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CORRESPONDENCE

Erasmus syndrome: systemic sclerosis and silicosis co-occurrence

Dear Editor,

Erasmus syndrome which is the development of systemic sclerosis (SSc) in a patient after exposure to silica either together with silicosis or without, is a very rare entity. In the literature there are very few cases. Here we present a patient with Erasmus syndrome whose pulmonary and skin findings remained stable after 1 year of follow up.

A 34-year-old man was having chest pain and dyspnea since 2010 and was then diagnosed as having silicosis. He was a worker in the powder painting and teflon sandblasting industries and had worked for many years without using a dust mask and without proper air conditioning. He was also an ex-smoker with a history of 10 pack years. After diagnosed with silicosis, he quit the job and has been working as a bus driver since then. In 2012 he began to have attacks of Raynaud phenomenon and arthritis of the wrist joints besides cough and dyspnea.

He was admitted to our Rheumatology Outpatient Clinic in June, 2016. On his physical examination he seemed underweight, he had cold and slightly swollen and cyanotic hands but sclerodactily was not significant. He had neither digital tip ulcers nor pitting scars. His modified Rodnan skin score was 6/51. No pathological sounds were heard on chest auscultation. His antinuclear antibody (ANA) test was positive with nuclear, fine speckled pattern and titer was 1/2560. Anti-Scl-70 antibody and anti-Ku antibody were also positive in the extractable nuclear antigen (ENA) profile.

On echocardiography 25 mmHg of pulmonary artery pressure was detected. On his chest X-ray bilateral fibrotic changes and areas of bronchiectasis were visible. High-resolution computed tomography (HRCT) of the lungs revealed bilateral massive fibrotic changes on superior and inferior lobes, traction bronchiectasis, pleural thickenings, as well as mediastinal and hilar multiple calcified lymph nodes (Fig. 1). Pulmonary function tests reflected a forced vital capacity (FVC) of 65%, forced expiratory volume in one second (FEV_1) of 59%, FEV_1/FVC of 76%. Diffusion capacity of carbon monoxide (DLCO) test could not be done due to lack of availability.

His hemoglobin value was 13.5 mg/dL, sedimentation rate was 25 mm/h and C-reactive protein was 7 mg/L. According to 2013 American College of Rheumatology/European League Against Rheumatism

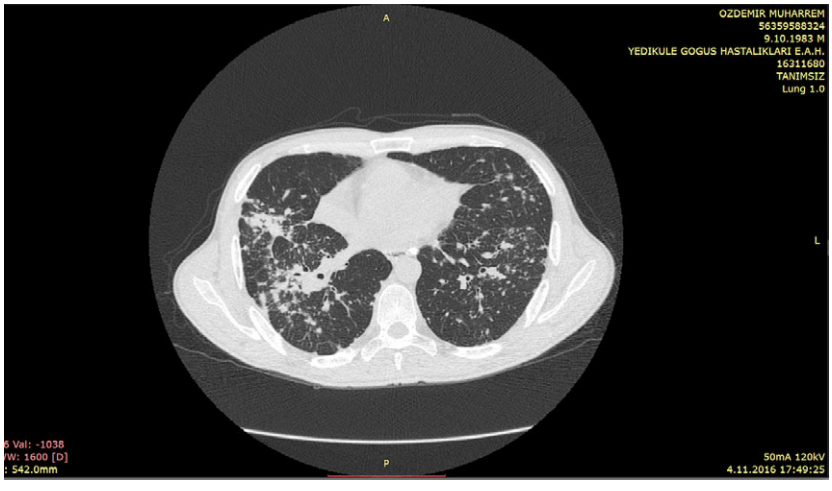

Figure 1 Basal high-resolution computed tomography.

systemic sclerosis classification criteria he registered nine points (Fig. 2).[1]

We diagnosed the patient as diffuse SSc and started methotrexate 15 mg/week and folic acid 1 × 1/week for arthritis and 10 mg of amlodipin and 100 mg of asetylsalicilic acid per day for Raynaud syndrome. One year after there was no progression of the lung disease as can be seen in the new HRCT images (Fig. 3) and pulmonary function tests.

Silicosis is one of the pnuemoconioses caused by inhalation of the silica dust and results in chronic inflammation and progressive lung fibrosis especially in the upper lobes in the long term.[2,3] Unfortunately, to date there is no effective treatment strategy other than symptomatic treatment.[4]

Silica exposure can also cause several autoimmune diseases like rheumatoid arthritis, systemic lupus erythematous, systemic sclerosis and so on.[5,6] Erasmus syndrome is the development of SSc in a patient after exposure to silica. In fact this name was abandoned after it was realized Bramwell discovered this association long before Erasmus.[7,8] This syndrome is described in some specific industrial workers, like stonemasons,[7] gold miners,[8] marble workers,[2] jewelry workers,[9] denim sandblasting workers,[10] ceramic workers and dental technicians.[6] According to a large meta-analysis of 15 case-control studies, the odds ratio of developing SSc for the patients who were exposed to silica is denoted as 2.81 (95% CI 1.86-4.23; $P < 0.001$).[6] In another study, the risk of development of SSc is more than 24 times greater in people who have previously been diagnosed as having silicosis.[11] In a recent systematic review, it is pointed out that silica is especially a risk factor for male SSc patients, and also the diffuse form and interstitial lung disease (ILD) are more common in exposed patients than in unexposed ones and also death is more common in exposed patients.[12,13]

According to a large Brazilian cohort study, nine of 947 SSc patients were diagnosed as having Erasmus syndrome; all of these patients had ILD, Raynaud's phenomenon and esophageal dysmotility.[14]

In a study by Tomokuni *et al.*,[15] anti-topoisomerase (anti-scl-70) positive silicosis patients with no clinical symptoms of SSc have been reported to have increased partial pressure CO_2 alveolar values and lower FVC percentages than anti-scl-negative silicosis patients, so anti-scl-70 positivity is stated to be related with progression of lung fibrosis.

Item	Sub-items	Weight/score
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints(sufficient criterion	–	9
Skin thickening of the fingers(only count the higher score)	Puffy fingers Sclerodactyly of the fingers(distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	2 4
Fingertip lesions(only count the higher score)	Digital tip ulcers Fingertip pitting scars	2 3
Telangiectasia	–	2
Abnormal nailfold capillaries	–	2
Pulmonary arterial hypertension and/or interstitial lung disease(maximum score is 2)	Pulmonary arterial hypertension Interstitial lung disease	2 2
Raynaud's phenomenon	–	3
SSc-related autoantibodies(anticentromere, antitopoisomerase 1[anti-Scl-70], anti-RNA polymerase-III) (maximum score is 3)	Anticentromere 3 Anti-topoisomerase I Anti-RNA polymerase-III	3

Figure 2 American College of Rheumatology/European League Against Rheumatism 2013 systemic sclerosis (SSc) classification criteria.

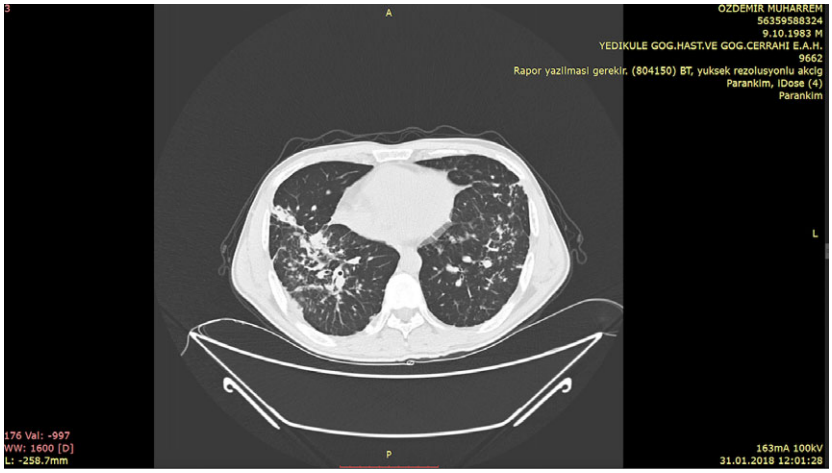

Figure 3 High-resolution computed tomography 1 year after treatment.

Pathogenesis is not fully understood but can be simply explained as accumulation of silica in alveoli causing damage to epithelial cells and stimulating chronic inflammation and auto-antibody production like anti-scl-70 and anti-centromere, with collagen accumulation and fibrosis eventually developing. Many cytokines like interleukin (IL)-1-β, tumor necrosis factor-α, interferon (IFN-α)-transforming growth factor (TGF-β)-IL-10 and reactive oxygen and nitrogen species, apoptotic pathways, immune cells like T cell subtypes, B cells, macrophages, fibroblasts, epithelial cells, are all involved in this process.[3,4]

In the treatment decision of Erasmus syndrome, severity, duration and progression rate of ILD is important, because it is the main cause of morbidity and mortality. In reported cases with Erasmus syndrome (methyl)prednisolone, methotrexate, endothelin receptor antagonists, acetyl salicylic acid, amlodipin/nifedipin are the medicines that have most commonly been used.[2,9] In one study it was shown that SSc-related ILD mostly progresses in the first 4 years of the disease.[16] According to Goh *et al.*,[17] if extent of lung fibrosis on HRCT is above 20%, then it is called extensive disease and immunosuppressive treatment is necessary; if extent of lung disease on HRCT is indeterminate, then FVC can be used. If FVC values are below 70% then immunosuppressive treatment is again needed. Also treatment is usually effective in the early stages of the lung disease and if there is progressive deterioration of FVC (more than 15%) or DLCO (more than 10%) in a 12 month period then therapy must be given.[18] Parenteral cyclophosphamide followed by mycophenolate mofetil (MMF) or azathioprine with or without prednisolone is the most commonly used regimen in interstitial lung disease treatment.

As lung fibrosis was present for 6 years and no deterioration of lung function was noted since the patient's admission to our clinic, immunosuppressive treatment like cyclophosphamide or MMF was not considered for our patient. In an editorial review by Papiris *et al.*[19] it is said that so far full fibrotic lung damage cannot be repaired, therefore rheumatologists should not use immunosuppressive drugs for these kinds of patients because immunosuppressive drugs are not proven to be effective and they may cause very serious side effects like lung toxicity or infections. For this patient, not scleroderma but silicosis is the main reason for lung damage, so in order not to give further harm to the patient by causing opportunistic infections, we prefer to give only methotrexate for arthritis and for prevention from progression of skin and lung disease. And after 1 year of follow up there was no progression in the severity of lung disease as the new CT images and pulmonary function tests remained the same. If fibrosis progresses, hematopoietic stem cell transplantation or lung transplantation may be considered for this patient.[18]

In our opinion, future research about treatments targeting the cytokines like TGF-platelet-derived growth factor and endothelin-1 or inflammatory and fibrosing cells that take roles in the pathogenesis of silicosis and systemic sclerosis are strongly needed.

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