Erasmus syndrome: The association of systemic sclerosis and silicosis

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Abstract

Erasmus syndrome is the association of the exposure to silica and the subsequent development of systemic sclerosis, a rare occurrence, with scarce data in medical literature, which can be attributed to little knowledge of the syndrome and underdiagnosis. It is important to recognize this association as it has a worse respiratory prognosis than the idiopathic form of systemic sclerosis and since autoimmune diseases are rarer in men, it is easy to do exposure research when they occur. We describe the case of a 59-year-old man, a bricklayer by craft since the age of 15, who presented with respiratory symptoms and skin alterations and in whom this syndrome was diagnosed during his recent admission.

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Introduction

Silicosis is an occupational disease caused by exposure to crystallized silica by inhalation, retention, and inflammatory reaction that leads to irreversible pulmonary fibrosis. It occurs especially in quarrying, mining, masonry, and sandblasting workers [1,2].

Exposure to silica is not only associated with silicosis, but also with chronic obstructive pulmonary disease (COPD) and lung cancer, as well as an increased risk of tuberculosis and autoimmune diseases; the latter especially linked to intense exposures, due to the increase of the synthesis of antibodies and immune complexes, even in the absence of the disease [2,3]. Association has been found with systemic sclerosis or scleroderma (SSc), systemic lupus erythematous, rheumatoid arthritis, dermatomyositis/polymyositis, and vasculitis associated with neutrophil cytoplasmic antibodies (ANCA) [2-4].

SSc has been defined as a generalized disorder of endothelial dysfunction, characterized by progressive fibrosis and vascular obliteration in the skin, gastrointestinal tract, lungs, heart, and kidneys [3]. Although the etiology is not clear, it is known that environmental factors play an important role: silica dust, vinyl chloride, epoxy resin, bleomycin, aromatic hydrocarbons, and oils have been identified. However, the effects of exposure are reversible in all except silica, especially in particles smaller than one micrometer, since they are inert and can remain in the tissue indefinitely [3].

Erasmus syndrome (ES) is characterized by the association of silica exposure with or without silicosis and the subsequent development of SSc, especially in men, given its occupational relevance [5]. It is indistinguishable clinically, serologically, and immunologically from an idiopathic SSc, but occurs with more severe lung damage [2,4,5]. We describe a male patient, who worked as a bricklayer for more than 40 years, with compatible tomographic findings for silicosis and who developed SSc after exposure, for which ES was diagnosed.

Case Report

A 59-year-old male patient, a bricklayer by craft since the age of 15, working with cement, bricks, roofs, and paints and

never using protective equipment during the job. He denies being a smoker, the last time he reported tobacco use was at the age of 18. He refers being a healthy person throughout his life, but since October 2016 he reports dry cough, accompanied by dyspnea beginning December 2017. Thus, he sought medical attention and was diagnosed with COPD, for which a chest x-ray was requested, which was interpreted as normal (Figure 1a), and spirometry, which was not performed at that time. He was treated with albuterol and ipratropium in the outpatient clinic. In control with internal medicine in June 2019, he refers to the diagnosis of COPD, however, he has no respiratory symptoms, so spirometry is requested. It reports a normal flow-volume curve (Figure 1b), so COPD is ruled out. He reports occasional use of bronchodilators as needed. In June 2021, he presented respiratory symptoms and fever, an X-ray was taken that was interpreted as multilobar pneumonia, probably due to SARS-CoV-2, with outpatient management with moxifloxacin and formoterol-budesonide, with a good response. Complete vaccination schedule for SARS-CoV-2 in July. An echocardiogram was performed in November 2021, which reported a left ventricular ejection fraction of 58%, with slight dilation of the right cardiac cavities and systolic pressure of the pulmonary artery of 45-50 mmHg, with an intermediate probability of pulmonary hypertension. In December 2021, he was admitted to Hospital Santa Clara, reporting a year of episodes of dry cough, night sweats and weight loss of approximately 6 kg, and subjective fever, but with 8 days of exacerbation of symptoms. Physical examen revealed oxygen saturation of 85%, without added pulmonary sounds, telangiectasias are observed on the face, sclerodactyly (Figure 1c) and the patient reports color changes in the hands with cold, it was considered Raynaud's phenomenon (Figure 1d).

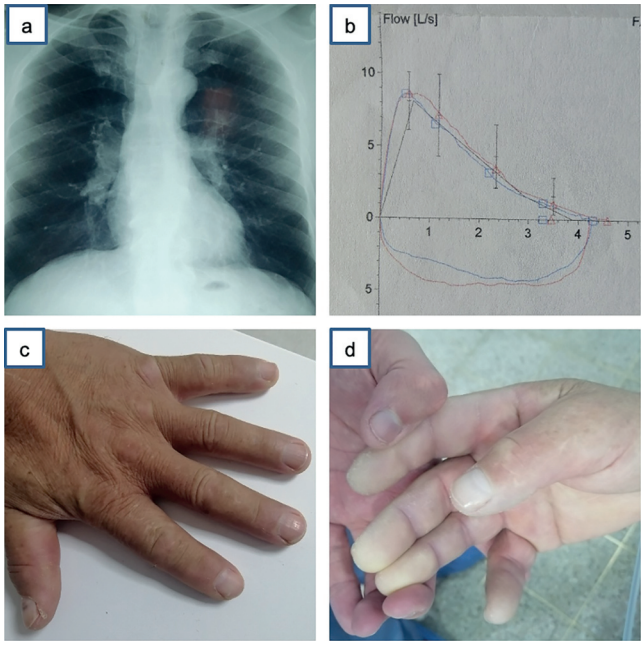

Figure 1. a) Normal chest X-ray from 2017. b) Normal flow-volume curve. c) Patient's hand showing sclerodactyly. d) Raynaud's phenomenon was evidenced during the bronchoscopy.

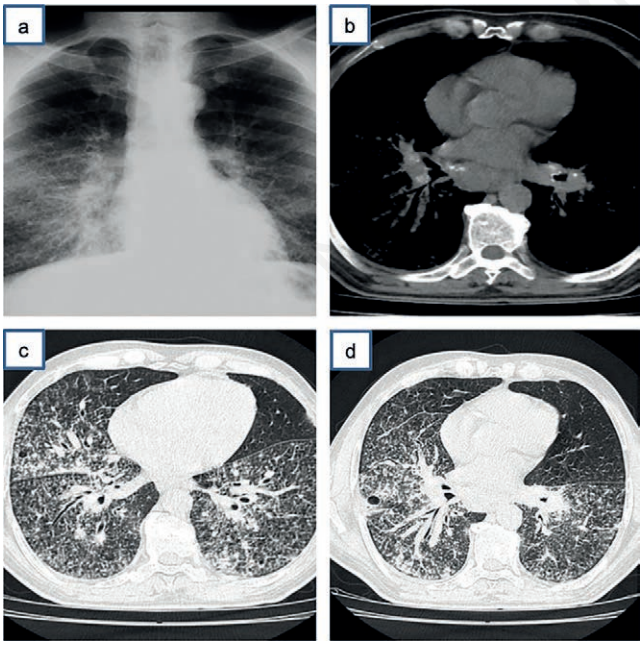

Figure 2. a) Chest X-ray June 2021, with multiple bibasal pulmonary nodules. b) CT sca in mediastinum window showing calcified hilar and mediastinal lymph nodes. c and d) CT scan in the pulmonary window with multiple centrilobular micronodules, which converge in some areas, with a tendency to consolidate, and some small pulmonary cysts.

A chest X-ray was performed, which showed multiple predominantly bibasal micronodules (Figure 2a), as such, a miliary pattern was considered. The bloodwork reported no leukocytosis, but polyglobulia (hemoglobin 17 g/dl and hematocrit 52%). Due to the radiographic pattern, tuberculosis was suspected and smear microscopy and GeneXpert MTB/RIF in the sputum and high-resolution computed tomography (HRCT) of the chest were requested. This study reported calcified mediastinal lymphadenopathy (Figure 2b), diffuse centrilobular micronodules, albeit with a greater bi-basal predominance, with areas of convergence and tendency to consolidate (Figure 2 c,d). With 3 negative sputum smears and negative GeneXpert, evaluation with pneumology was requested. Confirming a history of exposure to dust in masonry for more than 40 years, providing with previous radiographs from 2015, in which it is normal, the patient denies important changes in his practice. Due to skin and echocardiogram findings, antinuclear and anti-Scl-70 (topoisomerase I) antibodies were requested. Bronchoscopy was performed, observing generalized inflammation and edema of the bronchial mucosa with mild and moderate anthracosis. Bronchoalveolar lavage was taken for microbiological studies, which were negative. Reactive antinuclear antibody (ANA) results were received at 1/320, homogeneous pattern, with positive anti-Scl-70 at 116.8 EU/ml and negative extractable antinuclear antibodies (ENAS). Considering prolonged exposure to silica, with suggestive tomographic findings and bronchoscopy findings, silicosis is diagnosed; In addition, with telangiectasias, sclerodactyly, Raynaud's phenomenon, and positive anti-Scl-70, he meets the criteria for SSc, thus presenting the association known as Erasmus syndrome. He was evaluated by rheumatology, considering that the skin involvement is limited and there is no pattern of interstitial lung disease. Follow-up by outpatient consultation in conjunction with pneumology, with control of pulmonary function tests and a new HRCT to decide on immunosuppressive treatment, nifedipine was indicated to treat Raynaud's phenomenon.

Discussion

The development of systemic sclerosis after exposure to silica is considered a very rare complication. In 1957, Erasmus evaluated gold mine workers in South Africa, with high exposure to silica, of which 32% had ES, confirming that it is a rare complication, further confirmed by Rodman with 42% of patients with prolonged exposure to silica [1,3,4,5]. ES presents long after exposure with a mean of 16.4 years (4-36 years), and in 72% of cases the first organ affected is the lung, with an increased risk of bibasal pulmonary fibrosis [2,3]. As in the case described, with an exposure of more than 40 years, respiratory symptoms are both the initial and the most problematic. An increased incidence of ES has been shown in patients with silicosis, and the risk is 4 times higher than the general population, with an odds ratio varying from 0.87 to 37 in other publications [6]. It may be higher depending on the intensity of exposure more than the duration, but it is an infrequent association and with few epidemiological data worldwide [3,6], we did not find publications in Colombia. In patients exposed to silica, the incidence of SSc varies from 16-37%, it has been found that 10-44% of patients with silicosis without SSc have elevated anti-Scl-70, being the predominant antibody, which suggests its relationship with pulmonary fibrosis [2-4,7]. However, fewer patients with high titers of ANA (>1:1,280) compared to those with an idiopathic disease, although the latter may be positive in 34% of patients with silicosis [2-4,7,8]. The patient complies with all these statements, with positive anti-Scl-70, predominantly bibasal lung damage that may be part of the explanation in this case for not being predominantly apical, which is the most typical of silicosis. The latency may be longer than the exposure period. In a series of cases, latency ranged from 5-48 years [3]. Cases have also been observed in patients with high exposure to silica but with shorter exposure time (5-10 years), these patients manifest accelerated silicosis, and this form has been related to greater susceptibility to an autoimmune disease [1,2].

Chronic exposure to silica causes humoral and cellular alterations such as positive rheumatoid factor, hypergammaglobulinemia (in up to 64% of patients), and alteration of T lymphocytes [2,3,7] and interleukin 2 (IL-2) soluble receptors [1,2,9]. The increase in cytokines such as IL-1, IL-6, interferon-gamma, and tumor necrosis factor-alpha stimulate collagen production and fibroblast proliferation, leading to skin sclerosis, vascular occlusion, and pulmonary fibrosis [1,2,7,9]. This is supported by the fact that elevated levels of soluble IL-2 receptors are found in ES [3]. Silica particles are covered by collagen, which leads to fibrosis, establishing the characteristic granulomas of silicosis [7].

When the silica particles are phagocytized by the macrophages, it induces the release of inflammatory cytokines, producing significant acute and chronic inflammation, and by not being able to eliminate the particles, the macrophage becomes dysfunctional, which explains the increased risk of tuberculosis [3,4,7,9]. But when the macrophage dies and the particles are released, they are phagocytized by other macrophages, perpetuating the inflammatory reaction [3,4,7,9]. Another theory suggests that the production of free radicals by macrophages is increased, which together with cytokines, damage type I pneumocytes and increase the proliferation of type II pneumocytes, as well as greater recruitment of inflammatory cells, producing alveolitis and loss of function. The epithelial barrier, which carries silica particles to the interstitium, which could explain pulmonary interstitial fibrosis [2-4,9].

The most frequent clinical findings are Raynaud's phenomenon (81-100%), sclerodactyly, and interstitial lung disease (50%), with few cases of esophageal dysmotility [8,10]. The lung parenchyma may exhibit an interstitial pattern in SSc, either nonspecific interstitial pneumonia or usual interstitial pneumonia, a nodular pattern of silicosis, or both [3]. In chest tomography, we observe linear images, ground-glass opacities, honeycomb patterns, micro centrilobular nodules, or changes indistinguishable from the idiopathic form [2,3]. Our patient shows a nodular pattern of silicosis, but from the basal areas. Multiple theories try to explain why silica is deposited in the apices, but it has been considered that workers at high altitudes, like our patient, have very good pulmonary vital capacity; this added to the size of silica particles, these may have greater deposits in basal areas [11]. We can find mediastinal or hilar adenomegalies in 35% of cases and 12% in combination, this is related to greater exposure, as shown in the case [6]. Radiological changes may precede or follow the diagnosis of ES after a few years. The main change at the functional level is the reduction in the diffusing capacity for carbon monoxide, with or without a restrictive pattern in spirometry [3].

Silicosis has no standard treatment, and silica-induced SSc is treated in the same way as idiopathic SSc. Case reports of ES have described the use of methylprednisolone, mycophenolate, cyclophosphamide, azathioprine, methotrexate, acetylsalicylic acid, antagonists of endothelin receptors, nifedipine, and amlodipine [10,12].

Spontaneous regression of some cases of idiopathic SSc has been documented but never in ES [4,5]. They seem to have shorter survival compared to idiopathic SSc because they present with greater lung damage. One study describes smoking patients, with pulmonary hypertension, enlarged lymph nodes, and with diffuse cutaneous SSc have worse respiratory outcomes [4-6]. In men, autoimmune diseases are rarer compared to women, so it may be suggested to investigate exposure to silica or silicosis in all men with SSc since it has been described that 50% were exposed [4-6].

Conclusions

Erasmus syndrome is still an infrequent association, rarely reported in the medical literature, as well as other autoimmune diseases that have been related to occupational diseases. We must always take into account cases in male patients since they are the ones who carry out the work in risk for silicosis. The case presented meets most of the described characteristics of ES, very similar to other cases reviewed, although the radiological image is not typical of silicosis, with two possible explanations as to what could be the reason of such behavior. The therapeutic management of SSc was postponed until lung function is evaluated. There is an important lesson to always investigate autoimmune diseases when having a patient with silicosis that has some systemic compromise, such as skin involvement. Since these associations generally worsen the patient's prognosis, especially from the respiratory point of view, the lack of knowledge about this association can explain the underdiagnosis of it in our setting.

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