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Case report

Erasmus syndrome – silicosis and systemic sclerosis☆

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ABSTRACT

Silicosis is the most frequent pneumoconiosis, resulting from the inhalation of mineral dust containing silica or silicates. It is mainly characterized by irreversible lung fibrosis, being associated with the development of other diseases, such as pulmonary tuberculosis, lung cancer and autoimmune conditions. The connective tissue disease following exposure to silica occurs usually 15 years after the initial exposure. Erasmus syndrome consists of the association of systemic sclerosis following exposure to silica with or without silicosis. We report the cases of two patients diagnosed with silicosis, who developed systemic sclerosis.

Síndrome de Erasmus – silicose e esclerose sistêmica

Palavras-chave:
Esclerodermia
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RESUMO

A silicose é a pneumoconiose mais frequente, decorrente da inalação de sílica ou de poeiras minerais contendo silicatos, caracterizada principalmente pela fibrose pulmonar de caráter irreversível. Está associada com o desenvolvimento de outras doenças, incluindo tuberculose pulmonar, câncer pulmonar e doenças autoimunes. A doença do tecido conjuntivo posterior à exposição à sílica ocorre geralmente após 15 anos do início da exposição. A síndrome de Erasmus refere-se ao desenvolvimento de esclerose sistêmica em indivíduos previamente expostos à sílica e que apresentavam ou não silicose. Os autores relatam dois casos de pacientes com diagnóstico de silicose que desenvolveram esclerose sistêmica.

☆ Study conducted at the Hospital Universitário Getúlio Vargas, Universidade Federal do Amazonas, Manaus, AM, Brazil.

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Introduction

Pneumoconiosis is a group of lung diseases associated with exposure to dust particles, such as, silica, cobalt and talc. The disease is usually related to occupational exposure.[1] Inhalation of silica dust associates with the occurrence of silicosis, chronic obstructive pulmonary disease, lung cancer, and renal failure, and the increased risk for pulmonary tuberculosis and autoimmune diseases, such as systemic sclerosis (SSc), rheumatoid arthritis and systemic lupus erythematosus.[1,2]

Systemic sclerosis is an autoimmune disease with vascular changes and diffuse tissue fibrosis. The association of previous exposure to silica and SSc was described by Erasmus in 1957.[2,3]

This study reports two cases of Erasmus syndrome in patients with history of occupational exposure to silica, who, ten years after being diagnosed with pneumoconiosis, developed SSc. The first patient had skin manifestations characteristic of diffuse SSc, while the second had limited SSc (CREST syndrome).

Case 1

The patient is a 35-year-old male with an occupational history of quartz crushing from 1996 to 2001. He was released from work because of dyspnea on exertion. He sought a pulmonologist, who, after clinical assessment and complementary tests, made a presumptive diagnosis of pneumoconiosis, due to the presence of 95% free silica in the sand resulting from crushing.

Lung biopsy was performed and the histopathology evidenced mononuclear inflammatory infiltrate with frequent areas of fibrosis, suggesting bronchiolitis *obliterans* with organizing pneumonia (BOOP). Once established the diagnosis of subacute silicosis, pulse therapy was initiated with methylprednisolone (1 g) for three days, and maintenance with prednisone. The symptoms subsided.

Ten years after the diagnosis of pneumoconiosis, the patient was admitted to the Rheumatology Service of the Hospital Universitário Getúlio Vargas (HUGV), in the city of Manaus, Amazonas state, reporting dyspnea on mild exertion, dysphagia to solids, postprandial vomiting, digital ulcers, and 5-kg weight loss in 30 days. He reported neither smoking nor illegal drug use.

On physical examination, the patient was emaciated, showing scleroderma facies, sclerodactyly, diffuse skin thickening with modified Rodnan score of 30, facial telangiectasia, leukomelanoderma, Raynaud's phenomenon, distal phalangeal resorption, digital micro-scars, ulcerated lesions on his right medial malleolus and elbows. Pulmonary auscultation: reduced respiratory sounds in the bases. Cardiac auscultation: regular heart rhythm with P2 > A2, and blood pressure of 160/90 mm Hg. The laboratory tests were as follows: hemoglobin, 10.9 g/dL; hematocrit, 35%; leukocyte count: 9700/mm^3; erythrocyte sedimentation rate (ESR), 20 mm; negative C-reactive protein; antinuclear antibody (ANA) HEp-2, 1:1280, nuclear speckled pattern; negative anti-Scl 70 antibody and rheumatoid factor. Negative serology for HIV, HBV and HCV. Negative tuberculin skin test. Normal urinalysis. Spirometry: moderate restrictive ventilatory disorder. Chest computed tomography (CT): ground glass opacities (Fig. 1). Echocardiogram: left ventricular ejection fraction of 63% and pulmonary artery systolic pressure of 53 mm Hg. The diagnosis of diffuse SSc was established on clinical basis. Prednisone (40 mg/day), amlodipine (10 mg/day) and cyclophosphamide (1 g/month) were initiated. The patient's clinical findings improved.

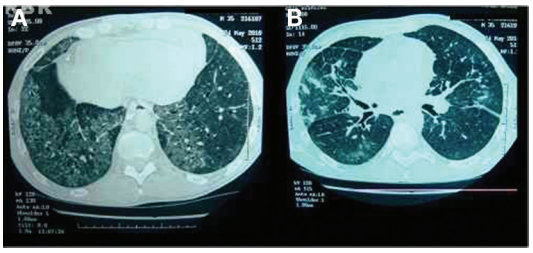

Fig. 1 – Reticulonodular infiltrate, ground glass opacities, some of confluent aspect, disseminated throughout the parenchyma in both lungs, and bronchiectasis in the lower lobes.

Case 2

The patient was a 38-year-old male, miner, who worked with explosives without observing occupational safety and health regulations. He initiated parenchymatous lung disease ten years before seeking medical help.

His chest CT showed pleural pneumopathy mainly in the upper lobes, left pleural effusion and mediastinal lymphadenomegaly. Lung biopsy showed macrophage infiltrate, pulmonary fibrosis and silica particles in the tissue (polaroid materials at 90º). The pleural effusion culture was positive for tubercle bacilli. Treatment with tuberculostatic drugs for six months was initiated.

The patient was referred to the Rheumatology Service of the HUGV, reporting skin thickening in the face, forearms and hands for one year, associated with distal dysphagia to solids and dyspnea on exertion. One month before, as his symptoms got worse, he was hospitalized with dyspnea on mild exertion, epigastralgia with worsening of dysphagia, fatigue and ulcers in his hands. He reported neither smoking nor alcoholism.

His physical examination showed microstomia, sclerodactyly, modified Rodnan score of 14, leukomelanoderma, Raynaud's phenomenon, digital resorption, disseminated skin ulcers (Fig. 2), polyarthritis of his proximal interphalangeal joints, wrists, elbows, knees and ankles. Cardiac auscultation showed regular cardiac rhythm with P2 > A2. Pulmonary

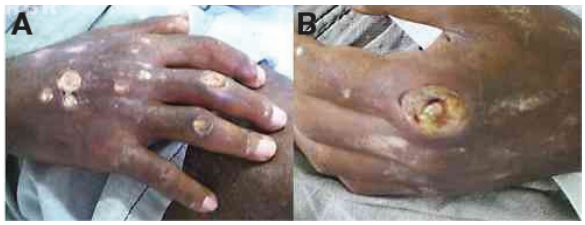

Fig. 2 – Sclerodactyly and ulcers on extensor surfaces.

auscultation: respiratory sounds with crepitant rales in the bases. Laboratory findings: hemoglobin, 8.9 g/dL; hematocrit, 32%, leukocyte count: 14700/mm^3; ESR: 34 mm; negative serology for HIV, cytomegalovirus, and toxoplasmosis; rubella IgM, negative, and IgG, positive; negative culture and search for tubercle bacilli in the sputum. Tuberculin skin test: 3 mm. Anti-Scl 70 and anti-DNA antibodies, negative, and ANA HEp-2, 1:5120, nucleolar pattern. Echocardiography: severe pulmonary hypertension and right overload. Spirometry: restrictive ventilatory disorder. Chest CT: sequela of the specific inflammatory process in the upper lobes, subpleural and intraparenchymatous nodular images, cystic bronchial dilations, some of which were confluent, with a honeycombing aspect, and bilateral pleural thickening. The diagnosis of limited SSc was established, and the following drugs were initiated: nifedipine retard (20 mg, 12/12 h); omeprazole (40 mg/day); metoclopramide and oxacillin (1.5 g, 6/6 h). Severe sepsis from a skin focus developed. The antibiotic spectrum was widened and intensive care support initiated, but the patient died.

Discussion

Silicosis is a pneumoconiosis caused by inhalation of free silica. It is associated with abnormalities of the humoral and cellular immunity, and positivity for antinuclear antibody and rheumatoid factor, hypergammaglobulinemia and alterations in T-helper and T-suppressor lymphocytes.[3,4]

Silicosis is divided into three clinical presentation forms: acute, accelerated, and chronic. The acute form occurs months after an intense exposure to silica particles, finely divided and newly broken, as in sand crushing and rock perforation. The accelerated form occurs 5-10 years after exposure to silica particles. The chronic form is the most common presentation of silicosis, occurring usually 10-15 years after exposure or latency.[1]

Systemic sclerosis is a chronic inflammatory, autoimmune disease characterized by the excessive production of collagen, which causes tissue fibrosis, small vessel impairment and specific autoimmune response.[5-7] There is evidence of the association of SSc with occupational and environmental factors. In 1957, Erasmus reported cases of SSc in gold miners in South Africa, who had been exposed to silica powder.[8-10]

The mechanism of the association of exposure to silica and SSc seems to involve the inflammatory response triggered by silica after phagocytosis and release of mediators by activated alveolar macrophages.[9] Initially, silica particles induce, through either their direct contact with water and lipoproteins of the bronchioloalveolar lining or activation of the macrophages and epithelial cells, the formation of free radicals. When the production of such radicals exceeds the antioxidant defense mechanisms, the following might happen: damage of type I pneumocytes; increased activation of macrophages; induction and proliferation of type II pneumocytes. When proteolytic enzymes are released, more reactive species of oxygen and nitrogen build up, in addition to the release of inflammatory cytokines, such as tumor necrosis factor alpha, transforming growth factor β, interleukin 1, and interleukin 6. Those cytokines recruit macrophages, neutrophils and lymphocytes, causing alveolitis and consequent epithelial barrier integrity loss, thus allowing the entrance of silica particles into the interstitium. The net result is the overproliferation of fibroblasts and collagen production, with consequent interstitial fibrosis.[1,4,5,7,9]

The connective tissue disease occurs, on average, 15 years after exposure to silica, with image patterns of linear ground glass opacities, honeycombing and small subpleural nodules; such changes cannot be distinguished from idiopathic SSc.[10,11]

A meta-analysis has suggested that exposure to silica is associated with an increase in the incidence of SSc, especially in the male sex, but further studies are required.[12,13]

The anti-Scl 70 antibody relates to skin and peripheral vascular involvement, and pulmonary interstitial fibrosis. The patients here reported, both negative for the anti-Scl 70 antibody, showed a restrictive pulmonary pattern, which can be present in both SSc and silicosis. Rustin et al.[13] have reported 17 patients with SSc associated with silica, of whom, 14 had limited SSc and 3 had diffuse SSc. All patients had Raynaud's phenomenon, while pulmonary interstitial fibrosis occurred in 16 patients, 8 of whom were positive for the anti-Scl 70 antibody.

Briefly, pneumoconiosis due to exposure to silica can evolve to SSc. It is worth noting that occupational exposure relates to an increase in the occurrence of severe diseases, and that primary prevention can be performed by using individual protection devices for professionals exposed.

Conflicts of interest

The authors declare no conflicts of interest.

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