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Refractory Pleuritis in a Patient with Silicosis, Systemic Sclerosis, and Sjögren's Syndrome: Considering the Potential Role of Adjuvant-Induced Autoimmunity

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Patient: Male, 65-year-old
Final Diagnosis: Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) • silicosis • Sjögren's syndrome • systemic sclerosis
Symptoms: Fatigue • fever
Clinical Procedure: —
Specialty: Immunology

Objective: Rare coexistence of disease or pathology

Background: Silicosis, which is caused by the inhalation of crystalline silica, is known to be associated with a variety of autoimmune diseases. Recently, a new pathogenesis called autoimmune/inflammatory syndrome induced by adjuvants (ASIA) has been reported, which occurs after exposure to substances with adjuvant activity, including silica, and shares clinical features observed in several autoimmune diseases.

Case Report: A 65-year-old man with silicosis was admitted to our hospital due to fever and chronic fatigue. Symptoms such as sicca and Raynaud's phenomenon and pleural effusion appeared as new findings on admission. Examination led to a diagnosis of systemic scleroderma (SSc) and Sjögren's syndrome (SjS). Considering that SjS was the main cause of the disease, corticosteroid therapy was initiated. However, the patient's general condition deteriorated, leading finally to his death. Silica acts as an adjuvant, inducing chronic inflammatory cytokine release.

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Thus, prolonged exposure to silica can contribute to the development of autoimmune diseases such as SSc and SjS. In this case, the refractory pleuritis may have been related to the pathogenesis of ASIA. ASIA is difficult to manage if the causative adjuvant cannot be eliminated.

Conclusions: We described a case of newly diagnosed SSc and SjS with therapy-resistant pleuritis in a patient with silicosis. Silicosis complicated with corticosteroid-resistant autoimmune disease suggests that ASIA, an adjuvant disease, is involved in the pathogenesis. Therefore, not only SSc and SjS but also the pathogenesis of ASIA should be considered in such cases. Since adjuvant exposure is a causative factor in ASIA, avoiding such exposure is crucial.

Keywords: **Autoimmune Diseases • Pleurisy • Scleroderma, Systemic • Silicosis • Sjögren's Syndrome**

Abbreviations: **ASIA** – autoimmune/inflammatory syndrome induced by adjuvants; **BALF** – bronchoalveolar lavage fluid; **CT** – computed tomography; **HLA** – human leukocyte antigens; **IL** – interleukin; **NLRP3** – Nod-like receptor family pyrin domain-containing 3; **SjS** – Sjögren's syndrome; **SSc** – systemic sclerosis

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/947856

Introduction

Silicosis, which is an occupational lung disease caused by the inhalation of respirable dust containing crystalline silica, has been reported to be associated with a variety of autoimmune diseases [1]. Hua et al [2] reported that among 154 artificial stone workers with silicosis, 33 (21.4%) were diagnosed with autoimmune diseases or autoimmune serological abnormalities. Therefore, the possibility of silicosis being complicated by immunological abnormalities is not rare. Until now, silicosis complicated with systemic sclerosis (SSc), known as Erasmus syndrome [3], and that complicated with Sjögren's syndrome (SjS), have been reported. Pulmonary involvement in SSc more frequently includes interstitial pulmonary fibrosis and pulmonary arterial involvement, whereas in SjS it more commonly includes interstitial pulmonary fibrosis and bronchiolitis [4]. However, cases of SjS complicated with pleuritis are relatively rare [5-7]. There are also few reported cases of pleuritis due to silicosis [8]. Recently, the concept of autoimmune/inflammatory syndrome induced by adjuvants (ASIA) as an adjuvant disease has been proposed [9]. Typical clinical manifestations of ASIA are chronic fatigue, arthralgia, myalgia, fever, sicca, cognitive impairment, and neurological symptoms, which are remarkably similar to the manifestations of SjS [10]. Silica as an adjuvant contributes to the chronic release of inflammatory cytokines, resulting in persistent high levels of systemic inflammation and promoting autoimmunity [1,9]. Therefore, in genetically predisposed individuals, prolonged exposure to silica can contribute to the onset of autoimmune diseases such as SSc and SjS. Here, we report a rare case of silicosis with SSc and SjS, potentially linked to the pathophysiology of ASIA, which was difficult to treat due to the presence of refractory pleuritis.

Case Report

A 65-year-old Japanese man was admitted to our hospital with fever and chronic fatigue. He had worked with granite in the stone industry for 45 years and was diagnosed with silicosis 10 years previously. He had a past history of smoking, with 45 pack-years. There was no known history of allergies or disorders other than silicosis. Physical examination on admission showed bilateral fine crackles, with oxygen saturation of 93% on room air. Thickening and swelling of the fingers with Raynaud's phenomenon were observed. Chest computed tomography (CT) revealed bilateral multiple nodules with pleural effusion (**Figure 1A**), and mediastinal lymphadenopathy with calcification (**Figure 1B**). Positron emission tomography-CT showed high 18-fluorodeoxyglucose accumulation in the mediastinal lymph nodes and bilateral pleura (**Figure 1C, 1D**). As shown in **Table 1**, laboratory examinations revealed slightly decreased hemoglobin (10.8 g/dL, normal range 14.0-18.0 g/dL) and albumin (2.1 g/dL, normal range 3.8-5.2 g/dL). Elevated C-reactive protein (5.6 mg/dL, normal range <0.30 mg/dL), ferritin (1655 ng/mL, normal range 50-200 mg/dL), and soluble interleukin-2 receptor (824 U/mL, normal range 121-613 mg/dL) were observed. Sialylated carbohydrate antigen KL-6 (449 U/mL, normal range <500 U/mL) and surfactant protein-D (57.2 ng/mL, normal range <110 ng/mL) were both normal. Antinuclear antibody was positive (2560-fold, with a nucleolar pattern), and both anti-scleroderma-70 antibody (>240 U/mL) and anti-SS-A antibody (>240 U/mL) were elevated. No elevations were observed in other autoantibodies such as anti-double-stranded DNA antibody, anti-Sm antibody, anti-RNA polymerase III antibody, and anti-cyclic citrullinated peptide antibody. There was no decrease in C3 or C4 complement. The result of the T-SPOT.TB test, an interferon-gamma release

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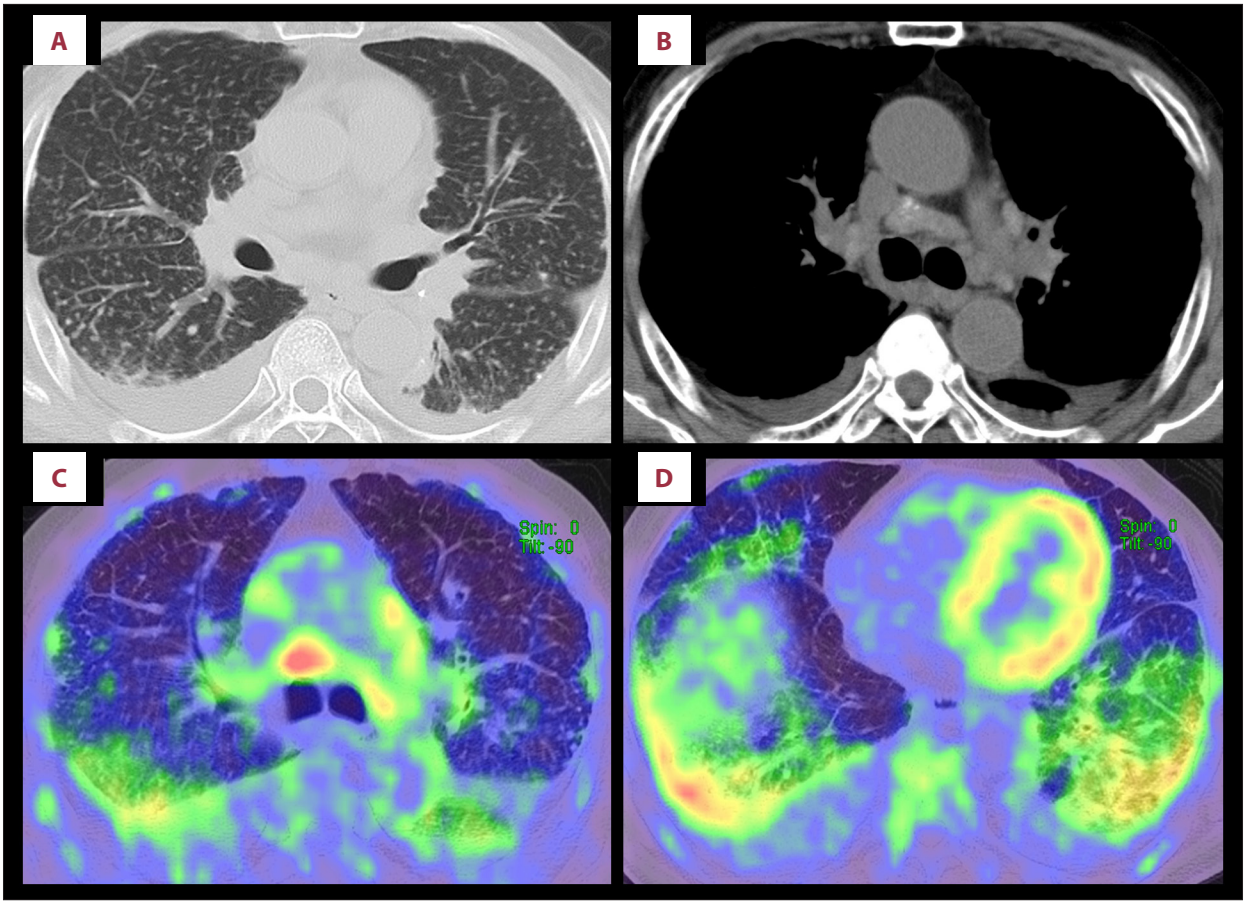

Figure 1. Chest CT on admission showed (**A**) bilateral multiple nodules with upper-lobe dominance, interlobular septal thickening, and lower-lobe-dominant consolidation with pleural effusion, and (**B**) mediastinal lymphadenopathy with calcification. Positron emission tomography-CT showed high 18-fluorodeoxyglucose accumulation in the (**C**) mediastinal lymph nodes (SUV maximum of 5.7), and (**D**) bilateral pleura (SUV maximum of 5.1). CT – computed tomography; PET – positron emission tomography; SUV – standard uptake value.

assay, was negative. Pulmonary function testing showed moderate restriction with a vital capacity of 2.38 L (percent predicted of 61.8%) and a decrease in diffusing capacity of the lung for carbon monoxide of 54.5%. Echocardiography showed an ejection fraction of 60% and no evidence of cardiac dysfunction or pulmonary hypertension such as wall motion failure or valve abnormalities.

We performed thoracentesis and found no malignant cells or bacteria in the right pleural effusion. The levels of lactate dehydrogenase in effusion were elevated to 961 U/L, while adenosine deaminase and hyaluronic acid were increased to 25.8 U/L and 53 700 ng/ml, respectively, although these increases were not statistically significant. Thoracentesis revealed increased lymphocytes (macrophages, 10.0%; lymphocytes, 80.0%; neutrophils, 10.0%; and eosinophils, 0%) in the pleural effusion. Skin biopsies from the fingers and forearms showed swelling of collagen fibers in the dermal layer, and lip biopsy revealed lymphocytic infiltrates in the interstitial area around the conduit. Moreover, bronchoalveolar lavage fluid (BALF) from the right middle lobe lesion revealed an increased number of total cells and lymphocytes (total cell counts, 13.06×10^4/mlBALF; alveolar macrophages, 72.4%; lymphocytes, 22.7%; neutrophils, 4.5%; eosinophils, 0.3%; and CD4/CD8 ratio, 0.1). Transbronchial lung cryobiopsy from the right lower lobe showed silicotic nodules (**Figure 2**). Based on the laboratory, radiological, and pathological findings, we diagnosed the patient as having silicosis complicated with both SjS and SSc. No other cause of pleuritis was identified apart from these newly recognized autoimmune diseases. Suspecting SjS-predominant pleuritis due to systemic inflammatory symptoms, we began administering treatment with oral corticosteroids at 30 mg/day. However, the pleuritis progressed. We added cyclosporine 200 mg/day to the treatment, and increased the dose of corticosteroids, but no effect was obtained and the patient's general condition deteriorated. He died due to the disease 18 months after treatment initiation.

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Table 1. Laboratory findings on admission.

Hematology		
White blood cell	5700	/μL
Neutrophils	81	%
Lymphocytes	13	%
Monocytes	4	%
Eosinophils	1	%
Red blood cells	394	×10⁴/μL
Hemoglobin	10.8	g/dL
Hematocrit	33.2	%
Platelets	42.6	×10⁴/μL
Coagulation test		
PT	71.3	
PT-INR	1.22	
APTT	38.6	s
Fibrinogen	379	mg/dL
D-dimer	2.1	μg/mL
Immunologic test		
IgG	2097	mg/dL
IgA	244	mg/dL
IgM	53	mg/dL
IgE	38	IU/mL
Blood chemistry		
Total protein	6.2	g/dL
Albumin	2.1	g/dL
AST	27	U/L
ALT	19	U/L
LDH	341	U/L
Total bilirubin	0.4	mg/dL
BUN	14	mg/dL
Creatinine	0.81	mg/dL
Na	136	mEq/L

Blood chemistry		
K	4.1	mEq/L
Cl	102	mEq/L
CRP	5.6	mg/dL
BNP	11.7	pg/mL
Ferritin	1655	ng/dL
s-IL2 receptor	824	U/mL
KL-6	449	U/mL
SP-D	57.2	ng/mL
Antinuclear antibody	2560	fold
SS-A antibody	>240	U/mL
SS-B antibody	6.2	U/mL
scleroderma-70 antibody	>240	U/mL
centromere antibody	0.5	U/mL
CCP antibody	<0.5	U/mL
ARS antibody	<5.0	
PR-3 ANCA	<1.0	U/mL
MPO-ANCA	<1.0	U/mL
Biological test		
β-D glucan	<6.0	pg/mL
T-SPOT (IGRA)	(-)	
MAC antibody	<0.5	U/mL
BALF findings (right B⁴)		
Recovery rate	85/150 (57)	mL (%)
Total cell count	13.06	×10⁴/mlBALF
Macrophages	72.4	%
Lymphocytes	22.7	%
Neutrophils	4.5	%
Eosinophils	0.3	%
CD4/CD8 ratio	0.1	
Bacterial culture	Negative	
Acid-fast bacillus culture	Negative	

APTT – activated partial thromboplastin time; ARS – aminoacyl-tRNA synthetase; AST – aspartate aminotransferase; ALT – alanine aminotransferase, BALF – bronchoalveolar lavage fluid; BNP – brain natriuretic peptide; BUN – blood urea nitrogen; CCP – cyclic citrullinated peptide; CRP – C-reactive protein; IgA – immunoglobulin A; IgE – immunoglobulin E; IgG – immunoglobulin G; IgM – immunoglobulin M; IGRA – interferon-gamma release assay; KL-6 – krebs von den lungen-6; LDH – lactate dehydrogenase; MAC – mycobacterium avium complex; MPO-ANCA – myeloperoxidase anti-neutrophil cytoplasmic antibody; PR3-ANCA – proteinase 3 anti-neutrophil cytoplasmic antibody; PT – prothrombin time; PT-INR – prothrombin time-international normalized ratio; s-IL2 – soluble interleukin-2; SP-D – surfactant protein-D.

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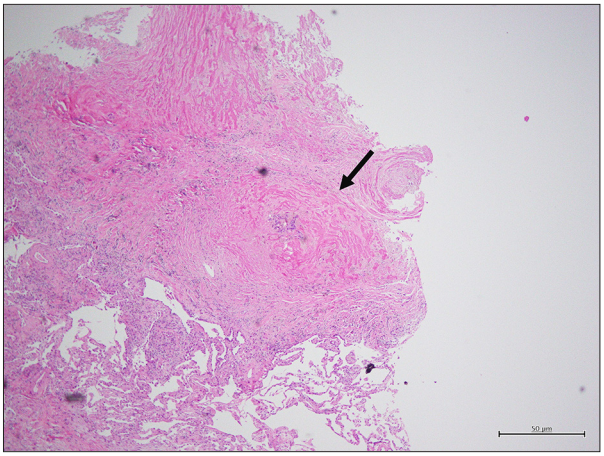

Figure 2. Hematoxylin-eosin staining of the right lower-lobe tissue obtained by transbronchial lung cryobiopsy revealed silicotic nodules (arrows).

Discussion

Silicosis has been reported to be associated with a variety of autoimmune diseases [1]; not only with SSc and SjS, but also with complications due to rheumatoid arthritis [11], systemic lupus erythematosus [12], and dermatomyositis [13]. An intriguing aspect of the present case was the coexistence of SSc and SjS, along with pleural effusion, resulting in symptoms suggestive of an autoimmune disease. Since pleural effusion did not occur during the course of silicosis before the patient's admission to our hospital, we determined that this complication was due to a newly developed autoimmune condition.

Although pleuritis is relatively rare in SSc [14] and SjS [5-7], its frequency is reported to be 5% and 1%, respectively [4]. Collagen diseases most frequently associated with pleural effusion complications include systemic lupus erythematosus (around 50% of cases) and rheumatoid arthritis (around 20% of cases) [4]. However, there were no findings in this case that supported these diagnoses.

Pleural effusions in SSc patients are often reported in cases with findings of pulmonary arterial hypertension [15], but clinically significant cases of pleural effusion are uncommon [16]. The pathogenesis of pleural effusions in SSc is not fully understood, but is likely related to microvascular injuries and heart failure [4]. On the other hand, while pleuritis in SjS is rare, it is more likely to occur in secondary SjS [5,6,17]. Although the optimal treatment for SjS-related pleuritis has not yet been established, previous reports have indicated that corticosteroid treatment can improve pleuritis [5]. In other words, the response of SjS patients with pleural effusions to treatment of corticosteroids supports the diagnosis of SjS-related pleuritis [5]. In the present case, there was no evidence of cardiac failure or pulmonary hypertension attributable to SSc, and systemic inflammatory findings were suspicious for SjS. Therefore, corticosteroids were used as a diagnostic treatment. However, the effects of corticosteroids and immunosuppressive treatment were not observed and the inflammation persisted.

To date, there have been a few reports of silicosis with pleuritis [8,18], and the relationship between them has remained unclear. In a previous study of 110 autopsied cases of chronic silicosis, pleural effusions were found in 35% of cases, among which 68% had other causes, including pneumonia, cardiac failure, hypoalbuminemia, pneumothorax, and abdominal malignancy, and only 11% of cases were purely silicosis-related [19]. Several mechanisms have been speculated to be the cause of pleural effusions due to silica nanoparticles: increased pulmonary interstitial fluid levels and permeability of pleural capillaries due to inflammation and the production of reactive oxygen species, mechanical lymphatic obstruction, and damage to the microlymphatic system and its function of fluid reabsorption [18]. Such mechanisms suggest that pleural effusions caused by silica are difficult to treat, and are not expected to improve.

In addition, it has also been suggested that silica can act as an immune adjuvant and cause chronic inflammation. Silica as an adjuvant contributes to the chronic activation of T cells, resulting in loss of regulatory T cell function and disruption of self-tolerance [1]. Furthermore, phagocytosis of silica deposited in the alveoli by macrophages causes functional abnormalities and chronic release of inflammatory cytokines, resulting in persistent high levels of systemic inflammation [1]. Inflammation after inhalation of silica is dependent on the inflammasome, which is induced by the activation of the Nod-like receptor family pyrin domain-containing 3 (NLRP3), resulting in generation of inflammatory interleukin (IL)-1β [20]. Impairment of lung function increases with disease progression, even after the patient is no longer exposed. Therefore, removing adjuvants might be crucial in reducing the severity of this inflammatory response. The present case suggests that contributing factors to the poor response to the immunosuppressive therapy involved silica acting as an immune adjuvant and triggering persistent inflammation.

Shoenfeld et al [9] proposed a disease concept of autoimmune/inflammatory syndrome induced by adjuvants (ASIA) as a pathology in which autoimmunity is triggered by adjuvants, including silica. Recently, cases of ASIA associated with various adjuvants have been reported worldwide, leading to increasing accumulation of cases on a global scale [21]. ASIA is characterized by immune dysregulation caused by chronic exposure to adjuvants, leading to persistent inflammation and development of autoimmune phenomena. A previous report suggested that silicone breast implants can act as adjuvants, triggering autoimmune diseases such as psoriasis and

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Sjögren's syndrome [22]. Similarly, another study described a case in which Takayasu arteritis was potentially induced by silicone breast implants, further supporting the role of adjuvant exposure in the pathogenesis of autoimmune diseases [23]. Silica, another well-known environmental adjuvant, has been implicated in activation of innate immunity, inducing inflammatory cytokine production and promoting autoimmunity in genetically susceptible individuals. As mentioned above, silica has been shown to activate the NLRP3 inflammasome, leading to release of pro-inflammatory cytokines such as IL-1β and IL-18, which contribute to persistent inflammation and tissue damage [20]. Given that ASIA is characterized by immune dysregulation triggered by adjuvants, it is plausible that NLRP3 inflammasome activation is a key pathway, linking silica exposure to the development of refractory inflammation and autoimmunity. Recent studies have reported that inflammasome activation is involved in various autoimmune diseases, including SSc and SjS, both of which have been associated with ASIA [24]. Therefore, persistent activation of NLRP3 may have contributed to the refractory pleuritis observed in the present case by amplifying the inflammatory response and promoting corticosteroid resistance.

Typical clinical symptoms of ASIA are chronic fatigue, arthralgias, myalgias, pyrexia, sicca symptoms, cognitive impairment, and/or neurological symptoms [25]. In the present case, the symptoms and autoimmune disease were consistent with the ASIA diagnostic criteria based on the following findings. From the main criteria, a clearly defined adjuvant exposure history and the presence of typical symptoms (fever, chronic fatigue, sicca symptoms) were observed. From the minor criteria, the presence of autoantibodies, other clinical symptoms (Raynaud's phenomenon), and the occurrence and progression of autoimmune disease were also consistent. Therefore, the diagnosis in the present case could be explained as a phenotype of ASIA. However, the pleuritis in this case can also be attributed to the complications of SSc and SjS, and its refractory nature warrants careful consideration of its pathogenesis. Although silicosis has been implicated in the development of autoimmune diseases, the mechanisms underlying pleuritis in autoimmune diseases are diverse, and it is difficult to conclude that the pathogenesis in this case was strictly related to ASIA. Since ASIA is a diagnosis of exclusion, it is also reasonable to consider this case as a refractory pleuritis associated with SSc and SjS, rather than solely attributing it to ASIA. Therefore, while the involvement of ASIA remains a potential hypothesis, the refractory pleuritis observed in our patient could have primarily been driven by the underlying autoimmune conditions, including ASIA.

It is well known that silicosis is a chronic progressive disease with no effective treatment. In cases where silicosis is complicated by autoimmune disease and pleuritis occurs, immunosuppressive treatment for the relevant autoimmune disease is first considered. However, the treatment effect will be poor if silica adjuvant is involved in the pathogenesis. In recent years, the regulation of NLRP3 activation, a cause of persistent inflammation, has been identified as a promising target for treatment of silicosis and silica-induced autoimmune diseases [26]. Recent studies have identified several promising inhibitors of NLRP3 inflammasome activation. For example, MCC950, a selective NLRP3 inhibitor, has been reported to be effective in reducing IL-1β release and ameliorating lung inflammation in preclinical silicosis models [27]. Additionally, OLT1177, an orally active NLRP3 inhibitor, has been shown to have potential in clinical trials for treatment of inflammatory diseases and may be relevant for silica-induced conditions [28]. The clinical application of NLRP3 inflammasome inhibitors is an area of growing interest and potential.

Conclusions

We described a case of silicosis complicated with SjS and SSc, which was difficult to manage in the treatment of refractory pleuritis. When silicosis presents with pleural effusion, a detailed search for the cause of the pleuritis, including autoimmune disease, is necessary. When an autoimmune disease is diagnosed, immunosuppressive treatment should be considered. However, when treatment is ineffective, the potential involvement of ASIA should be explored as a contributing factor to the pathogenesis. It is crucial to avoid silica exposures, since the removal of adjuvants is the most important aspect of ASIA treatment. Furthermore, prospective studies investigating ASIA in silicosis patients are needed to gain a deeper understanding of the disease, as well as to improve management strategies.

Patient Consent

Obtained.

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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