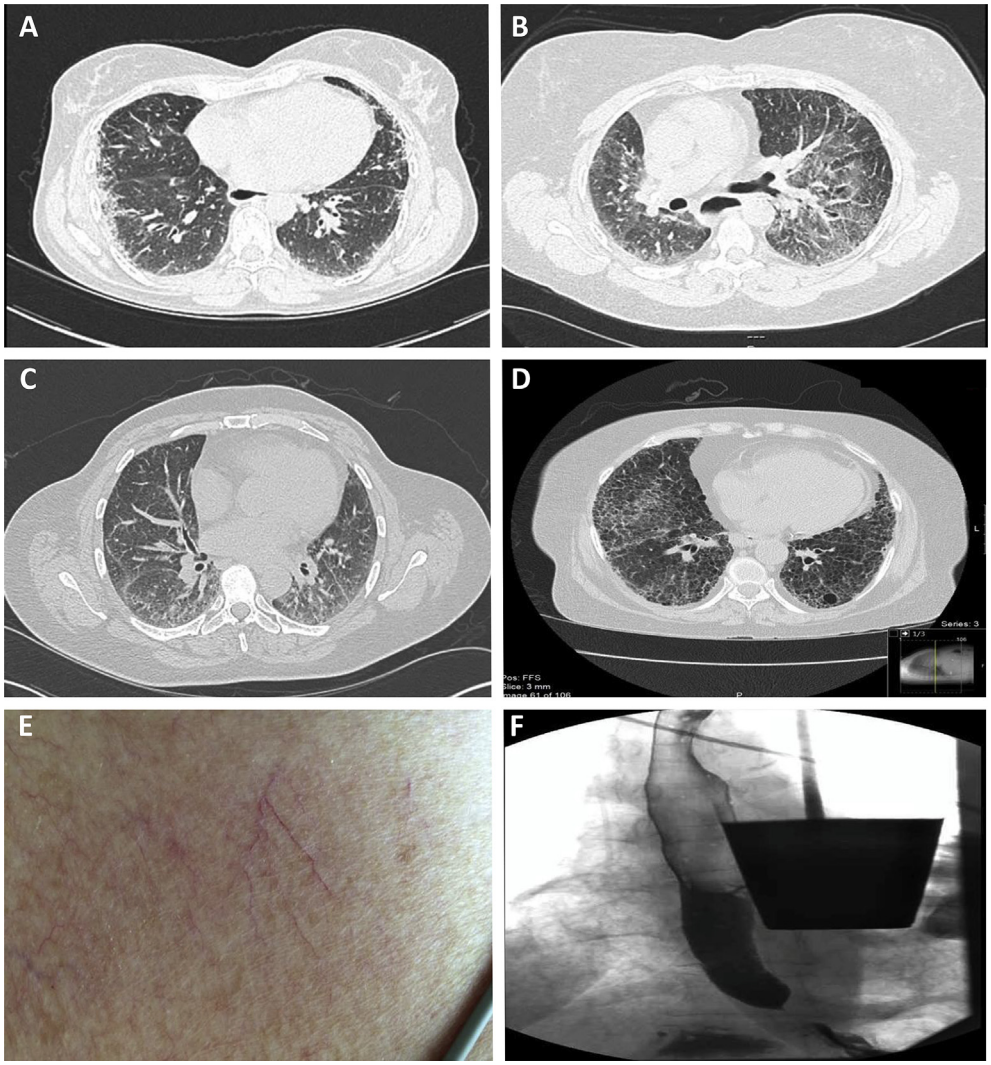

Fig. 1. Lung involvement in Ssc-ILD and related abnormalities. A, High resolution chest CT of patient of Case 1. B, High resolution chest CT scan of Care 2. C, High resolution chest CT scan of Care 3. D, High resolution chest CT scan of Care 4. E, Skin telangiectasia detected in Case 4. F, Barium swallow performed in Case 4 showing retention of fluid in esophagus.

and followed closely. She showed a mild improvement in her FEV1 over the next 2 years with little change in her FVC, and a gradual decline in her 6-min walk test (6MWT) decreasing from 391 to 330 m (74% predicted). During this time, she was also started on oxygen therapy at 2L per minute. Unfortunately, after 3 years of therapy she developed mild hematologic complications which triggered discontinuation of cyclophosphamide; this was followed by further decline in her lung physiology and symptoms. She is currently on prednisone with little effect on her clinical condition; other options are being considered.

2.2. Case 2

A 55-year-old Indian female presented with a 3-month history of dyspnea on exertion, cough, and skin tightness around her neck. Physical examination was positive for pulmonary bibasilar crackles. She underwent a high-resolution chest computer tomogram that was consistent with non-specific interstitial pneumonitis (Fig. 1B); initial serologies were negative with an ANA titer of 1:80. She was referred to Rheumatology for presumed scleroderma and the diagnosis was confirmed. In addition, this patient had a known history of uterine masses, and since scleroderma may represent a paraneoplastic syndrome [31], the immediate concern was the possibility of an underlying malignancy. She therefore underwent screening colonoscopy and mammography, which were normal, but was found to have uterine benign fibroids. A diagnosis of serology-negative Scleroderma was made and SSc-ILD. Further evaluation showed a decreased DLCOHb to 59% predicted and she was started on Mycophenolate Mofetil. Despite therapy, she continued to show a downward trend in lung physiology as well as worsening of her symptoms. She was then transitioned to cyclophosphamide, but continued to show deterioration of her lung physiology with worsening dyspnea on exertion. The patient was started on Tacilizumab (an interleukin-6 antagonist) and continues to be followed.

2.3. Case 3

A 60-year-old Caucasian female with a history of hypothyroidism presented with a 9-month history of worsening dyspnea on exertion following an upper respiratory tract infection. During her initial presentation, she also complained about swollen hands, skin discoloration, and symptoms consistent with Raynaud's phenomena. Her physical examination showed pulmonary bibasilar

crackles and a normal cardiac examination. Her initial PFTs showed a FEV1 of 1.48L (64% of predicted), FVC 1.8L (60% of predicted), TLC 2.62L (61% of predicted) and a DLCOHb 36% of predicted. A high-resolution chest computer tomogram was consistent with non-specific interstitial pneumonitis with basal sub-pleural reticulation and ground glass opacification (Fig. 1C). She was referred to Rheumatology and found to have an elevated ANA of 1:320 and positive anti-centromere antibodies. Given her symptoms, she was started on Mycophenolate Mofetil which resulted in improvement in her PFTs 6 months later, with an increase in her FEV1 to 1.71L (75%), FVC 2.03L (69%), and TLC 2.86L (67%), but her DLCOHb dropped to 34% of predicted. Currently, she is participating in a clinical trial.

2.4. Case 4

A 63-year-old female presented with progressive dyspnea of 3-years duration. Her past medical history was notable for severe gastroesophageal reflux disease and Reynaud's phenomenon. Her physical examination was notable for telangiectasia (Fig. 1E) and pulmonary bibasilar crackles. There was no evidence of skin thickening on exam. Her initial PFTs showed an FEV1 of 1.28L (60% of predicted), FVC 1.76L (61% of predicted), TLC 2.8L (62% of predicted), and a D/VAsbHb 74% of predicted. A high resolution computed tomography of the chest was consistent with non-specific interstitial pneumonitis (Fig. 1D). An esophagogram showed decreased peristalsis and mildly distended esophagus (Fig. 1F). Serology was positive for an ANA titer of >160, with positive anti-centromere antibodies. A diagnosis of Scleroderma-sine-Scleroderma was made and she was started on oral Cyclophosphamide and steroids. Her follow up PFTs were notable for a decrease in DLCO to 28%, with an FVC of 1.96L (70%). Her course was complicated by multiple hospitalizations due to pneumonia and she died two years after the initial diagnosis.

3. Discussion

SSc-ILD is a fibrosing lung disorder characterized by the activation of immune cells and hyperplasia of fibroblasts leading to increased production and turnover of collagen, among other consequences, in the setting of scleroderma [8]. This results in increasingly fibrotic lungs that are prone to respiratory failure. Almost 90% of subjects with scleroderma who lack symptoms of respiratory compromise show changes consistent with ILD on CT imaging, and 100% show histopathological changes on autopsy [9,10]. Thus, early detection of ILD in the setting of scleroderma is imperative since it has prognostic value, and may prompt early treatment and frequent follow up.

To date, the treatment of SSc-ILD is limited to targeting inflammatory pathways with corticosteroids or other immunosuppressive therapy [4]. This therapeutic approach is largely empirical and parallels strategies historically used in treating idiopathic pulmonary fibrosis and related disorders. Cyclophosphamide is currently the most studied immunosuppressive therapy in SSc-ILD, but there remains a scarcity of randomized controlled trials in the literature. To date only two large randomized controlled trials comparing cyclophosphamide to placebo have been conducted. The first by Tashkin et al. showed a small but significant improvement in FVC and quality of life [11]. However this improvement did not persist 12 months after the cessation of cyclophosphamide strongly suggesting the need for continued maintenance therapy [12]. The second trial by Hoyles et al. showed no significant difference in pulmonary function, disease burden on high resolution computer tomogram, or gas exchange between the use of Intravenous pulse dose cyclophosphamide versus placebo [4]. In 2015, a study looking at the safety and effectiveness of Mycophenolate Mofetil reported that this drug might be beneficial in the stabilization of lung function in SSc-ILD, although the significance and longevity of this benefit remains uncertain [13]. Other single center studies and case reports have documented stabilization of pulmonary function tests and imaging scores with the use of Mycophenolate Mofetil in patients who did not respond to cyclophosphamide [14], although this difference was only noted in patients with a shorter disease course [12]. Tashkin et al. later compared treatment with Mycophenolate mofetil for 2-years versus cyclophosphamide for 1 year. While they noted significant improvement in lung function, they were unable to confirm greater efficacy at 24 months with Mycophenolate mofetil despite its superior tolerability and toxicity profile [15,16].

Recently, treatment with humanized monoclonal antibodies has added a new alternative to the treatment repertoire. In the EUSTAR cohort study, Rituximab was shown to be effective in the improvement of skin fibrosis and prevention of worsening lung fibrosis [17] supporting the concept of targeting B cells in SSc-ILD. Other emerging treatment options include modulators of profibrotic cytokines such as IL-6 inhibitors and anti-IL-3 antibodies and other humanized monoclonal antibodies [18–22]. The availability of biological agents with potential therapeutic activity in SSc-ILD calls for aggressive screening of ILD in SSc patients.

Although helpful, the results of the aforementioned studies emphasize the need for further investigations directed at identifying more effective treatment strategies. The limited number of patients with SSc-ILD in any given center, the lack of relevant animal models, and delayed diagnosis have hindered the conduction of large, well-randomized, placebo-controlled clinical trials in this condition. In 2014, the FDA provided fast-track approval of two anti-fibrotic drugs, pirfenidone and nintedanib, for the treatment of idiopathic pulmonary fibrosis based on the results of randomized clinical trials [23]. Although these drugs delay decline in lung function, they do not improve lung function and their impact on survival remains unclear. Also, non-specific interstitial pneumonitis is the most common histological pattern in Ssc-ILD [24] as opposed to the usual interstitial pneumonitis pattern, the latter being characteristic of idiopathic pulmonary fibrosis. Nevertheless, the possibility of transitioning the use of these drugs to other fibrotic lung diseases remains a viable possibility. Pirfenidone, for example, has been found to be safe in scleroderma patients with some improvement in certain cases [25,26]. A phase III placebo-controlled randomized clinical trial for evaluation of nintedanib in SSc-ILD (SENSCIS) is being conducted at the time of the writing of this document.

Ideally, the development of novel treatment strategies depends on a robust pipeline of data generated through pre-clinical studies performed in relevant animal models. Unfortunately, no animal model exactly resembles the human disease. An animal model has been developed based on the subcutaneous administration of hypochlorus acid (HOCL). This model is associated with the production of anti-topoisomerase antibodies and other characteristics of systemic sclerosis [27], and could be vital in understanding the mechanisms involved in disease development, and in testing the effectiveness of future treatment approaches.

As in many systemic inflammatory rheumatologic conditions, patients with scleroderma have an increased risk of malignancies, particularly lung, bladder and hematologic cancers [28]. This increased risk may be due to chronic inflammation and fibrosis leading to malignant transformation or secondary to the immunosuppressive therapies used to treat scleroderma [29]. In a pilot study by Shah et al., 23 scleroderma patients positive for RNA Polymerase III were noted to have an increase in a cluster of cancer diagnoses that coincided with the onset of their scleroderma

symptoms [28]. Moreover, these patients had a unique nucleolar expression of RNA Polymerase III in their cancerous cells that was not present in other scleroderma autoantibody patients or normal controls. These data suggest that patients with a new diagnosis of scleroderma and RNA Polymerase III autoantibody, or an older age of scleroderma onset, may benefit from aggressive malignancy screening at diagnosis [30].

In summary SSc-ILD represents the most frequent cause of death in scleroderma, with a 10-year survival ranging from 29 to 69% [24]. The management of SSc–ILD patients remains a great challenge due to the paucity of well-conducted clinical trials and lack of highly relevant animal models. Early detection of pulmonary involvement based on clinical exam (e.g., pulmonary crackles), yearly pulmonary function tests, and evaluation of lung involvement by high-resolution computed tomography if SSc-ILD is suspected are critical for the optimal management of these patients. Ultimately, the development of relevant animal models and the availability of prospective, randomized, placebo-controlled clinical trials are indispensable to the advancement of treating SSc-ILD.

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