A 44-year-old stone worker with progressive dyspnea: lessons from a new twist on an old foe

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Abstract

Silicosis is typically an indolent lung disease caused by long-standing occupational exposure to respirable crystalline silica, classically in professions such as sandblasting and mining. An increasingly popular industry that has earned particular interest because of its association with silicosis is customization and installation of artificial stone countertops for domestic applications. In addition to causing a spike in cases of chronic and accelerated silicosis, both quite familiar to respiratory clinicians, outbreaks of artificial stone silicosis have brought to the fore a historically rare entity known as acute silicosis, or silicoproteinosis, a more rapid presentation of the disease. Failure to suspect this uncommon condition can lead to diagnostic confusion and therefore ineffective treatment as was true initially of the patient we describe herein. The case description is followed by a clinical, radiological, and pathological overview of acute artificial stone silicosis (or silicoproteinosis), which is an emerging pneumoconiosis with sparse coverage in the literature to date. This case also adds to the few existing reports on the use of therapeutic whole lung lavage for silicoproteinosis.

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Case Report

A 44-year-old man was referred to our institution by his pulmonologist for an eight-month history of progressively worsening dyspnea, non-productive cough, and chest tightness. The patient had been completely healthy prior to the onset of these symptoms and took no medications. There was no other significant past medical history. He was a never-smoker. He had immigrated to the United States from Mexico 28 years earlier. His occupation for the 20 years leading up to illness had involved cutting, polishing, and installing kitchen countertops made of marble and, more recently, of artificial stone. His use of respiratory protective equipment while performing this work was reportedly inconsistent.

Upon initial presentation to his pulmonologist, the patient underwent chest computed tomography (CT), which demonstrated innumerable micronodules accompanied by mediastinal lymphadenopathy (Figure 1). Right upper lobe transbronchial biopsy at that time (not available for review) was reported as showing non-necrotizing granulomatous inflammation with negative stains for micro-organisms. Based on these findings, he was diagnosed with sarcoidosis and started on prednisone at a dose of 40mg daily, but this did not lead to improvement in his symptoms. After four months of prednisone therapy, repeat chest CT (Figure 2) revealed the appearance of new ground glass opacities. Based on this finding, another bronchoscopy with biopsy was performed out of concern for development of *Pneumocystis jirovecii* pneumonia (PJP). Histology was non-diagnostic, and bronchoalveolar lavage testing for PJP was negative. Hence the patient was admitted to our institution for further evaluation.

At presentation, his vital signs were notable for tachycardia to 115 beats/min and a resting oxygen saturation on room air of 85%, which increased to 94% with supplemental oxygen delivered via a 50% mask. There was no fever. He was alert, oriented, and not in

respiratory distress. Is jugular venous pulse was not elevated, and there was no edema. Diffuse bilateral crackles were present on chest auscultation. The remainder of the physical examination was unremarkable.

Diagnostic studies revealed the patient's serum hemoglobin was elevated at 16.5 g/dL (normal range 12-15.5 g/dL). Serum leukocyte count was 15.6K/mm^3 (normal range 4.5K-11K cells/mm^3) with a neutrophil predominance (82%). Erythrocyte sedimentation rate was <1. Serum lactate dehydrogenase level was 591 U/L (normal range 84-240 U/L). Angiotensin converting enzyme level was 17 U/L (normal range 5-40U/L). Laboratory evaluation for infectious diseases, including a respiratory virus panel, testing for the severe acute respiratory syndrome coronavirus-2, testing for the human immunodeficiency virus, and serum 1,3-β-D-glucan assay were all negative. Serological testing for connective tissue disease was likewise unrevealing.

His admission chest radiograph showed bilateral mixed airspace and interstitial opacities more prominent in the lower lung zones (Figure 3A). Chest CT demonstrated innumerable centrilobular micronodules present concurrently with areas of so-called "crazy paving:" combined ground glass opacity (GGO) and interlobular septal thickening (Figure 3 B,C).

Pulmonary function testing (PFT) was performed and revealed a forced vital capacity (FVC) of 1.9L (50% of predicted), a forced expiratory volume in 1 second (FEV_1) of 1.7L (55% of predicted). The FEV1/FVC ratio was 89%. Diffusing capacity for carbon monoxide was 45% of predicted. The 6-minute walk test was stopped after 4 minutes and 130 meters due to desaturation to 85% despite supplemental oxygen *via* 35% mask.

At this point, it was felt that the patient's clinical course was inconsistent with the initial diagnosis of sarcoidosis, and progression of his lung disease despite steroid therapy was unexplained and worrisome. He was therefore brought to the operating room for video-assisted thoracoscopic surgery (VATS) lung biopsy of the right upper, middle, and lower lobes (Figure 4). Representative tissue sections obtained during this procedure are depicted in Figure 5. Grossly, both lungs were studded with innumerable nodules (Figure 3). Microscopically, these nodules were composed of central areas of fibrosis with a concentric, hyalinized appearance surrounded by variable numbers of histiocytes and lymphocytes, (Figure 5). Airspaces were filled with granular, eosinophilic material that exhibited positive periodic acid-Schiff (PAS) staining (Figure 5C). Polarization demonstrated needle shaped crystalline structures, predominantly at the periphery of these nodules (Figure 5D). Stains for fungi and acid-fast bacilli were negative. In aggregate, these histopathological findings were diagnostic of silicoproteinosis, an acute form of silicosis.

Clinical discussion

The link between inhalation of stone dust and respiratory illness has been recognized for centuries. In modern times the corresponding clinical entity has been attributed to respirable crystalline silica (RCS) and is termed silicosis. Silica (SiO_2) is a ubiquitous component of rocks and sand that causes lung toxicity when it is pulverized in the course of industrial manipulation. The clinical scenario most familiar to respiratory clinicians is the indolent fibrotic lung disease that develops in sandblasters over decades of exposure known as chronic silicosis. Because RCS lung toxicity is proportional to the cumulative dose, higher intensity of exposure over shorter periods of time has produced cases of accelerated silicosis wherein the duration of exposure is less than 10 years. This more sparsely described form of silicosis has earned increased recognition in recent years due to its association with certain peculiar occupations such as denim jean sandblasting and jewelry polishing [1]. A rapidly growing industry that has earned particular interest because of this association - and one of direct relevance to the current case - is customization and installation of artificial stone countertops for domestic applications. This manmade material, known by a variety of commercial names [2], has an extraordinarily high silica content: >90% silica by weight as compared to granite (30%) or marble (3%). Customization of this material, which involves cutting and polishing the stone slabs, typically occurs in enclosed spaces and, unfortunately, workers are often not properly protected [3]. As a result, there is risk of extremely high levels of exposure to RCS. The booming artificial stone industry has led to a resurgence of silicosis in the form of artificial stone silicosis in Spain, where the first description originated in 2009 [4],

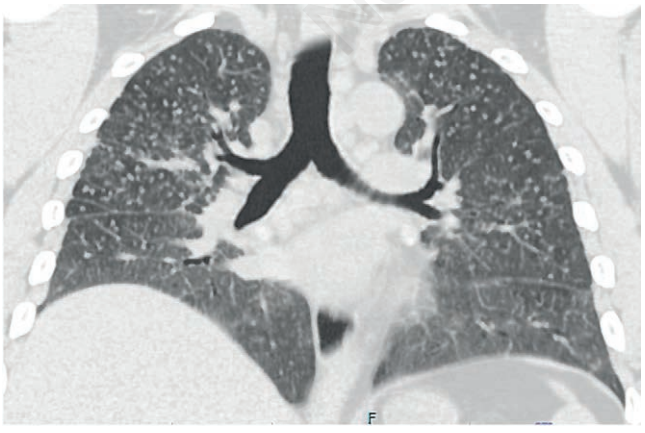

Figure 1. Coronal reconstruction of the initial outpatient chest CT performed without intravenous contrast and set to lung window demonstrating diffuse bilateral centrilobular nodularity. There was also associated mediastinal lymphadenopathy (*not shown*).

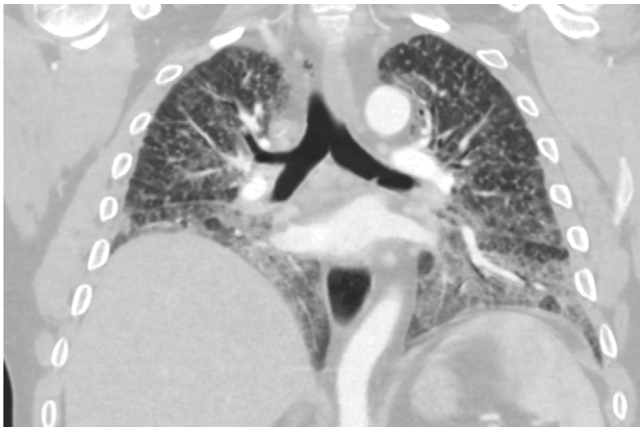

Figure 2. Coronal reconstruction of the initial outpatient chest CT performed without intravenous contrast and set to lung window four months after initial chest CT (Figure 1) demonstrating diffuse bilateral centrilobular nodularity and new findings of lower lobe predominant ground glass opacities.

in Israel, where it accounts for a disproportionate percentage of lung transplantations [5]; and more recently in the United States, where the affected demographic is very similar to our patient: young Hispanic immigrants employed as manual laborers [3].

In addition to causing a spike in cases of accelerated silicosis, outbreaks of artificial stone silicosis have brought to the fore an entity known as silicoproteinosis, or acute silicosis, first described by Buechner and Ansari [6] in 1969 and reported very infrequently thereafter until recent years. Akin to accelerated silicosis, this most rapidly progressive of all forms of silicosis (over weeks to a few years) likely owes its association with artificial stone installation to the unusually high intensity of exposure inherent in this occupation. The term "proteinosis" was originally appended to the name because of histological resemblance to pulmonary alveolar proteinosis (PAP), an entity already known by that time. Silicoproteinosis may be considered a type of secondary, rather than autoimmune, PAP and as such positivity for autoantibodies against granulocyte-macrophage colony stimulating factor would not be expected [7]. Accordingly, our patient tested negative for these autoantibodies. The clinical presentation of silicoproteinosis is that of progressive dyspnea, often with accompanying constitutional symptoms. The latter were not prominent in our patient's course, at least on admission to our institution, but it is possible that they were masked by corticosteroid therapy. The PFT pattern of silicoproteinosis is that of restriction with reduced diffusing capacity as was true of our patient. The natural history of silicoproteinosis is one of inexorable physiological [8] and clinical [9] decline towards fatal respiratory failure. Lung transplantation is considered to be the only definitive management option. Favorable short-term clinical [10] and radiological [11] response to therapeutic whole lung lavage (WLL), a staple of PAP management, has been reported in silicoproteinosis, but more robust data to support its use are lacking. Evidence of efficacy of corticosteroids in silicoproteinosis is likewise anecdotal [12].

In retrospect we surmise that our patient initially presented to his pulmonologist with progressive silicosis, perhaps of the accelerated type, which was misdiagnosed as sarcoidosis based on a clinicoradiological picture compatible with the latter and lung histopathology reportedly showing non-necrotizing granulomas. It appears that the findings were not considered in the context of the patient's special occupational history, and this may explain why biopsy tissue was not examined under polarized light microscopy. Misdiagnosis of conventional silicosis as sarcoidosis is a well-known phenomenon as the two diseases share many overlapping features; not surprisingly, diagnostic confusion has already been reported in artificial stone silicosis as well [13]. Failure of presumed sarcoidosis to respond to corticosteroid therapy appropriately raised concerns and prompted repeat CT imaging, which revealed interval development of crazy paving. At that point, it was

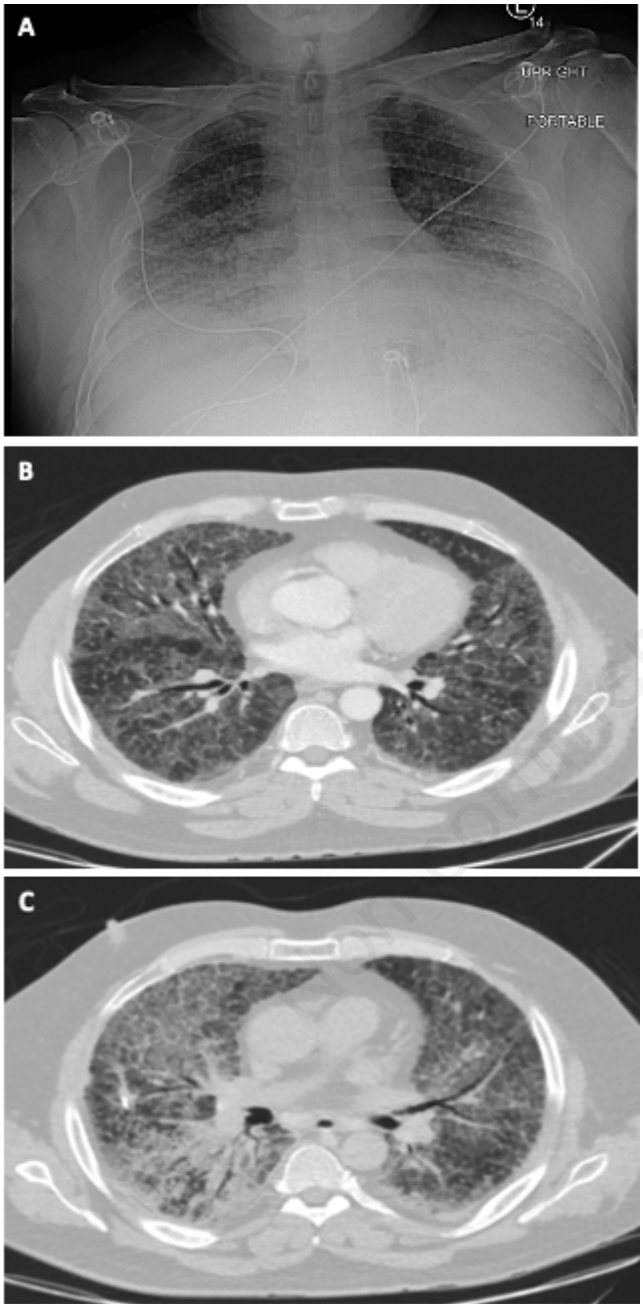

Figure 3. A) Admission portable chest radiograph demonstrating bilateral nodular infiltrates along with airspace opacities in the lower lung zones. B) Axial section from subsequent chest CT performed without intravenous contrast and set to lung window demonstrating innumerable branching nodules in a centrilobular distribution. C) Axial section of chest CT at a more caudal level than panel B demonstrating the additional finding of ground glass opacity associated with interlobular septal thickening in a "crazy paving" pattern.

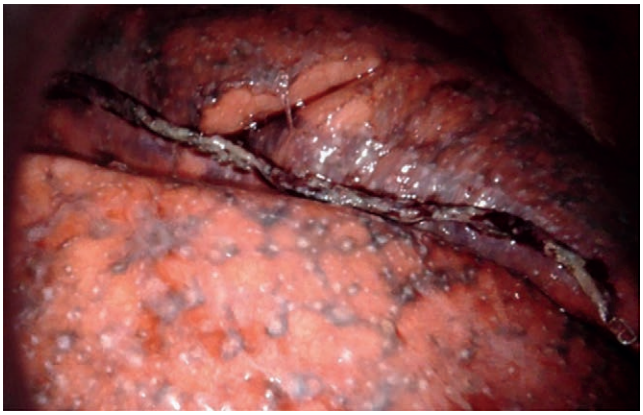

Figure 4. Photograph obtained at surgical lung biopsy demonstrating the right lung studded with innumerable nodules.

understandably reasoned by the patient's pulmonologist that he had developed a complication of corticosteroid therapy, namely PJP, which has an established association with the crazy paving CT pattern [14]. In actuality, as the surgical lung biopsy at our institution eventually demonstrated, the patient was developing silicoproteinosis, accounting for progression despite corticosteroid therapy and for appearance of crazy paving. Once we established this diagnosis, the patient underwent staged WLL separated by a 3-week interval. Progressively clearing WLL return aliquots are depicted in Figure 6. Soon after his second WLL session, the patient became free of supplemental oxygen. Unfortunately, on a follow up visit it was discovered that he had resumed his former occupation and had once again become oxygen-dependent.

Radiological discussion

At chest CT, simple chronic or accelerated silicosis is predominantly a nodular disease with a centrilobular distribution and predilection for the upper lobes. Nodules can also assume a perilymphatic distribution. Fibrosis in both a usual interstitial pneumonia (UIP) and non-UIP pattern may accompany the nodular lesions [15]. Lymphadenopathy is a typical associated finding, and it is often calcified: the classic description being that of "eggshell" calcification. Silicosis is considered complicated if CT demonstrates large conglomerate nodules and even masses referred to as progressive massive fibrosis (PMF). These lesions can be calcified and can be hypermetabolic on positron emission tomography, complicating differentiation from malignancy [16]. When silicosis patients, as was initially true of this case, present with diffuse micronodular disease and mediastinal lymphadenopathy at CT, it is not unusual for sarcoidosis - a far more common diagnosis - to be favored radiologically, especially if there is a prominent component of perilymphatic nodularity.

As in our case, silicoproteinosis may superimpose its CT manifestations on the background of nodules produced by underlying chronic or accelerated silicosis. The most common CT finding in the largest published series consisting of 13 patients was airspace consolidation [17] (12/13, 92%). GGO was less common, identified in 8 of the 13 patients (62%). Notably, crazy paving was not observed at all. The present patient is among the few examples in the literature of crazy paving in association with silicoproteinosis [18,19]. This is in contrast to the clinically related entity of autoimmune PAP in which crazy paving is a nearly universal finding [20]. Additional distinguishing features between silicoproteinosis and autoimmune PAP are parenchymal calcifications and nodularity: both are common in the former and absent in the latter [21].

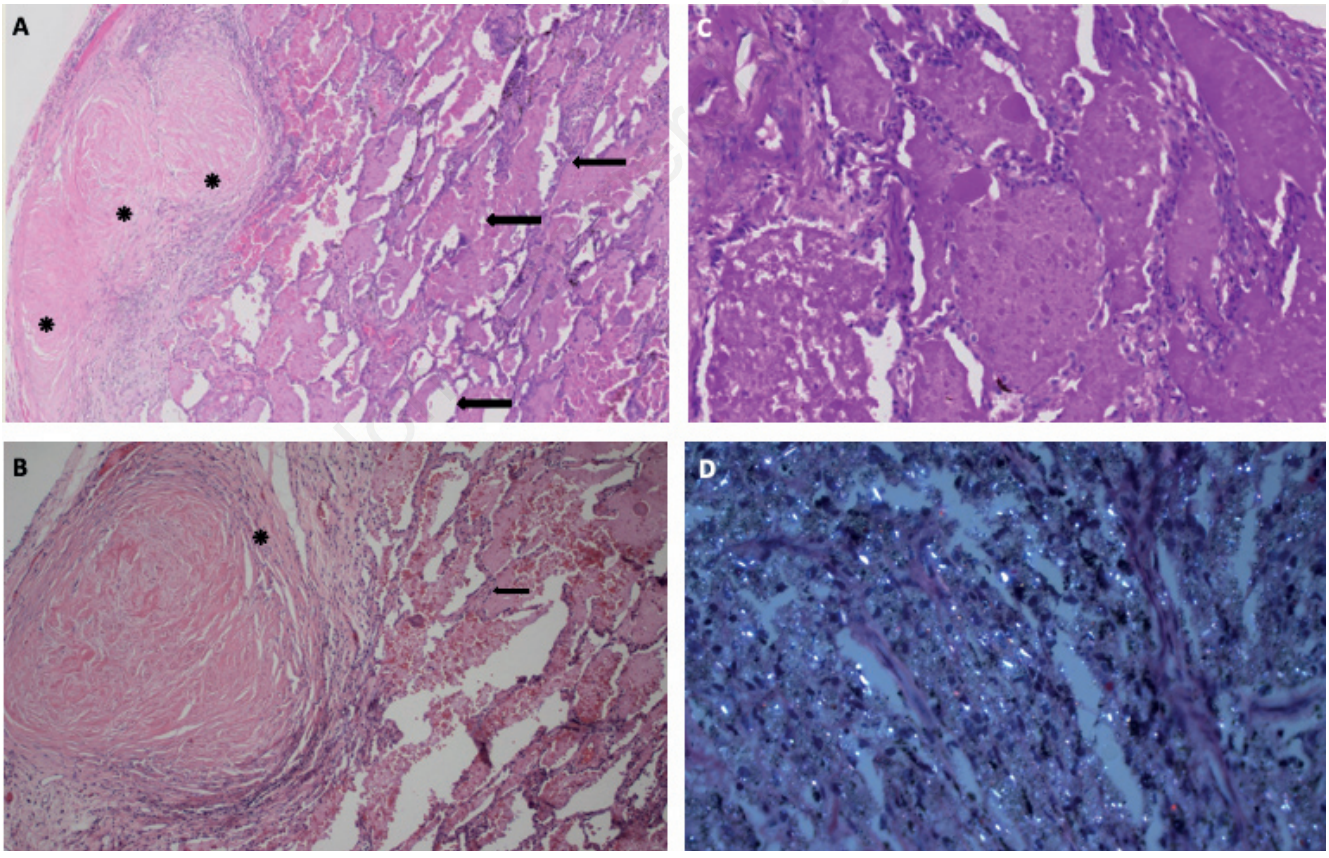

Figure 5. A-D) Histology. A) H&E stain of the surgical lung biopsy showing discrete sub-pleural nodules created by concentric fibrosis (asterisks) with a peripheral rim of inflammatory cells and filling of the adjacent alveolar spaces with amorphous eosinophilic material (arrows) (original magnification 20x). B) Higher magnification image (original magnification 200x) of the section in panel A offers a closer look at one of the nodules (asterisk) and at the eosinophilic intra-alveolar material (black arrow). C) Periodic Acid Schiff (PAS) staining of the lung biopsy highlights the accumulation of a PAS-positive substance within alveoli (original magnification 100x). D) Polarized light microscopy revealing innumerable brightly birefringent silicate particles (original magnification 100x).

Pathological discussion

The first responders in the lung to inhalation of RCS are resident alveolar macrophages (AM). Upon phagocytosis of the dust particles, AMs may undergo apoptosis or activation, leading in both scenarios to recruitment of inflammatory cells and an initial alveolitis [22]. In addition to mononuclear cell infiltration, another tissue response that occurs is histiocytic aggregation resembling granuloma formation. Release of profibrotic cytokines within this inflammatory milieu leads to dense collagen deposition by fibroblasts in concentric bundles that constitute the silicotic nodule characteristic of chronic and accelerated silicosis. Especially in the latter, the nodule periphery may still contain inflammatory cells and histiocytic aggregates; this outer rim corresponds to the leading edge of the fibrotic process as it advances in what has been described as a "centrifugal" fashion [23]. This "younger" cuff is also the part of the nodule that is most likely to contain identifiable silicate particles which typically accompany inhalation of silica, seen as brightly birefringent needle-shaped structures by polarized light microscopy (Figure 5D). The center of the silicotic nodule, and in many cases the entire nodule, appears densely fibrotic at time of histological examination. The microscopic correlate of PMF is coalescence of expanding fibrotic nodules into conglomerate lesions. Discrete nodular scars may coexist with interstitial fibrosis as has also been observed at CT [5].

Much like its radiological picture, the lung pathology of silicoproteinosis is that of PAP superimposed on underlying histology of chronic or accelerated silicosis. Notably, the background nodular and interstitial disease may not be as conspicuous as it is in pure silicosis. This was observed in the first description of silicoproteinosis by Buechner and Ansari and led to diagnostic confusion with PAP in two of the four original cases [6]. As in PAP, the alveolar spaces in silicoproteinosis are filled with an acellular granular eosinophilic exudate that stains positive with periodic acid-Schiff (Figure 5C). This alveolar filling process corresponds to the consolidation and GGO that are the signature CT findings of silicoproteinosis [24]. The exact mechanism behind the association between acute silicosis and alveolar proteinosis is not established, but extrapolation from other forms of secondary PAP suggests reduced surfactant clearance due to alveolar macrophage dysfunction, which in the context of the pathogenesis of silicosis could be quantitative, qualitative, or both [25].

Figure 6. Progressively clearing whole-lung lavage effluent (left to right) obtained over the course of the procedure.

Conclusions

The present patient represents the convergence of two separate features of silicosis that both warrant greater awareness among respiratory clinicians. The first is etiological in that this case joins the growing list of examples of the emerging pneumoconiosis known as artificial stone silicosis, which to this day remains relatively obscure even though its global impact is on the rise. The other enlightening feature of this case is that it dispels the notion that in modern times silicoproteinosis is a historical relic. It serves as a reminder that this rarest form of silicosis needs to be considered now as much as ever in the appropriate clinical and occupational setting. To close the loop, awareness of the not-so-exotic entity of silicoproteinosis is rendered ever more important by the emergence of artificial stone silicosis, which appears to be especially prone to an acute presentation.

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