SILICOSIS-ASSOCIATED FIVE-DISEASE MULTIPLE AUTOIMMUNE SYNDROME WITH SEVERAL PULMONARY COMPLICATIONS: A CASE REPORT AND LITERATURE REVIEW

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Abstract. *Connective tissue diseases constitute a group of inflammatory disorders that can concurrently affect multiple organs. Pulmonary manifestations of connective tissue diseases include interstitial lung disease, pulmonary hypertension, pleural diseases, and airway compromise. Both interstitial lung disease and pulmonary arterial hypertension have high morbidity and mortality in these patients. Interstitial lung disease affects 40-50% of patients with connective tissue diseases, predominantly systemic sclerosis, rheumatoid arthritis, and inflammatory myopathies. Parenchymal compromise is heterogeneous and depends on the underlying disease. Conversely, pulmonary arterial hypertension is found mostly in systemic sclerosis, systemic lupus erythematosus and mixed connective tissue disease. Delays in the diagnosis of connective tissue disorder associated interstitial lung disease are frequent as evidence is limited and as they often present concomitantly or overlap with other pulmonary diseases. Timely diagnosis and treatment are fundamental to decrease mortality. Treatment varies by the type of connective tissue disease, nevertheless, evidence of these complications in the context of multiple-autoimmune syndrome is still limited. We present a complex case of a 47-year-old male with a multiple-autoimmune syndrome (systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, Sjögren syndrome and mixed connective tissue disease) complicated by interstitial lung disease and pulmonary hypertension, and occurring concurrently with silicosis (Erasmus syndrome), and pulmonary embolism. This case shows the diverse manifestations of connective tissue of the lungs, emphasizes the intricate nature of diagnosing and managing connective tissue disorder-related pulmonary complications in the context of multiple autoimmune syndromes, and the importance of a multidisciplinary team for the diagnostic and therapeutic approach of the patient.*

Key words: *multiple-autoimmune syndrome, interstitial lung disease, connective tissue disease, pulmonary hypertension, non-specific interstitial pneumonia, systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, sjögren syndrome, erasmus syndrome*

Introduction

Connective tissue diseases (CTD) encompass a group of inflammatory disorders affecting multiple tissues and organs. Conditions such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjogren's syndrome (SS), idiopathic inflammatory myopathy (IIM), systemic sclerosis (SSc), and mixed connective tissue disease (MCTD) fall within the CTD spectrum [1]. While most autoimmune diseases are more prevalent in women (approximately 63.9%), the male-to-female ratio varies depending on the type of disease. SS, SLE, SSc, and autoimmune thyroid disease demonstrate the highest incidence rate ratios when comparing both genders [2].

Similar pathophysiological pathways exist among different CTDs, leading to the phenomenon known as polyautoimmunity [3]. Approximately 12-25% of individuals with autoimmune conditions show a predisposition to acquiring further autoimmune disorders [2, 4]. The coexistence of three or more autoimmune diseases was firstly described in 1988 as multiple autoimmune syndrome (MAS) [5]. The presence of MAS has been documented in about 2.1% of patients with autoimmune diseases. However, the concurrent existence of five diseases has been seldom reported in the literature [2, 6, 7]. Since it is a rare condition, to date, there are no studies evaluating the epidemiological characteristics of MAS. Nevertheless, several factors such as female gender, familial autoimmunity, articular involvement, and anti-Ro positivity have been associated with the presence of polyautoimmunity [8].

Environmental factors such as exposure to silica have been directly linked to a two to eightfold risk of developing RA (Caplan syndrome) and SLE, as well as a 24-fold risk of developing SSc (Erasmus syndrome) and ANCA-associated vasculitis [9-

14] . The rarity of Caplan and Erasmus syndromes poses challenges for conducting cohort studies, and the current knowledge relies on case-control studies. It is estimated that the prevalence of these syndromes can reach up to 19% for Caplan's syndrome and 16% for Erasmus syndrome [15, 16]. Although both SSc and RA are more prevalent in women, these syndromes are reported more frequently in men, given a more frequent occupational exposure to silica.

Complications of SSc (particularly respiratory complications) are more frequent in patients with silica exposure compared to those not exposed [9]. The most important include interstitial lung disease (ILD) and pulmonary hypertension (PH) as they are important causes of morbidity and mortality among these patients [17]. While silicosis can generate ILD per se, it is always necessary to rule out that pulmonary involvement is not due to a CTD. This is because, despite the high mortality of ILD, timely treatment has a significant impact on the prognosis and progression, especially in the early stages of CTD-ILD [18]. Treatment choices are contingent on the specific connective tissue disease (CTD), with the most evidence available regarding ILD-SSc. Several randomized controlled trials (RCTs) support the use of cyclophosphamide and mycophenolate mofetil for the treatment of ILD-SSc [19]. Newer evidence also suggests the benefits of rituximab, tocilizumab, and nintedanib in this scenario [19]. There is not strong evidence on how to treat ILD associated with other specific CTDs, and often treatment recommendations are based on expert consensus.

We present a case of a patient with silicosis that developed a five-disease multiple-autoimmune syndrome (SLE, RA, SSc, SS, and MCTD) presenting with both CTD-ILD, PH and a pulmonary embolism, in whom the diagnosis was difficult and adds information on pulmonary complications of multiple autoimmune syndromes in intricate clinical settings.

Case report

We present a 47-year-old patient with a history of simple silicosis diagnosed seven years ago. He worked in an emerald mine since the age of 20, where he was exposed to silica and chlorate detonation residues. The patient presented to our consultation with a three-year clinical history of non-productive cough, pleuritic chest pain, and symmetric inflammatory polyarthralgia affecting proximal interphalangeal joints, metacarpophalangeal joints, elbows, shoulders, and knees. He had previously sought medical attention at another hospital, where a diagnosis of systemic lupus erythematosus (SLE) was established. His daily medication regimen included azathioprine (50 mg b.i.d.) and prednisolone (45 mg per day).

At consultation he reported sicca symptoms, persistent dyspnea, and unyielding arthralgias (following the same distribution previously depicted). At physical examination with sclerodactyly, puffy fingers, clinical evidence of Raynaud phenomenon on fingers and ears. Autoimmunity studies were positive for ANA (1/2560 with fine speckled pattern), anti-Ro (177 uG/mL), anti-Sm (155 uG/mL), anti-RNP (> 200 uG/mL), anti-CCP (28 U/mL), and negative for anti-La (6.75 uG/mL), anti-B2-glycoprotein, and anticardiolipin antibodies. C3 complement levels were normal (116.7 mg/dL), but C4 levels were diminished (6.75 mg/dL).

As for dyspnea studies, a high-resolution chest-CT showed diffuse interstitial lung disease with non-specific interstitial pneumonia (NSIP) pattern with organizing pneumonia (Figure 1 and 2). Tomographic signs of simple silicosis, such as multiple small nodules with a perilymphatic distribution and calcification, as well as hilar lymphadenopathy, were also evident. Spirometry showed CVF 1.63 (33%) VEF1 1.35 (34%) VEF1/CVF 103%, suggesting a restrictive ventilatory pattern, and a diminished DLCO/VA (KCO). Pulmonary volumes calculated by plethysmography showed a diminished TLC and RV/TLC. These findings confirmed the presence of ILD (Figure 1 and 2).

Due to the concomitance of silicosis a pulmonary cryobiopsy (inferior right lobe) was performed on the patient. The histology was consistent with NSIP, and a mediastinal nodule biopsy showed reactive lymphoid hyperplasia. An echocardiogram showed a left ventricle with a normal function (ejection fraction: 65%), mild diastolic dysfunction, normal valve function, dilated right cavities, a normal TAPSE of 22 mm, a tricuspid regurgitation velocity (TRV) of 2.8 m/s an estimated PSAP of 102 mm Hg and mild pericardial effusion. A right ventricle catheterization diagnosed pulmonary artery hypertension with a mean pulmonary artery pressure of 39 mm Hg, a capillary pulmonary artery pressure of 8 mm Hg and a pulmonary vascular resistance of 6 uW. Pro-BNP was negative (30 pg/mL). Coronary angiography was negative for coronary atherosclerotic disease.

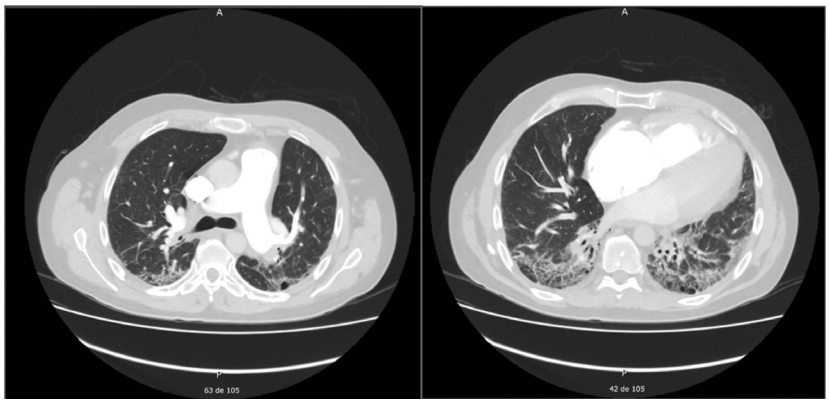


Fig. 1. Chest CT in an axial view. Panel A shows an enlarged pulmonary artery as indirect signs of pulmonary hypertension. Panel B shows areas of ground glass opacities of peripheral distribution with immediate subpleural sparing, reticular opacities with minor subpleural reticulation as signs of fibrotic NSIP

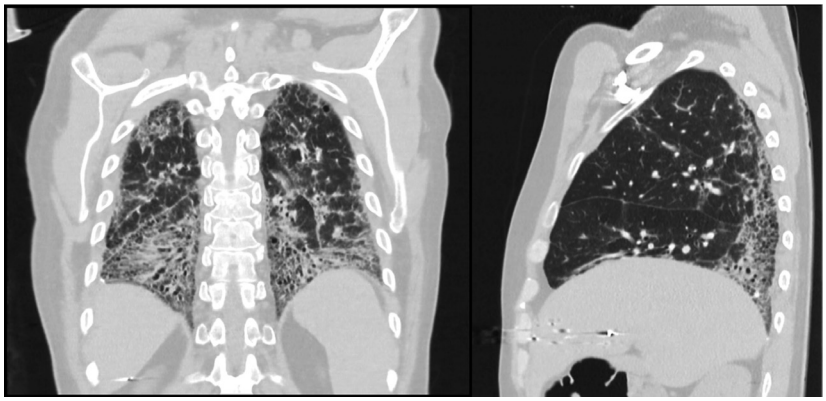


Fig. 2. Chest CT in a coronal (panel A) and sagittal (panel B) views showing signs of ILD with loss of pulmonary volumes, apicobasal gradients, and reticular opacities. Multiple calcified micronodules as signs of simple silicosis are also present

The patient fulfilled criteria for systemic lupus SLE (2019 EULAR/ACR criteria [20]: 15 points; serositis, arthritis, positive ANAs 1/2560 with fine speckled pattern, low complement levels, positive anti-Sm, positive anti-RNP), RA (2020 EULAR/ACR criteria [21] in three phases, a new approach to classifying RA. The work focused on identifying, among patients newly presenting with undifferentiated inflammatory synovitis, factors that best discriminated between those who were and those who were not at high risk for persistent and/or erosive disease -- this being the appropriate current paradigm underlying the disease construct 'RA'.\ nRESULTS: In the new criteria set, classification as 'definite RA' is based on the confirmed presence of synovitis in at least one joint, absence of an alternative diagnosis better explaining the synovitis, and achievement of a total score of 6 or greater (of a possible 10 : 7 points; small-joint polyarthritis of metacarpophalangeal, carpal and proximal interphalangeal, positive anti-CCP), SSc (2013 EULAR/ACR criteria [22]: 25 points; Raynaud's phenomenon, puffy fingers, pulmonary hypertension, positive anti-RNP) (figure 3), pSS (2017 ACR/EULAR criteria [23]: 5 points; sicca syndrome, positive anti-Ro) and MCTD (positive Alarcon-Segovia criteria [24]). Thus, MAS was diagnosed, but no clinical activity was evident.



Fig. 3. Clinical features of our patient showing clinical signs of SSc. Upper panel showing microstomia and telangiectasia. Lower panel showing sclerodactyly

Clinical, paraclinical and histopathological evidence was sufficient for a MAS-ILD diagnosis, and the simultaneous presence of SSc/RA and silicosis was consistent with Erasmus and Caplan syn-

dromes. Due to the extensive imaging findings of ILD and the associated impairment in pulmonary function tests, it was deemed that pulmonary hypertension was secondary to ILD and could be classified as group 3.

Due to the predominant features of SSc, MAS was treated accordingly with nifedipine (30 mg b.i.d.), sildenafil (50 mg b.i.d.) and azathioprine (50 mg b.i.d.) and rituximab therapy. Nevertheless, the patient presented an allergic reaction to the agent (serum sickness) after the first dose. In our follow-up period, the patient received two doses. A month after the start of therapy the patient presented a sub-segmentary pulmonary embolism (posterior segment of the right upper lobe and the medial segment of the medial lobe).

Upon a 6-month follow-up, CT scan showed stability of pulmonary fibrosis and pulmonary function tests showed mild improvement (FVC 44%, FEV1 48%), no evidence of the previously documented pulmonary embolism was found. Management with antifibrotic was thus deferred. An echocardiogram showed a significant reduction in PSAP (43 mmHg) and an improvement of TAPSE (21 mm). Upon this period there was no evidence of MAS activity (with stable complement, C-reactive protein and anti-DNA levels).

Discussion

Polyautoimmunity is defined as presence of two or more autoimmune diseases (ADs) within an individual [3], while multiple autoimmune syndrome (MAS) is characterized by the coexistence of three or more different ADs in a single patient [5]. MAS classification is based on prevalence and associations. MAS-1 includes myasthenia, thymoma, polymyositis, and giant cell myocarditis, MAS-2 comprises SS, RA, primary biliary cirrhosis, SSc, and autoimmune thyroid disorders, and MAS-3 involves 10 autoimmune diseases such as autoimmune thyroid disease, myasthenia/thymoma, pSS, pernicious anemia, idiopathic thrombocytopenic purpura, Addison's disease, insulin-dependent diabetes, vitiligo, autoimmune hemolytic anemia, and SLE [25].

The diagnosis of MAS often requires recognizing the most predominant disease to guide the treatment choices. Our patient showed a predominance of clinical features related to systemic sclerosis (SSc). Numerous epidemiological studies have shown the co-occurrence of other autoimmune diseases in SSc patients [26]. The phenotype of SSc patients with overlap syndromes encompasses the MAS-3 spectrum, with pSS, thyroid disease, primary biliary cirrhosis, RA, inflammatory myopathies, and SLE being the most frequently found. As mentioned earlier the coexistence of five different autoimmune diseases, as in our case, has been scarcely reported in the literature [5]. This is the first case describing the combination of SSc, SLE, SS, MCTD and RA.

There is significant uncertainty regarding the severity of individual autoimmune diseases when they are part of MAS. Some authors argue that CTDs are more severe in the presence of polyautoimmunity; however, there is evidence suggesting that this does not influence severity and may even be a protective factor in some cases [27].

This case exhibits different pulmonary complications of MAS as well. First, CTD-related ILD (CTD-ILD) is a common pulmonary manifestation and is present in 40-50% of patients with CTDs [17, 28]. The prevalence of ILD is 91% for SSc, 80% for DM/PM, 67% in MCTD, 58% in RA, and 13% in SLE [29]. The presence of a progressive fibrosing phenotype is mostly related to RA-ILD followed by SSc-ILD and SLE-ILD [30]. As depicted earlier, the timely identification of CTD-ILD is crucial to prevent disease progression and worse outcomes in terms of mortality [18, 19]. To date, there are no clinical trials studying therapeutic options for MAS-ILD. Evidence is often extrapolated from the context of RA-ILD and SSc-ILD; however, specific information in this scenario is needed. Some agents, such as Rituximab, have been used with positive results in this regard. In our case, the use of this agent was effective in halting the worsening of pulmonary function tests and the radiological progression of the disease.

Secondly, the other pulmonary complication presented in our case was CTD-PAH. CTD-PAH can be found mainly in patients with SSc (75% of cases of CTD-PH), and it has a prevalence of 8-12% in SSc, 3-4% in MCTD, and 1-5% in SLE [31]. Furthermore, there is an association between ILD and the development of PAH, either as a complication of ILD-induced chronic hypoxia (group 3 PH) or as simultaneous manifestations of CTD (group 1 PAH). Notably, there is no direct proportional relationship between the severity of ILD and the development of PAH [32]. In patients with CTD-ILD, one study reported a 20% incidence of PH, with another study reporting SSc-ILD estimated prevalence to be as high as 55% [33, 34]. Although, most evidence regarding ILD-related PAH is derived from idiopathic pulmonary fibrosis studies, newer clinical trials have included patients with PH secondary to CTD-ILD. The INCREASE trial demonstrated that inhaled Treprostinil increased

exercise capacity, assessed with 6-minute walk test, in patients with PAH due to ILD (24% of the patients included had CTD-ILD) [35]. Further research in this area presents a significant need in this field.

Diagnosing CTD-ILD and CTD-PH can be challenging due to the complexities of CTD diagnosis and the potential coexistence of other lung diseases, such as silicosis. Silicosis is the most common pneumoconiosis, originating from the inhalation of crystalline silica. The inhaled particles are phagocytosed by alveolar macrophages, which increase the production of pro-inflammatory cytokines (such as interleukin-1 and tumor necrosis factor-alpha) that activate T-cells, ultimately leading to lung fibrosis. Silicosis is known to trigger various immune responses [11]. It has been associated with hypergammaglobulinemia, positive autoantibodies (such as anti-nuclear antibodies, Scl-70, anti-centromere protein B, and Sjogren syndrome-related antigen), positive rheumatoid factor, and altered T-helper function [36, 37]. Recently, it has been proposed that this relationship persists with the exposition alone, even in the absence of silicosis [38].

The association between silica exposure and the development of autoimmunity is well-documented (particularly increasing the risk of SSc, RA, SLE and ANCA-associated vasculitis). The coexistence of silicosis and RA was firstly described in 1953 as Caplan syndrome, while its association with SSc was depicted later in 1957 as Erasmus syndrome [39, 40]. The exact pathophysiology behind these associations is yet to be understood. It has been proposed that apoptosis derived from silicosis induces the production of TNF-alpha, reactive oxygen species, and products of arachidonic acid metabolism that increase inflammation and production of fibrogenic molecules [37]. This phenomenon is cyclically repeated as apoptotic macrophages release the silica that is phagocyted again by new alveolar macrophages. Silica acts as an epitope for antigen presentation that stimulates a continuous immune response [36, 37].In our patient, three out of the four diseases most closely related to silicosis-induced autoimmunity were present (RA, SSc, and SLE).

Our patient had UIP confirmed by biopsy with organizing pneumonia pattern (OP) in CT scan. When there is evidence of OP pattern, IIMs always must be ruled out. Our patient had negative creatinine phosphokinase, aldolase, and liver enzymes. Having MAS diagnosis, related to an abnormal antibody production by B cells, increases the possibility of having this diagnosis and worsens the patient's prognosis.

This case underscores the need for a comprehensive understanding of the diverse pulmonary manifestations in MAS and emphasizes the challenges in distinguishing between underlying autoimmune entities and environmental factors, such as silicosis, in complex clinical scenarios. Further research in this area is crucial for refining treatment strategies and improving outcomes for patients with MAS-related pulmonary complications.

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