

Interstitial Lung Disease in Systemic Scleroderma, Complicated with Bilateral Pulmonary Aspergilloma: An Unusual Association

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ABSTRACT

Aspergilloma or mycetoma is a saprophytic fungal infection that colonizes pre-existing excavated lung lesion. However, its association with systemic sclerosis related interstitial lung disease is unusual and scarcely found in literature. We report a middle aged female with long standing systemic sclerosis, who was on immunosuppressive therapy for many years, presented with repeated haemoptysis. Although provisionally pulmonary tuberculosis was suspected, imaging investigations showed presence of bilateral masses inside bullous air spaces along with air-crescent sign suggestive of fungal ball. Subsequent Computed tomography guided needle aspiration from lung mass confirmed *Aspergillus fumigatus* as aetiological agent on fungal culture. Patient was treated conservatively for haemoptysis and with oral antifungal drug as surgical removal of fungal ball was not an option due to poor pulmonary reserve. Although she had been treated with itraconazole for more than three years, she had recurrent haemoptysis during this period without any significant regression of size of the aspergilloma. Management of aspergilloma in a background of extensive interstitial lung disease remains poorly defined and complicated. Thereby, overall prognosis is unfavourable and depends on evolution of both underlying scleroderma as well as aspergilloma.

Keywords: Breathlessness, Recurrent haemoptysis, Systemic sclerosis

CASE REPORT

A 34-year-old non-smoker female, presented with repeated haemoptysis since two months in a background of systemic sclerosis (SSc) associated interstitial lung disease (ILD). She had non-productive cough, progressive breathlessness with wheeze since last 12-years without any prior haemoptysis. She denied any history of recent fever, chest pain, loss of appetite or weight reduction. On examination, she had clubbing of hand and feet, bilateral pedal edema without any palpable lymphadenopathy. Blood pressure was 164/100mm of Hg. She also had Cushingoid facies with fish mouth appearance and mild hirsutism. There was bilateral coarse crepitus with polyphonic wheeze and oxygen saturation by pulse oximetry (SpO_2) was 88% at rest in room air.

On review of her previous illness, she was diagnosed to have SSc at age of 18-years based on symmetric thickening and tightening of skin over hand and forearm along with anti-Scl-70 antibody positivity. She was put on oral prednisolone since diagnosis of SSc, which was gradually tapered and maintained on low-dose (10mg/day) steroid since last 12 years. Subsequently she developed cough with progressive breathlessness and was diagnosed to have ILD based on high resolution computed tomography (HRCT) findings at the age of 22. She also had Raynaud's phenomenon for which she underwent surgical sympathetic denervation of right upper limb in the same year. She also developed digital tip ulceration which secondary infection, for which distal part of her left fourth finger was amputated [Table/Fig-1].

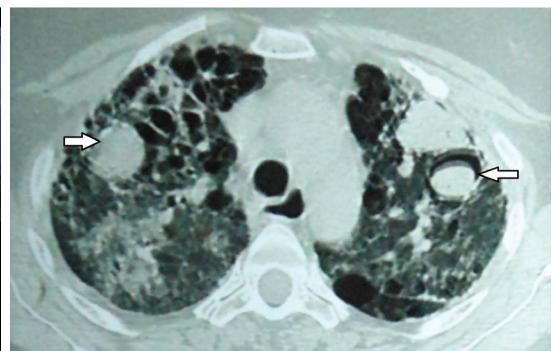
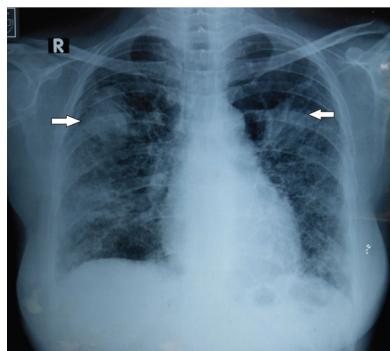
Following admission, she was evaluated for haemoptysis. Although she was initially suspected to have pulmonary tuberculosis in background of long-term immunosuppressive therapy in tuberculosis endemic country, repeated sputum examination for acid-fast bacilli yielded negative result. Sputum gram stain and cultures were negative as well. Chest X-ray (Postero-anterior view) revealed a well defined mass lesion in right upper lung zone along with a poorly defined mass lesion in left upper zone in a background of extensive reticular opacity involving both mid and

lower zones [Table/Fig-2]. A patch of consolidation was also noted in right mid-zone. Complete haemogram, plasma glucose, renal and liver function tests were normal except for Haemoglobin of 11.1 gm/dl and an erythrocyte sedimentation rate (ESR) of 32 mm/hour. Subsequent HRCT thorax showed extensive bilateral honeycombing, interlobular septal thickening, patchy right upper lobe consolidation, paraseptal emphysema with bullous lesions in both upper lobes. A fungal ball was noted in left upper lobe with air-crescent sign along with another mycetoma in right upper lobe [Table/Fig-3]. But a prone position HRCT imaging failed to demonstrate displacement of fungal ball with change of patient's position. Sputum for fungal stain and fungal culture was negative. CT-guided needle aspiration was carried out from left upper lobe mass to confirm the aetiology and fungal culture from the aspirate yielded *Aspergillus fumigatus*. Additional investigations revealed the possibility of pulmonary hypertension based on 2D-echocardiography although right heart catheterization was not done. On six minute walk test, she was able to walk for only 180m along with a significant drop in the SpO_2 . Fibreoptic bronchoscopy was performed but the bronchoalveolar lavage (BAL) fluid analysis was inconclusive. During her hospital stay, she was put on oral itraconazole (200mg twice daily) and cyclophosphamide therapy (50mg twice daily) apart from cough suppressant, sedative and other conservative measures. A thoracic surgical opinion was taken, but no active surgical intervention was advised because of very poor pulmonary reserve.

The patient was discharged subsequently with itraconazole, cyclophosphamide, nifedipine, losartan, tadalafil and inhalational bronchodilator. Based on arterial blood gas (ABG) report, she was put on long-term oxygen therapy. Since then patient is being followed up at regular interval and is on antifungal therapy for more than three years. Although the clinical course is marked by recurrent haemoptysis, pulmonary lesions are found to be stable over these three years without any regression in size.



[Table/Fig-1]: Showing clubbing of fingers with amputated distal part of left fourth finger **[Table/Fig-2]:** Chest X-ray (PA view) showing a well defined mass lesion in right upper lung zone along with an air-crescent sign. Another mass like lesion in left upper zone along with extensive reticular opacity involving both mid and lower zones
[Table/Fig-3]: HRCT thorax showing a fungal ball in left upper lobe with air-crescent sign along with another mycetoma in right upper lobe



DISCUSSION

SSc is an immunological disease causing increased extracellular matrix deposition, small vessel vasculopathy, T- and B-lymphocyte dysfunction and autoantibody production. This can lead to thickening of skin and damage of heart, lung, gastrointestinal tract and kidneys. Pulmonary involvement, when assessed histologically, can be detected in 70% to 100% of patients [1]. ILD is the predominant lung manifestation in this setting. Here we reported a case of SSc with ILD who presented with recurrent haemoptysis and was diagnosed to have bilateral pulmonary aspergilloma. Although *Aspergillus* can grow in any pre-existing cavity or bullous lung lesion, such association with SSc is very uncommon in clinical practice and are very rarely reported in literature. Bilateral aspergilloma in SSc is probably the first case being reported as per knowledge of the authors.

SSc can have a multitude of clinical manifestations with majority of the patients having skin thickening and variable involvement of internal organs. Latest classification criteria by American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) is currently the most used criteria for SSc diagnosis [2]. Women are predominantly affected with peak incidence between 45 and 64 years of age although our patient developed clinical features early in her life.

Pulmonary involvement is only second to skin in frequency in progressive SSc. Interstitial thickening along with honeycombed lung is the commonest lung parenchymal abnormality on chest imaging. Recurrent pulmonary infections are common and infectious complication is the commonest cause of death in such patients. Lung cancer is the most frequent malignancy in SSc, followed by breast cancer [3]. But a co-existence of this ILD with aspergilloma is extremely rare. A case of huge aspergilloma was reported from Madagascar in an immunocompetent patient with SSc-ILD who presented with repeated haemoptysis, dyspnea and pulmonary hypertension [4]. Similar cases of mycetoma have been reported in association with idiopathic pulmonary fibrosis [5], rheumatoid arthritis [6], chronic hypersensitivity pneumonitis [7], lung carcinoma [8], chronic berylliosis [9], Wegener's granulomatosis [10] etc.

A recent classification by Infectious Diseases Society of America (IDSA) divides aspergilloma into two categories: single pulmonary aspergilloma and chronic cavitary pulmonary aspergilloma (CCPA). CCPA is defined as occurrence of multiple cavities, which may or may not contain an aspergilloma, in association with pulmonary and systemic symptoms and raised inflammatory markers [11]. Index patient was a likely case of CCPA and this entity should not be confused with chronic necrotizing pulmonary aspergillosis (CNPA). CNPA (previously known as subacute invasive pulmonary aspergillosis) is usually associated with slowly progressive inflammatory destruction of lung tissue in patients having underlying pulmonary diseases and low grade immunosuppression.

However, difference between CNPA and CCPA is the prolonged time frame and genetic predisposition in the latter and defects in innate immunity has been described in CCPA [11]. Diagnosis of aspergilloma is usually made on clinico-radiological features and a lung biopsy is not routinely indicated. However, we carried out a CT-guided aspiration from intracavitary mass to rule out possibility of cavitating lung carcinoma as the fungal ball didn't assume dependent position on prone imaging.

Regarding management protocol, haemoptysis should be treated first. As per the IDSA guideline [11], optimal candidate for surgical resection are those with a single aspergilloma and surgery is the only definitive treatment. But surgery in CCPA carries high risk of morbidity and mortality; often a co-existent poor pulmonary function precludes thoracotomy [11]. Itraconazole or voriconazole is the primary therapy in this setting, although role of these antifungal agents are controversial. Often a long term therapy is needed, but duration of therapy remains poorly defined. Itraconazole therapy in our patient was without much success and aspergilloma showed no sign of regression over three years.

CONCLUSION

Although mycetoma is most commonly seen in post-tuberculosis pulmonary cavity in a tuberculosis endemic country, extensively honeycombed lung in SSc or any other ILD may predispose to development of aspergilloma. Regarding medical therapy, in spite of good penetration of itraconazole or voriconazole into the cavities, management of aspergilloma remained difficult, especially in the background of an ILD.

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