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Systemic Sclerosis and Pulmonary Tuberculosis Associated with Interstitial Lung Disease: A Case Report

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Abstract

A 59-year-old man had complaints of shortness of breath, thickened and dry skin especially on both hands. Results of thoracic HRCT obtained interstitial lung disease. A year after, the patient underwent geneXpert sputum test because he still complained of coughing with white phlegm and tightness while doing activity. The test obtained Mycobacterium tuberculosis 2+. He received anti-tuberculosis drugs. One month after infection, the patient was evaluated for Mycobacterium tuberculosis, while administration of anti-tuberculosis drugs was continued for up to 8 months. In the second year, the patient had severe restriction, and was given advanced anti-tuberculosis drugs in the sixth month.

Keywords: *Systemic sclerosis; interstitial lung disease; tuberculosis*

Introduction

Systemic sclerosis (SSc) has the highest mortality of all connective tissue diseases. Although it often affects many organs, pulmonary involvement, in particular, interstitial lung disease (ILD), is the main cause of death [(1)]. Patient with SSc has the risk to be infected by tuberculosis (TB) due to defective immunity or related to immunosuppressants therapy. Previous studies revealed disease that damaged lung structure such as chronic ILD can defect local immunity of the host and furthermore, increase the risk of TB infection [(2)]. We reported a case of a male patient, aged 59, with ILD associated with SSc and pulmonary tuberculosis.

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Case Report

A 59-year-old man, a private employee, had a history of smoking >10 years and had stopped since the last 8 years. He had no history of alcohol consumption and autoimmune thyroid disease (ATD) therapy. The patient visited hospital with complaints of thickened and dry skin, especially on both hands (Figure 1), and chest pain during activity. Transthoracic echocardiography and echocardiography results showed left ventricular hypertrophy and mild pulmonary hypertension.

History and physical examination led to suspected SSc. Then, the patient underwent chest X-ray examination (Figure 2). We obtained reticulogranular pattern in the right and left paracardial and cardiomegaly. Acid-fast staining was then carried out on sputum, but we found a negative result.

We performed a chest HRCT X-ray and obtained a reticular pattern image on the posterobasal of the right-left inferior lobe of the lung. These findings supported the characteristics of ILD (Figure 3). Based on the examination results, we conducted an assessment based on 2013 American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR) criteria for the SSc classification (Table 1). The patient was then diagnosed with SSc and ILD. The

patient was given with 7 cycles of immunosuppressant cyclophosphamide treatment, followed by cyclosporine for 3 months, then azathioprine for 6 months. The results of pulmonary function examination did not show restriction and obstruction.

One year after being diagnosed, the patient returned to the hospital complaining of a weak body, increased tightness during activity, coughing with white phlegm in the last 1 month, and night sweats. The patient was then hospitalized and underwent treatment for pneumonia. Sputum aerobic cultures showed the presence of Klebsiella pneumoniae. Ceftazidime 1-gram therapy was given every 8 hours intravenously according to the results of antibiotic sensitivity. Chest X-ray evaluation was examined and provided the following results in Figure 4.

GeneXpert results showed medium *Mycobacterium tuberculosis*, while rifampicin resistance was not detected. Examination of acid-fast sputum smear was carried out and the results were 2+. Category 1 tuberculosis treatment was started in this patient with ATD 3 tab 4 FDC.

Two months later the patient came back to the hospital with complaints of shortness of breath while doing activities. Physical examination of the patient showed anaemia in conjunctiva and "velcro" crackles in the lower third of right and left hemithorax. Laboratory tests showed pancytopenia as a side effect of the ATD. Initial management of the patient was nasal oxygenation, cessation of azathioprine and ATD FDC due to pancytopenia. The ATDs given were 750 mg levofloxacin every 24 hours orally, 300 mg INH every 24 hours orally, 1250 mg pyrazinamide every 24 hours orally, and 750 mg ethambutol every 24 hours orally, PRC transfusion 1 flask/day, 4 mg methylprednisolone every 24 hours orally and 5 mg amlodipine every 24 hours orally.

The congestion decreased after 3-day clinical treatment. Thoracic HRCT evaluation showed fibro infiltrates with multiple cavities and tree-in-bud pattern in the right lobe of right and left lungs, tree-in-bud pattern in the inferior lobe of the right lung, cystic bronchiectasis in right lung lobe, bronchial wall dilatation and tram track sign in posterobasal segment of the inferior right-left lung, and multiple enlargement of lymph nodes with the largest size ± 0.6 cm in the right axilla, ±0.5 cm left, and ±0.3 cm in the lower right paratracheal. Sputum aerobic cultures showed the presence of Klebsiella pneumonia (figure 3).

Hb and leukocytes decreased to 8.8 g/dL and 670/uL. Transfusion of PRC 1 flask/day was provided up to Hb=10 gr/dL. Immunosuppressant treatment was restarted with the administration of 180 mg of mycophenolic acid every 24 hours orally. One month after discharge, based on the results of consultations with clinical experts, the patients were given with ATDs 300 mg INH and 750 mg ethambutol for continuation phase for 8 months.

In the sixth month of the continuation phase ATD, the patient stated that complaints of tightness were still present, but the patient could be more comfortable with activities and no coughing. Examination of lung function was carried out and severe restriction was obtained. Phase of the ATD was continued and SSc-ILD treatment was followed-up with mycophenolic acid.

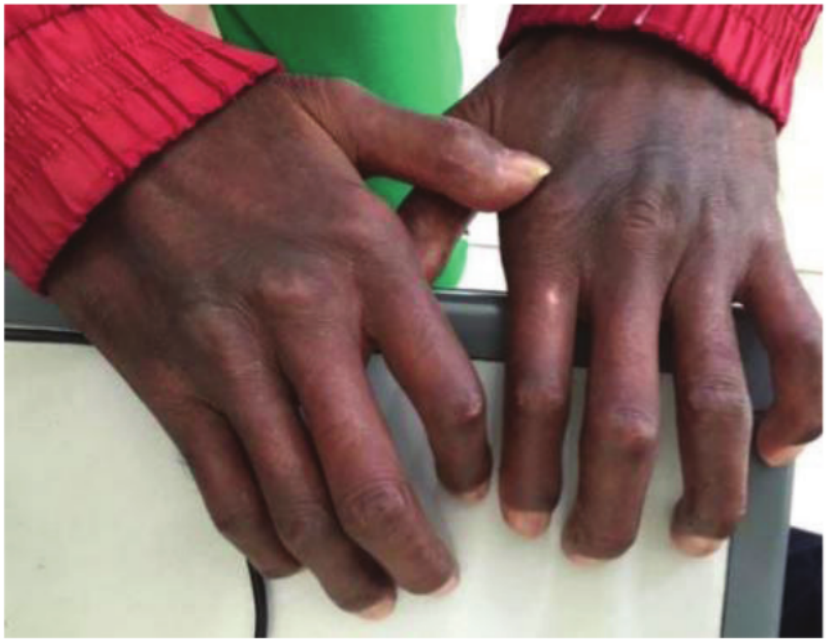

Figure 1. Skin on both hands thickened and dry

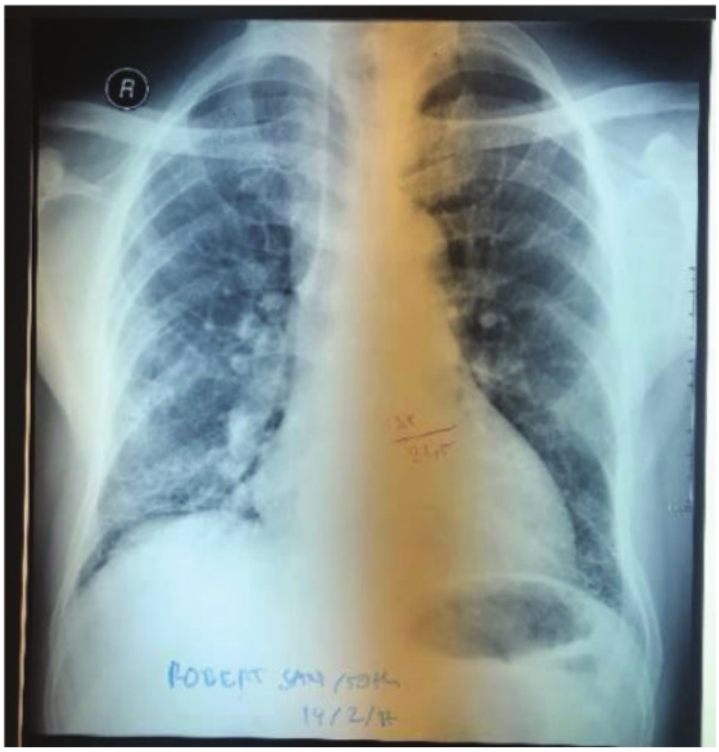

Figure 2. Chest X-ray post one month

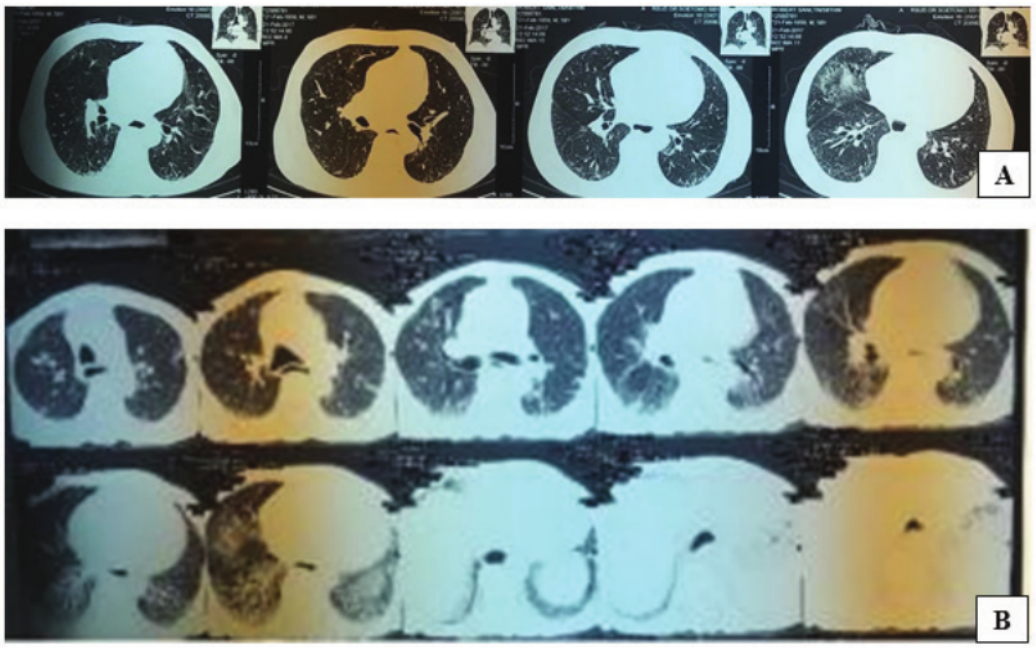

Figure 3. Chest HRCT in the first year (A) and in the second year (B)

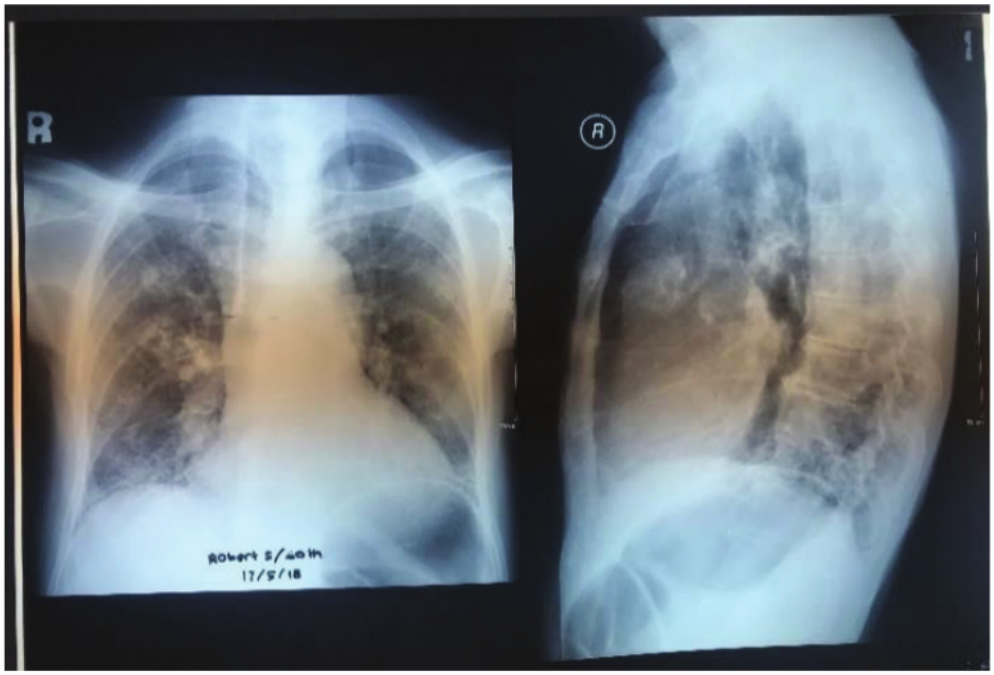

Figure 4. Chest X-ray Just like the chest X-ray of the previous year, reticulogranular pattern of the right and left paracardial, and cardiomegaly, were still visible, but now there was also a pattern of fibroinfiltrates.

Discussions

SSc is a heterogeneous disease and its pathogenesis is marked by 3 things, which are microvascular vasculopathy, autoantibody production, and fibroblast dysfunction resulting in an increase of extracellular matrix depositions. The gold standard to diagnose SSc is not found yet. American College of Rheumatology (ACR) made criteria to classify SSc in 1980 but the sensitivity and specificity were low. These criteria then updated by a joint committee between ACR and European League Against Rheumatism (EULAR) in 2013 with higher sensitivity and specificity (>90%) [3, 4].

Management of SSc includes early diagnose, early diagnose of internal organ involvement, identification of patients with risk of new organ complication, and deterioration of disease related to nonpharmacological therapy. Pharmacological management of SSc includes therapy of involved organ with the recommendation from EULAR [5].

Cyclophosphamide is recommended for ILD related to SSc (SSc-ILD) even though the side effect is quite much, especially in a progressive ILD (recommendation A). Azathioprine orally can also be given as an active therapy in SSc-ILD after administration of cyclophosphamide. A randomized controlled trial to compare effectivity of mycophenolate mofetil and cyclophosphamide in a patient with SSc-ILD and the result showed that both are equal in improving forced vital capacity (FVC) but the recommendation for mycophenolate mofetil usage is not made yet [5-7].

The pathogenesis of SSc is still unclear. Patient with the genetic predisposition of SSc, an external trigger makes the pathologic process start. Triggers of SSc can be a virus/bacteria (pathogen), chemical substance and pollutant (e.g, silica), Human Leucocyte Antigen/HLA (such as B8, DR5, DR3, and DR52), or a phenotype changing of body cells. SSc is a result of 3 related processes which are fibroproliferative vasculopathy of small vessels, abnormality of the innate and adaptive immune system that produce autoantibodies and cell-mediated autoimmunity, and fibroblast dysfunction that cause excessive accumulation of collagen and another extracellular matrix in the skin and internal organs [8].

Endothelial damage is the main process in SSc. Endothelial dysfunction causes the decrease of *endothelial NO synthase* (eNOS) enzyme production so that the production of basal nitric oxide decrease and lead to vasoconstriction of small vessels in extremities. This process causes hypoxia in peripheral extremities. Innate system immune will produce pro-inflammatory cytokines after exposure to external or internal triggers. Adaptive immunity in SSc is Th2 dominant. The t-cytotoxic cell in a patient with SSc play a role in adding the damage of endothelial with granzyme and Fas/FasL. Debris from the result of the apoptotic cell will become an antigen and trigger B cell to form autoantibody. The antigen in the body also binding with autoantibody, which is then along with cytokines, worsen the damage of endothelial and stimulate fibroblast to deposited collagen [9, 10].

Fibrosis is the end of the pathogenesis of SSc which continues to occur during the life of the patient. Fibroblast of a patient with SSc is having dysfunction due to trigger that continuously causing collagen deposition in skin and internal organs, includes the lung. Accumulation of collagens causes massive fibrosis in lungs and alveolitis which is then called SSc-ILD [9, 10].

There is an immune system dysfunction in a patient with SSc-ILD causing them to be easily triggered by external factors such as viral/bacterial infection, also pollutants that can cause disease manifestations even though only in a small amount [11].

Diagnose of SSc-ILD is accomplished by combining the presence of clinical symptoms, physical examination, pulmonary function test, and radiological finding. The patient can be asymptomatic in the early stage and then complain about dyspnea on effort, unproductive cough, and chest discomfort. In physical examination, “velcro” crackles can be found in auscultation. Pulmonary function test shows a decrease of diffusion capacity (DLCO) and forced vital capacity (FVC). HRCT showed infiltrate or subpleural density starts from the posterior segment of the inferior lobe, interstitial reticular infiltrates, and subpleural honeycombing. Traction and cystic bronchiectasis are the advanced forms of progressive disease course [12].

Indonesia is an endemic country of tuberculosis (TB) so patient with the immunocompromised state is in a very high risk of TB infection. Diagnose of TB is

assessed with the presence of clinical symptom of the respiratory tract which is a productive cough for more than 2 weeks, along with systemic symptoms and confirmed by microbiological and radiological findings. Detection of *Mycobacterium tuberculosis* (MTb) in the acid-fast bacilli staining or molecular rapid test is a gold standard to diagnose TB [13].

The side effect of ATD can be a hematological disorder and immune-mediated pancytopenia is one of them. The underlying mechanism of this emergence is the effect of immunity, interaction with the enzymatic pathway, and direct inhibition of the hematopoiesis system. The incidence of hematologic side effects is reported to be related to the use of rifampicin and also to isoniazid, pyrazinamide, and ethambutol but with a lower incidence than rifampicin [14, 15].

SSC-ILD has a poor prognosis with increasing mortality. The survival rate of patients with severe SSc-ILD is 30% at 9 years. The fastest decrease of pulmonary function and radiological worsening occurs in the first 3 years after the onset of disease [12].

Conclusion

Patient with SSc-ILD is susceptible to TB infection and the clinical symptoms of both diseases are very similar, making it hard to be diagnosed. SSc-ILD is a progressive disease and the presence of TB can cause deterioration of the ILD itself, decrease of pulmonary function, and decrease of patient's quality of life. This case is reported to highlight the importance of early detection of TB in a patient with immune disease and ILD. Appropriate management including the management of side effect is very important to prevent progression and improve the quality of patient's life.

Conflict of Interest: The authors declare that they have no conflict of interest.

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