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Artificial stone-associated silicosis with concurrent Cryptococcus infection

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Abstract

Acute silicoproteinosis is a disease that develops in weeks, and lasting for years, after massive exposure to silica dust in relatively closed spaces. It was rare, but the cases have recently increased worldwide due to the development of artificial stone industry. Compared with traditional silicosis, artificial stone-associated silicosis is more rapidly progressive and lethal. Hence, a correct diagnosis and optimal treatment are crucial. Here, we present the clinical course of a 33-year-old artificial stonemason who suffered from acute silicoproteinosis with concurrent Cryptococcus infection resulting in profound respiratory failure. This patient was treated by bronchoscope-assisted therapeutic segmental lung lavage and antifungal agent, under mechanical ventilator and ECMO support and recovered well. A brief review of acute silicoproteinosis and artificial stone-associated silicosis is also presented and highlights the new form of industry exposure to silica.

Introduction

Silicosis is caused by inhalation of silicon dioxide crystal dust, although other silicone form may be associated [1]. It is one of the most common occupational diseases involving the lungs; hence, prevention efforts have been made for many decades. In Taiwan, the prevalence of pneumoconiosis used to be the highest occupational disease (79.7%) according to a report in 1994 [2], but has decreased annually. In 2019, the incident of pneumoconiosis and silicosis was 138 and six cases, respectively [3]. Nevertheless, silicosis is still a worldwide problem due to a new source of exposure. Artificial stone is a high-silica-containing material; thus, the risk of silica dust exposure is high during fabrication [4]. The increasing cases of artificial stone-associated silicosis around the world were noticeable in the last decade, owing to this material's popularity [5]. Here, we present the first artificial stone-associated case of silicosis in Taiwan. This case highlights the importance of rapid diagnosis and treatment of acute silicoproteinosis with concurrent Cryptococcus infection in a critically ill young adult and emphasizes the significance of being wary of a new source of silica exposure and occupational protection.

Case Report

A 33-year-old male presented with clear consciousness in our emergency department due to rapid progression of productive cough with dyspnoea on exertion over the previous few days. He had no chest tightness, chest pain, cold sweating, back pain, pitting oedema, fever, or chills. He denied underlying medical or previous surgical history. He also denied travelling outside Taiwan, contact with wild animal, or patients with similar symptoms. He smoked 1 pack per day for 15 years and had been working in an artificial stone grinding factory for eight years.

Seven months before this admission, he came to our outpatient department (OPD) due to a six-month chronic and productive cough. Chest radiography and computed tomography (CT) of the chest were performed at that time

and showed bilateral upper lung mass-like conglomerate lesion with radiating strands, multiple nodules, and mild traction bronchiectasis (Fig. 1A). Accelerated silicosis was diagnosed. Health education, tiotropium, and antitussive agent were prescribed and he was under regular follow-up monthly in our OPD. However, due to deterioration of symptoms, he went to our emergency department for help. On physical examination, the patient's temperature was 36.8°C, the heart rate 108 beats per minutes, the respiratory rate 22 breathes per minutes, and the oxygen saturation was 76% under nasal cannula 3 L/min. Whitish sputum without foamy or blood tinged texture was noted. Bilateral crackle rales and rhonchi without wheezing or rales over both lung fields were found. Because paradoxical respiratory pattern and worsening of oxygenation developed, endotracheal intubation with mechanical ventilator support was performed and he was transferred to our respiratory intensive care unit for further management.

Laboratory data revealed no leucocytosis with slightly elevated C-reactive protein at 0.73 mg/dL (<0.5 mg/dL represent normal). Microorganism culture or serum test for virus infection were all unremarkable. As this case was presented in early 2018, SARS-CoV-2 was not tested. Chest radiography and thoracic CT were done, and showed bilateral upper lobe progressive massive fibrosis (PMF) with bilateral lower lung crazy-paving attenuation (Fig. 1B). Hence, diagnostic bronchoalveolar lavage (BAL) was performed. The cytologic smears of BAL fluid (BALF) reported positive in periodic acid-Schiff (PAS). Gomori methenamine silver (GMS) stain revealed intracellular and extracellular capsulated yeast, compatible with Cryptococcus infection (Fig. 2). Cryptococcus antigen latex agglutination test by of BALF revealed 1:64 and blood Cryptococcus antigen latex agglutination test showed 1:10, both showed positive finding (cut-off value ≥ 1:8 represents positive). BALF showed negative in bacterial culture, but fungus culture yielded *Cryptococcus neoformans*. Detailed working history was obtained from his wife. The work content including cutting, grinding, drilling, finishing, transporting, and installation the artificial stone. The main product of artificial stone from his factory was kitchen benchtop. During work, those employees did not use face mask, even though they were provided. The factory had ventilator equipment, however, the work area was still dusty. Some of the co-workers had similar symptoms, and one of them died. Hence, based on his occupational history and clinical data, silicosis associated to artificial stone with concurrent Cryptococcus infection was diagnosed.

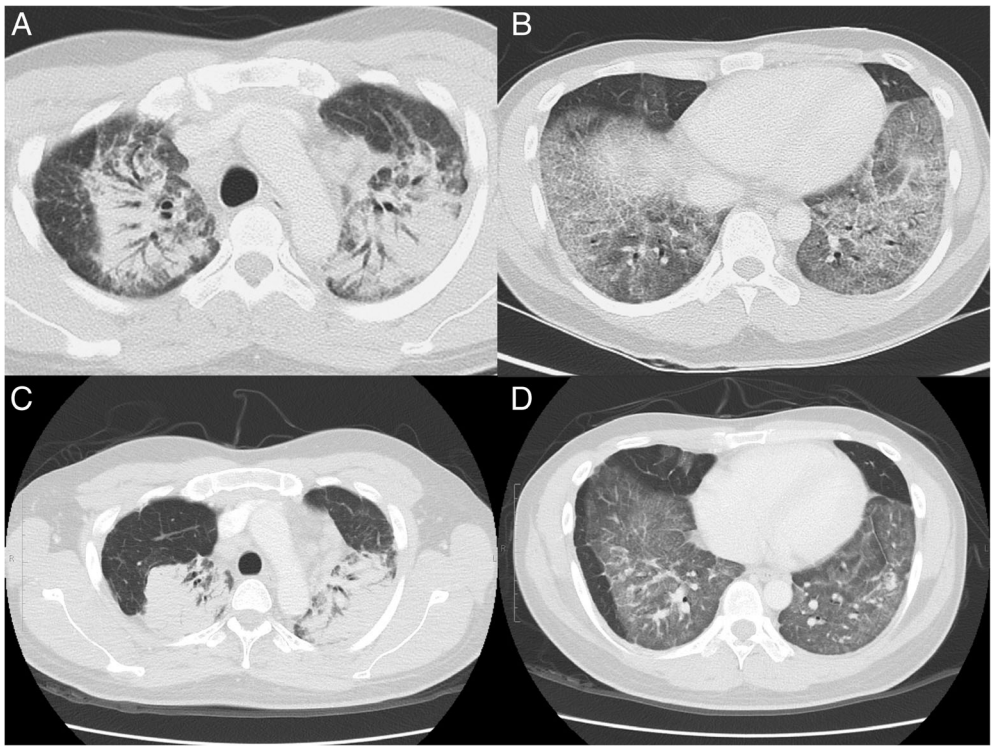

Figure 1. Chest computed tomography (CT) showing (A) bilateral upper lung progressive massive fibrosis and (B) bilateral lower lung "crazing-paving" attenuation. Follow-up thoracic CT one year later revealed (C) more conglomerate lesions in bilateral upper lobe with volume reduction, and D the crazy-paving pattern revealed regression in bilateral lower lobe.

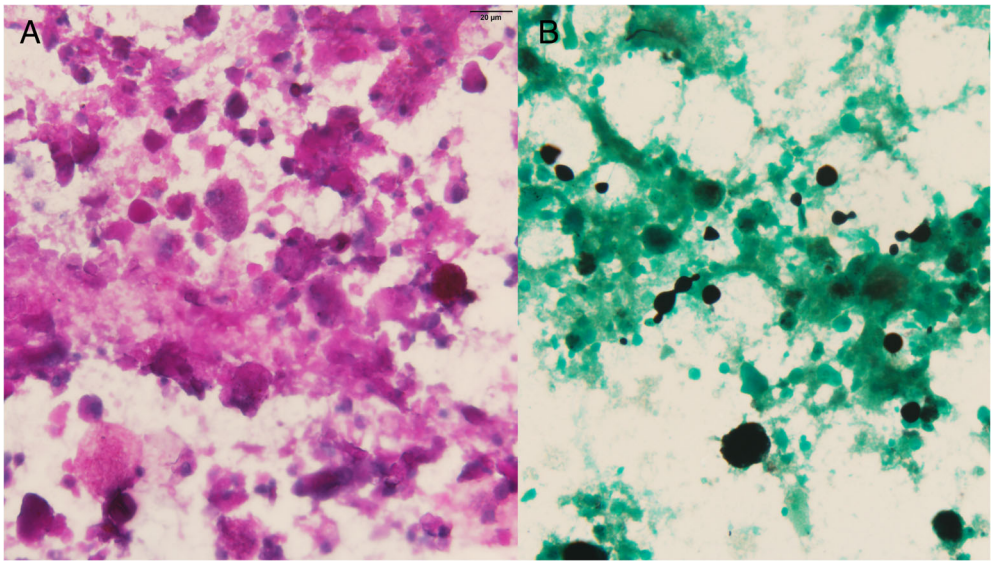

Figure 2. Cytology of bronchoalveolar lavage fluid resulting (A) positive on periodic acid-Schiff staining and (B) capsulated yeast-like fungal bodies with budding on Gomori methenamine silver staining.

Liposomal amphotericin B 300 mg per day with flucytosine 1500 mg per 6 h were administrated once Cryptococcus infection was confirmed, and shifted to flucytosine 1500 mg per 6 h with fluconazole 600 mg per day after discharge. Therapeutic segmental lung lavages (SLLs) by bronchoscope were performed twice in each lung under mechanical ventilation and venous to venous (VV)-extracorporeal membrane oxygenation (ECMO) support due to poor oxygenation. We instilled 5000 mL warm saline totally into one lung and retrieved the fluid in each therapeutic SLL. Totally, 20,000 mL warm saline was instilled and 17,649 mL fluid was retrieved in four times of therapeutic SLL.

The patient recovered gradually under antibiotics and therapeutic SLL treatment. VV-ECMO was removed one day after therapeutic SLL was completed. Ventilator was weaned off after 19 days of SLL. Finally, he was discharged and followed up at OPD by physicians of the pulmonology and infectious diseases department. Pulmonary function testing was arranged in OPD under stable condition. Severe restrictive ventilatory impairment was reported with forced expiratory volume in 1 sec (FEV_1) = 1.03 L (28% of predicted value), forced vital capacity (FVC) = 1.36 L (32% of predicted value), FEV_1/FVC = 75%, total lung capacity (TLC) = 3.12 L (56% of predicted value), and diffusing capacity of the lung for carbon monoxide (DLCO) = 10.72 mL/min/mmHg (35% of predicted value). Thoracic CT followed up one year later showed more conglomerate lesions in bilateral upper lobe with volume reduction. The "crazy-paving" pattern revealed regression in bilateral lower lobe (Fig. 1C, D) He was referred to the lung transplantation team for transplantation. The patient is still alive at the time of the writing of this report.

Discussion

Silicosis is a progressive and fibrotic lung disease attributed to the inhalation and deposition of free crystalline silica in the lungs. Three clinicopathologic types of silicosis have been described: chronic silicosis, accelerated silicosis, and acute silicoproteinosis. In chronic or accelerated silicosis, the symptoms and signs of chronic silicosis may be minimal and non-specific. Pulmonary function tests typically reveal airflow limitation with decreasing diffusing capacity of the lungs. Pure restrictive ventilatory impairment or mixed type of obstructive and restrictive ventilator impairment may also be present. The diagnosis of chronic silicosis is based on the history of exposure and the characteristic radiographic changes, such as silicotic nodule, eggshell lymphadenopathy, or PMF.

Acute and massive silica exposure may result in alveolar macrophage dysfunction, accumulation of non-degraded surfactant, and developing pulmonary alveolar proteinosis (PAP), also called silicoproteinosis [6]. Unlike autoimmune PAP caused by autoantibody against granulocyte-macrophage colony-stimulating factor (GM-CSF) homeostasis, which comprised approximately 90% of PAP cases, secondary PAP (included silicoproteinosis) only distribute 5–10% of cases [7]. Macrophage dysfunction also presents by deficient phagocytosis and decreased susceptibility to microorganisms and contributes to a higher incidence of unusual

infections observed clinically [6]. The pathophysiological mechanisms are involved in three ways: (1) by inhibiting the ingestion of phagocytic particles; (2) by decreasing the rate of ingestion; and (3) by reducing phagolysosome fusion [8]. The opportunistic organisms reported to be associated with PAP include Nocardia, mycobacteria, cytomegalovirus, *Pneumocystis jirovecii*, and Aspergillus [9–11]. Concurrent Cryptococcus infection with PAP was also published [12].

In acute silicoproteinosis, breathlessness may occur within months, followed by progressively impaired gas exchange and respiratory failure. The exposure history is crucial for diagnosis. Pulmonary function tests (or testing) usually show restrictive ventilatory impairment with impairment of gas exchange function. Chest X-ray film presents symmetrical bilateral lung "bat-wing" distributed opacity with air-space consolidation or hazy ground-glass opacity [13]. Other patterns can include mixed alveolar, interstitial, or nodular opacities and asymmetrical or focal abnormalities [14]. High-resolution chest CT (HRCT) of the chest is essential for diagnosing and typically shows the crazy-paving attenuation as ground-glass attenuation with a thickness of interlobar septa. Air-space consolidation, ground-glass opacity, and multiple small centrilobular nodules with confluence are also to be mentioned in the HRCT examination of silicoproteinosis patients [15]. Unlike autoimmune PAP, anti-GM-CSF antibody often resulted negative in secondary PAP. Lactate dehydrogenase (LDH) may elevate two to three times of upper limit of normal value in half of the PAP cases [13]. BAL or lung biopsy is often suggested for making a diagnosis by detection of silica, or lipoproteinaceous material accumulation in addition to opportunistic infection or other diagnosis is excluded clinically.

Silicoproteinosis is a rare disease; however, an increasing case number was noticed since 2010, owing to artificial stone's popularity in the last two decades [4]. Artificial stone, also termed engineered, agglomerated, or reconstituted stone, or quartz conglomerate, is a high-silica-containing material. Hence, the risk and amount of silica exposure in artificial stone fabrication are higher than in traditional stone fabrication. Compared with traditional silicosis, artificial stone-associated silicosis reported shorter exposure time, more rapid progression, higher incidence of spontaneous pneumothorax, higher chance to become a lung transplantation candidate, and higher mortality. The patients of artificial stone-associated silicosis were younger than traditional silicosis [5,16,17].

The most important treatment of silicoproteinosis is removing offending exposure. Otherwise, there are no available treatment options to influence the progression of the disease [16]. Therapeutic whole-lung lavage (WLL) could be helpful in respiratory compromised patients. Therapeutic WLL was first described by Ramirez et al. in 1963 [18]. Since the first iterations of WLL, therapeutic WLL has evolved into the modern-day practice of single or sequential bilateral lung lavage by isolating each lung with a double-lumen endotracheal tube under general anaesthesia [19]. Recently, one case series reported benefit of WLL in treating early artificial stone-associated silicosis patients [20].

SLL is also done through the bronchoscope (repeated BAL) in some centres. According to our institute's experience, SLL via bronchoscopy could clear the PAP lesions more effectively, shorten the time for therapeutic lung lavage, and had acceptable low risk. Consequently, SLL became the routine procedure for therapeutic lung lavage in our institute. Nevertheless, some reports indicated the inferior adequacy and efficiency of this technique and the arduous nature of the procedure, suggesting that SLL might be used in situations in which WLL is not available [21,22]. The thoracic CT performed one year later in our patient showed regression of crazy-paving attenuation but more conglomerates of PMF. Compared with the nearly complete regression of semi-solid centrilobular nodules reported by Chamber et al., the benefit of WLL or SLL still needs clarification [20]. Other treatment options, such as GM-CSF supplement via subcutaneous or inhaled route, mainly focus on autoimmune PAP and without evidence of benefit in patients with silicoproteinosis currently. In severe disease, lung transplantation may be considered [23,24].

Here, we present the first artificial stone-associated silicosis with concurrent Cryptococcus infection in a young male in Taiwan. This case has allowed us to review the literature on silicosis and pay attention to a new form of industrial exposure to silica as they are more frequently associated with acute or accelerated forms of silicosis affecting younger individuals.

Disclosure Statement

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

Author Contribution Statement

This study was supervised by Shi-Chuan Chang. The patient was under the care of Shi-Chuan Chang, Han-Chen Tsai, and Yu-Ting Lai. The report was written by Hsiang-Shi Shen.

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