Letter to the Editor

Erasmus syndrome: case description of a rare entity

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Background

Silicosis, one of the most common and serious occupational diseases in the world, is a lung disease caused by the long-term inhalation of dust containing a relatively high concentration of free silica (SiO_2), which leads to inflammation and diffuse fiber transformation in lung tissue (1). After onset, silicosis progressives, affecting the normal life of patients, potentially causing a loss in the ability to work and developing into respiratory failure or heart failure. One study revealed an unexpected association between silica exposure and a variety of systemic autoimmune diseases in addition to silicosis, including rheumatoid arthritis, primary systemic vasculitis, systemic lupus erythematosus, Wegener granulomatosis, and systemic sclerosis (SSc) (2). SSc is a multisystem disease characterized by inflammation and degeneration of the heart, lungs, kidneys, gastrointestinal tract, and synovium (3). Although its etiology is not fully understood, it is known that occupational exposure to substances such as vinyl chloride, benzene epoxide, organic solvents, and less commonly silica can contribute to its emergence. Erasmus syndrome (ES) is a highly rare disease that refers to the occurrence of SSc in patients with silicosis or those exposed to silica dust (4). A retrospective study of a large cohort in Brazil estimated the prevalence of ES in patients with SSc to be only 0.9% (5).

Here, we describe a rare case of a male patient who worked in artificial marble processing for more than 20 years, had tomographic findings consistent with those of silicosis, and developed SSc after exposure, for which ES was diagnosed.

Case presentation

A 45-year-old male patient was a laborer in artificial marble processing for more than 20 years, working with cement, gypsum, and unsaturable polyester resin and dust without using protective equipment. The patient developed cough expectoration and asthma after catching a cold and inhaling irritating gas in May 2020. On June 20, 2020, he was admitted to a local hospital and received chest computed tomography (CT) examination, which indicated infectious lesions of both lungs, mediastinal lymphadenopathy, and small pleural effusion. Hospitalization was recommended. In the process of waiting for hospitalization, the above symptoms worsened. For further diagnosis and treatment, he was admitted to the Department of Respiratory of The First Affiliated Hospital of Anhui University of Chinese Medicine on July 11, 2020. Neither a past history of infection nor any history of any chemotherapeutic drug

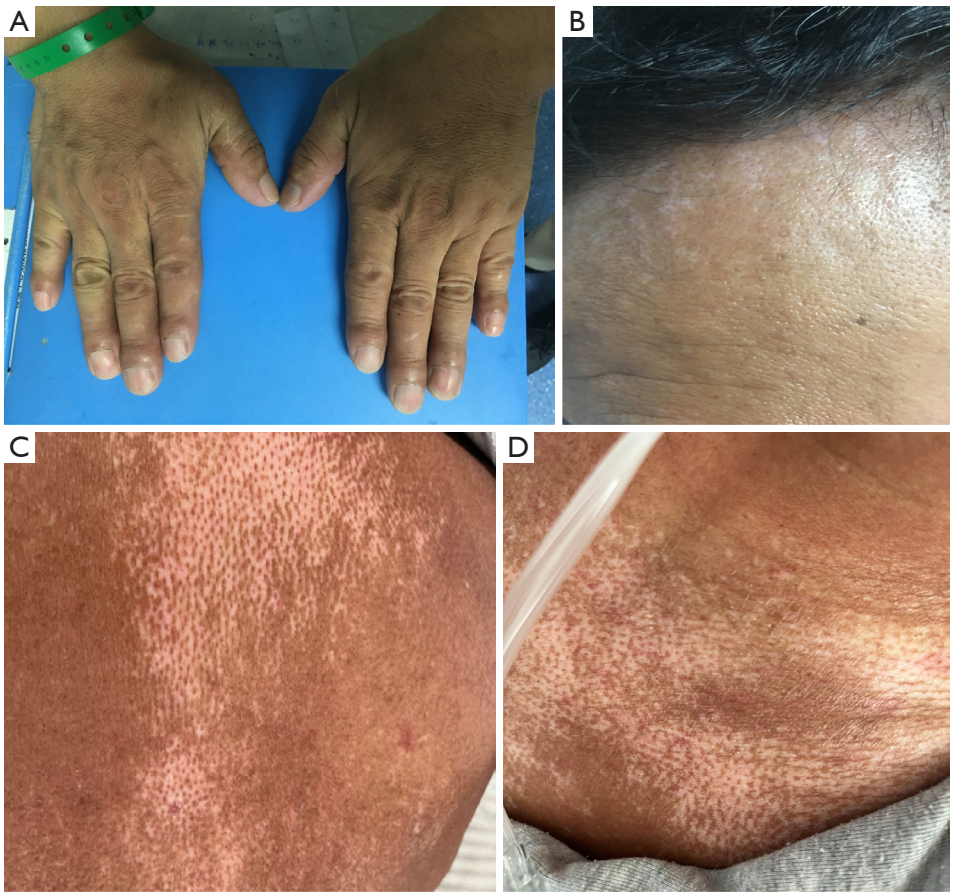

Figure 1 Skin manifestations of systemic sclerosis. (A) Sclerodactyly. (B) Salt-and-pepper discoloration on the forehead. (C) Salt-and-pepper discoloration on the back. (D) Salt-and-pepper discoloration on the neck.

administration or chronic drug intake in the past was indicated. The patient had a history of alcohol intolerance, no history of drug allergy, and a cumulative smoking history of 10 years with 20 cigarettes/d.

Physical examination on admission showed that the patient had sclerodactyly (*Figure 1A*) and difficulty making fists in both hands; a salt-and-pepper discoloration on the forehead (*Figure 1B*), back (*Figure 1C*), and neck (*Figure 1D*); low skin temperature, Raynaud phenomenon; low respiratory sound in both lungs; and no dry and wet rales. His heart rhythm was regular, with no murmurs. The liver and spleen were not large, and the lower limbs had no edema.

Complete blood count, urinalysis, liver and renal function tests, and serum electrolyte measures were within normal limits; however, the patient was hypoalbuminemic (31.5 g/L) and had increased levels of lactate dehydrogenase (522 μ/L) and C-reactive protein (14.82 mg/L) and an elevated erythrocyte sedimentation rate (44 mm/h). He was negative for the tumor markers of carcinoembryonic antigen, alpha-fetoprotein, cancer antigen 199, cytokeratin 19 fragment, and squamous epithelial cell antigen but was positive for ferritin (3,263.95 ng/mL). Polymerase chain reaction (PCR) for coronavirus disease 2019 (COVID-19) was negative. Autoantibody tests via the indirect immunofluorescence method revealed positive results for particle type (1:1,000) and nucleolar type (1:1,000). Western blotting indicated strong positivity for anti-nRNP/Sm antibody and anti-Scl-70 antibody. Tests comprising the colloidal gold method and antineutrophil cytoplasmic antibody (ANCA) method via indirect immunofluorescence indicated negative results for toxoplasma, rubella, cytomegalovirus, and herpes simplex (TORCH). The T-cell spot test for tuberculosis was negative. The pulmonary function test revealed mild restricted ventilation dysfunction and moderately reduced diffusion dysfunction (forced vital capacity was 73.2%,

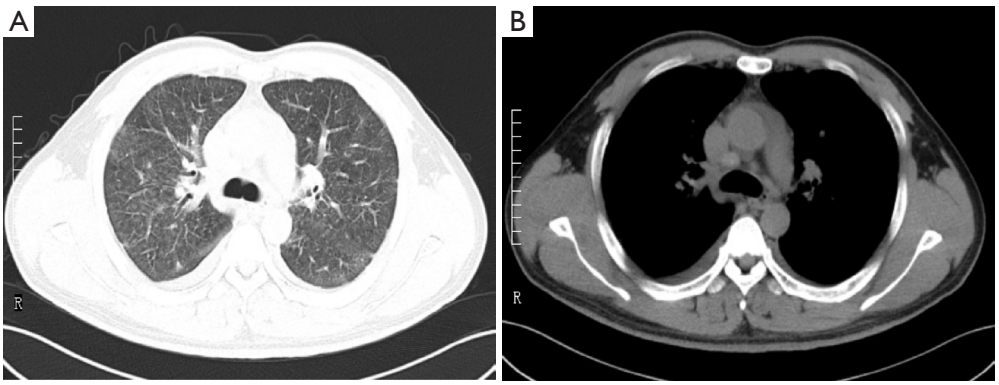

Figure 2 Chest computed tomography scan on July 15, 2020. (A) Diffuse lesions in both lungs. (B) Mediastinal lymph node enlargement.

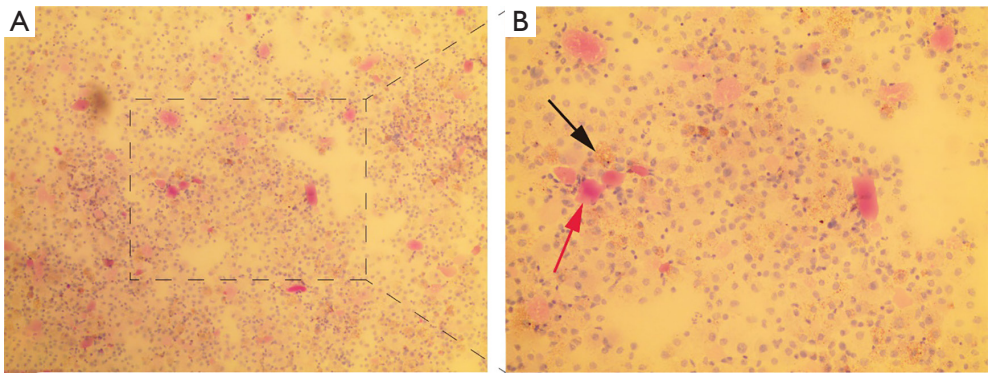

Figure 3 Cytokines in bronchoalveolar lavage fluid after hematoxylin and eosin staining. (A) 40×. (B) 100×. The black arrow indicates dust cells, and the red arrow indicates an irregularly round and pink-stained protein-like proteinoid substance.

forced expiratory volume in one second was 85.1%, diffusion capacity of carbon monoxide was 48.1%). Flexible bronchoscopy revealed widespread fine nodularity in the entire bronchial tree. A CT scan of the chest revealed diffuse lesions in both lungs (*Figure 2A*), accompanied by mediastinal lymph node enlargement and bilateral pleural effusion (*Figure 2B*).

Fiberoptic bronchoscopy and bronchoalveolar lavage were conducted on July 30, 2020. The cytological analysis of bronchoalveolar lavage fluid (BALF) revealed a large number of dust cells and a small number of scattered lymphocytes, eosinophils, ciliated columnar epithelial cells, and an irregularly round and pink-stained protein-like proteinoid substance (*Figure 3*).

The patient initially received an intravenous 40-mg dosage of methylprednisolone each day, followed by a gradual reduction to 12 mg of oral methylprednisolone each day for maintenance treatment for a period of 16 months. Throughout the course of treatment, the patient remained stable for several months. It is important to perform chest CT examination at regular follow-up, and after 16 months, chest CT scans revealed signs of progressive disease, characterized by the presence of cord-like high-density shadows in the upper sections of both lungs (*Figure 4A*) and enlarged mediastinal and hilar lymph nodes (*Figure 4B*). After communicating with the patient, we prescribed nintedanib at a dose of 150 mg twice daily on the basis of oral prednisolone treatment (*Figure 5*). The skin of the patient's face and hands became softer, and he could perform mild activity without the assistance of oxygen inhalation. Over the next two years, the patient experienced several upper and lower respiratory tract infections, accompanied by episodes of fever and dry cough, which were managed with antibiotics. On January 2023, the patient began to report a worsening exertional dyspnea. A subsequent chest CT scan revealed progression of the fibrotic masses in the

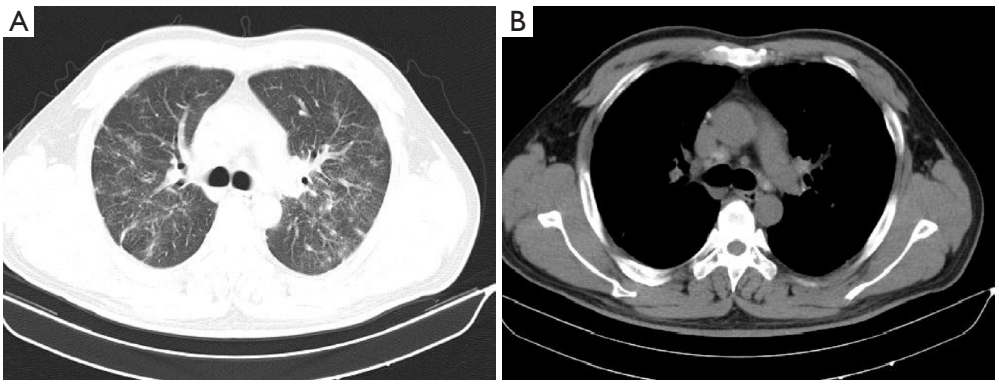

Figure 4 Chest computed tomography scan on April 15, 2021. (A) Cord-like high-density shadows in the upper sections of both lungs. (B) Pronounced mediastinal and hilar lymph node enlargement.

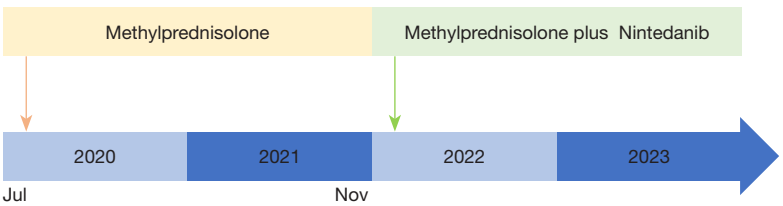

Figure 5 Timeline from July 2020 to October 2023.

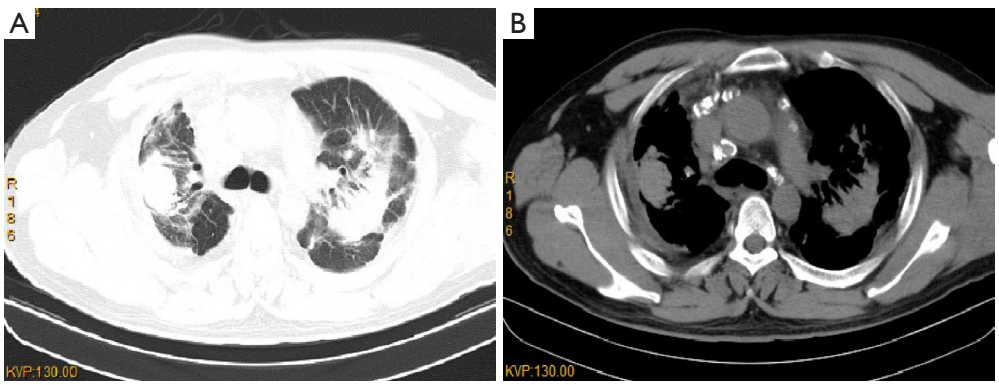

Figure 6 Chest computed tomography scan on March 10, 2023. (A) Progression of the fibrotic masses in the upper lobes of both lungs. (B) Multiple enlarged lymph nodes with calcification in the mediastinum and hilum of the lung, along with eggshell-like calcification of the lymph nodes.

upper lobes of both lungs (*Figure 6A*), multiple enlarged lymph nodes with calcification in the mediastinum and hilum of lungs, and eggshell-like calcification of lymph nodes (*Figure 6B*). Given the disease progression and limited treatment options, lung transplantation was indicated. However, the lack of donors and economic constraints have so far precluded the performance of lung transplantation.

All procedures performed in this study were in accordance with the relevant ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this article and accompanying images. A copy of the written consent is available for review by the editorial

office of this journal.

Discussion

Silicosis is a form of pneumoconiosis that results from the inhalation of silica particles and can cause progressive, irreversible, and often fatal lung inflammation and fibrosis (6). The development of silicosis can be divided into two main stages, the inflammatory stage and the fibrotic stage, which are primarily characterized by the accumulation of inflammatory cells and the deposition of collagen fibers, respectively (7). SiO_2 particles enter the lungs through the respiratory tract and stimulate alveolar macrophages to secrete inflammatory factors, causing neutrophils and lymphocytes to accumulate in the lungs and amplifying the inflammatory response (8,9). Subsequently, inflammatory factors induce fibroblasts to differentiate into myofibroblasts and epithelial cells to transform into fibroblasts, with the secretion and synthesis of a large amount of extracellular matrix eventually developing into irreversible pulmonary fibrosis (10). Silicosis can be pathologically classified as nodular, silicosis, progressive massive fibrosis, or diffuse interstitial fibrosis (11). In the early stage of the disease, patients do not have significant symptoms due to the compensatory capacity of the lungs. As the disease progresses, the degree of risk and the difficulty of treatment increase significantly. Patients with silicosis begin to show symptoms such as cough, sputum, dyspnea, and chest pain, but their symptoms appear similar to those of other respiratory diseases, and so it can be difficult to diagnosis patients according to these symptoms. Imaging methods are thus necessary for diagnosis, along with knowledge of occupational history and radiological findings. In our case, the patient's chest CT showed diffuse alveolar-like nodules, mediastinal lymph node enlargement, and a history of exposure to artificial stone dust. Based on clinical manifestations and laboratory examination, other similar lung diseases were excluded, and when diagnostic criteria for silicosis were compared, silicosis could be diagnosed. Silicosis increases the susceptibility to mycobacterial diseases, autoimmune diseases, and bronchial cancer (12). SSc after exposure to silica is considered to be an exceedingly rare complication.

SSc is an infrequent autoimmune disorder distinguished by immune dysregulation, endothelial impairment, vascular abnormalities, and dermal and visceral fibrosis (3). It mainly damages the internal organs including the lungs, heart, kidneys, and intestines, of which the lungs typically are the most commonly and seriously damaged (13,14). Chronic fibrotic change, thickening of the interlobular septum, and pleural effusion are the most common pulmonary imaging findings of SSc (15). The initial manifestations of SSc are considerably heterogeneous. The majority of patients commonly exhibit symptoms such as Raynaud phenomenon, skin swelling, skin tightness, skin sclerosis, and finger (or toe) end ulcer or gangrene. Conversely, a minority of patients may initially present with telangiectasia, joint pain, hand deformity, muscle weakness, weight loss, gastric reflux, intestinal symptoms, pulmonary fibrosis, pericardial effusion, or renal crisis. Patients with SSc often have specific autoantibodies, such as topoisomerase I (anti-TOPO/anti-SCL-70), anticentromeric antibodies, ribonucleoprotein, and anti-RNA polymerase III (RNApol3). Anti–SCL-70 antibodies are the predominant autoantibodies present in patients with silica-associated SSc and are typically associated with severe interstitial lung disease (16,17). An increase in the production of anti-SCL-70 antibodies might occur in genetically susceptible individuals exposed to silica. In this case, the patient had skin thickening of the fingers of both hands extending proximally to the metacarpophalangeal joint, which was accompanied by positive results for anti-SCL-70 antibodies and Raynaud phenomenon. Consequently, the patient was diagnosed with SSc according to the 2013 American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) SSc classification criteria (18).

There is presently no standard treatment for silicosis, and therapy mainly consists of symptomatic treatment and treatment for complications to delay progression, with no drugs being identified that can reverse or even halt its progression. The early detection of silicosis is essential to preventing lung injury and silico-related complications, and thus prevention is superior to cure. Currently, the main treatment of systemic scleroderma is immunosuppression and antifibrotic therapy (19). The treatment of ES is no different to that for idiopathic forms of SSc. Case reports of ES describe the use of methylprednisolone, mycophenate, azathioprine, cyclophosphamide, acetylsalicylic acid, methotrexate, endothelin receptor antagonists, amlodipine, and nifedipine for treatment (20-23). In our case, after diagnosis, the patient was treated with methylprednisolone. Upon discharge, the plaque color of both hands became lighter than previously, the swelling significantly subsided, and the skin temperature slightly increased. Methylprednisolone was gradually reduced, and treatment was continued. There is no literature on the use of

nintedanib in the treatment of ES. In this case, nintedanib was given on the basis of oral prednisolone treatment, the skin of the patient's face and hands became softer, and he could perform mild activity without the assistance of oxygen inhalation. Nintedanib, an intracellular tyrosine kinase (TK) inhibitor, can reduce the differentiation of myofibroblasts and the release of collagen in dermal fibroblasts in patients with SSc (24). Nintedanib has also demonstrated dose-dependent antifibrotic effects in different animal models of SSc, including in a bleomycin skin fibrosis model for preventive and therapeutic applications (25). In one clinical study, nintedanib inhibited the progression of pulmonary fibrosis (26), and it has been approved for treating SSc interstitial lung disease in many countries. It may ultimately be that lung transplantation is the only treatment that can improve the long-term prognoses for these patients. However, the availability of donors and concerns about comorbidity have limited the application of lung transplantation. Empirical research indicates that the 1-year and 5-year survival rates of patients with pulmonary fibrosis after lung transplantation are 81% and 66%, respectively (27), and the survival rate of patients with ES may be even lower.

Conclusions

The clinical course of patients with silicosis may be complicated with SSc. Here, we describe a rare case with the aim of raising awareness of the relationship between silicosis and SSc, reminding clinicians that maintaining a high index of suspicion is key to diagnosing ES. Patients with ES have significantly worse symptoms and shorter survival than do those with pure silicosis and SSc because they sustain greater lung damage. First, it is critical to take preventive measures and to monitor those occupationally exposed to silica. Second, early diagnosis and timely and rational treatment are crucial to improving the survival and prognosis of those with ES.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1841/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the relevant ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this article and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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