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Outbreak of autoimmune disease in silicosis linked to artificial stone

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Background	There is a well-established association between inhalational exposure to silica and autoimmune disease. We recently observed an outbreak of silica-related autoimmune disease among synthetic stone construction workers with silicosis referred for lung transplantation assessment.
Aims	To characterize the rheumatologic complications in silicosis within these highly exposed, clinically well-characterized patients.
Methods	We systematically reviewed data from all cases of silicosis due to synthetic stone dust referred to our pulmonary institute for lung transplant assessment, which represents the national centre for all such referrals. In addition to silicosis-specific data, we extracted data relevant to the clinical and serological manifestations of autoimmune diseases present in these patients.
Results	Of 40 patients in our advanced silicosis national data, we identified nine (23%) with findings consistent with various autoimmune diseases. Among these nine, three also had findings consistent with pulmonary alveolar proteinosis. Based on an expected autoimmune disease prevalence of 3% (based on the upper-end estimate for this group of diseases in European international data), the proportion of disease in our group represents a >7-fold excess (prevalence ratio 7.5; 99% confidence interval 2.6–16.7).
Conclusions	These cases underscore the strong link between silicosis and multiple distinct syndromes of autoimmune diseases. Vigilance is warranted for the recognition of autoimmune complications in persons with known silicosis; so too is consideration of the occupational exposure history in persons presenting with manifestations of autoimmune disease.
Key words	Autoimmune disease; pulmonary alveolar proteinosis; silicosis.

Introduction

Silicosis is a fibrotic occupational pulmonary disease that results from overexposure to crystalline silica-containing dust [1,2]. Although preventable through appropriate workplace precautions, silicosis not only remains an endemic disease worldwide but there has also been a resurgence of epidemic disease in recent years. For example, silicosis outbreaks have occurred in Turkey caused by poorly controlled sandblasting of both denim jeans and cooking utensils [3,4]. More recently, we reported a new and severe silicosis epidemic in Israel linked to a relatively new high-silica-content (93–94% crystalline silica) artificial decorative stone product. We described demographics, exposure histories and clinical, radiological and histological evaluations of 25 patients referred for evaluation, 10 of whom went on to lung transplantation over a 13-year period [5]. A similar outbreak has been reported in Spain, where another high-silica-content artificial stone product is manufactured and used [6–8].

There is a well-established association between inhalational exposure to silica and autoimmune disease, particularly in the context of intense exposure [2]. Silica

exposure has also been linked to increased levels of autoantibody production, immune complexes and excess production of immunoglobulin, even in the absence of the full clinical features of a distinct autoimmune disease [2].

The association between silica exposure and autoimmune disease was first described by Bramwell in 1914, who observed scleroderma among stone masons [9]. Fifty years later, Erasmus found an increased incidence of systemic sclerosis (SSc) among South African gold miners, later referred to as *Erasmus syndrome* [10]. In 1952, Caplan described the occurrence of multiple lung nodules in coal miners who also suffered from rheumatoid arthritis (RA), comorbidity known as *Caplan's syndrome* or *rheumatoid pneumoconiosis* [11]. Significant risk of developing SSc, RA, systemic lupus erythematosus (SLE), dermatomyositis/polymyositis and anti-neutrophil cytoplasmic antibody-positive vasculitis has been linked to silica exposure in various studies [1,2,12–19]. Because of the sporadic nature of silicosis and the variability in the presentations of autoimmune diseases, however, available data tend to be limited and condition-specific [12,20]. Moreover, pulmonary alveolar proteinosis (PAP), which is also associated with silica exposure, generally has not been considered in juxtaposition with conditions such as RA or SSc, even though this condition also has autoimmune characteristics.

Given the intensity of silica exposure and the severity of disease in our artificial stone-exposed patients, many of whom have received lung transplantation, the emergence of autoimmune manifestations might have been expected. Indeed, the clinical presentations of rheumatologic disorders that began to appear among our patients led us to systematically review the data of all our patients with artificial stone-associated silicosis, who represent the national incidence of disease severe enough to be referred to the single lung transplant referral evaluation centre in Israel. We did so in order to ascertain the extent and range of concomitant autoimmune comorbidity across a range of conditions in this heavily silica-exposure population with advanced lung disease.

Methods

We analysed data of 40 persons referred to our lung transplantation centre for advanced silica-related lung disease over a 15-year period from 1997 through 2012. The study was ethically approved (as part of data extraction from the silicosis cohort) by the hospital Helsinki committee. Signed consent was obtained for cases described. Since this is the single centre through which all such referrals are evaluated, we approached this data as reasonably capturing the national incidence of such disease in Israel. We have previously reported data on 25 of these 40 subjects, including 10 who went on to lung transplantation [5]. Fifteen additional subjects were newly referred since that report. Of 40 people, these data now includes 16 lung transplant recipients (i.e. 6 over and above the 10 initially reported). Patients with silicosis about whom we may have been contacted but who ultimately were not referred for direct evaluation at our transplant centre were not considered eligible for inclusion in this analysis.

We collected demographic information including age, gender, smoking history and duration of silica dust exposure. Age and smoking history (represented by pack years) and categorical variables were compared between subjects with and without concomitant autoimmune disease using the *t*-test and chi-square test, respectively.

Detailed medical histories, physical examinations, radiographic assessments and pulmonary function testing results were available for all subjects as part of our centre's diagnostic evaluation of lung disease severity and transplant candidacy eligibility. Radiographic findings consisted of plain chest radiographs for all subjects and high-resolution computerized tomographic (HRCT) scans for those subjects for which it was available. Pulmonary function tests included forced expired volume in the first second and forced volume capacity for all subjects and total lung capacity and diffusion capacity for carbon monoxide (DLCO) for subjects for whom it was available. The results are represented as percentages of the predicted normal values as calculated according to age and height for males [21].

Subjects with autoimmune disease were identified through chart review. This included all electronic medical records available from inpatient and outpatient care, speciality clinic documentation (such as rheumatology clinic reports) and additional clinical evaluation at referral and data that emerged as a part of clinical follow-up. Although a rheumatologist was not part of the study team, clinical input from a rheumatologist subspecialist was available for all cases that had such referrals. Further documentation of autoimmune disease was based on manual review of non-electronically maintained physicians' charts for clinical manifestations, serological studies and any other tests or interventions performed. This included pathological data where applicable (including the explanted lung for those undergoing transplantation). Subjects were considered as having autoimmune disease only if a constellation of symptoms, signs and serological data were consistent with a specific autoimmune entity. Patients who may have displayed clinical features of autoimmunity but not a full clinical and serological picture of a specific entity were considered negative for autoimmune disease.

We calculated a prevalence ratio based on the upper-end values for international prevalence data for this group of autoimmune diseases and calculated observed to expected prevalence ratio of a Poisson variable to its expectation [22].

Results

All 40 patients included in the study were male and had substantial occupational histories of silica exposure while working with a high-silica-content synthetic stone material. They all did similar work that included dry-cutting and polishing the stone for end use, predominantly for kitchens and other countertop applications. We identified nine patients with a specific diagnosis of autoimmune disease among the 40 persons with silicosis evaluated at our lung transplantation centre, representing 23% of the cohort. Age, smoking, silica exposure histories, the findings of radiographic imaging and lung function data for these nine subjects are summarized in Table 1. All had a history of exposure to silica for at least 6 years, with four of the subjects reporting exposure for 20 years or more. Four were still exposed at work when initially referred to our centre. The age of these nine subjects was not statistically different from the remaining 31 in the cohort, although they were 6 years younger overall (44.1 versus 50.4 years); cumulative smoking was similar (24.1 versus 28 pack years). Of the nine subjects, three underwent lung transplantation (Cases 2, 5 and 7). Of these, Cases 2 and 7 clinically manifested autoimmune

Table 1. Demographics, exposure history, radiographic and lung function data for nine cases of autoimmune disease in a cohort with silicosis

Case number	Smoking history, pack years	Duration of exposure, years	Radiographic findings by chest radiograph	Radiographic findings by HRCT	FEV_1 %[a] predicted	FVC %[a] predicted	TLC %[a] predicted	DLCO %[a] predicted
Case 1	150	20	Reticulonodular interstitial pattern; bilateral pleural effusions	NA	34	36	NA	NA
Case 2	15	14	Reticulonodular interstitial pattern	Mediastinal lymphadenopathy; alveolar infiltrates and ground glass opacities	32	34	46	41
Case 3	12	6	Reticulonodular interstitial pattern	Interstitial pneumonia	48	47	47	35
Case 4	24	6	Reticulonodular interstitial pattern	Mediastinal lymphadenopathy; alveolar infiltrates and ground glass opacities	40	83	58	57
Case 5	0	10	Reticulonodular interstitial pattern	Mediastinal lymphadenopathy; hilar lymphadenopathy with calcification; fibrotic changes in upper lobes	25	35	48	30
Case 6	1	26	Reticulonodular interstitial pattern	Mediastinal lymphadenopathy	110	102	119	88
Case 7	0	13	Reticulonodular interstitial pattern	Mediastinal lymphadenopathy	50	47	44	32
Case 8	0	24	Reticulonodular interstitial pattern	Peripheral nodules in a diffuse pattern; ground glass opacities of the lower lobes	49	49	48	64
Case 9	15	21	Reticulonodular interstitial pattern; hyperinflation; pleural thickening; multiple pulmonary nodules	Mediastinal lymphadenopathy; hilar lymphadenopathy with calcification; diffuse fibrotic and interstitial changes	48	49	63	29

DLCO, diffusion capacity for carbon monoxide; FEV_1, forced expired volume in the first second; FVC, forced volume capacity; NA, not available; TLC, total lung capacity.

[a]Results are represented as percentages of the predicted normal values as calculated according to age and height for males (all subjects were male).

disease prior to transplantation. For Case 5, referred to us with very advanced lung disease and respiratory failure, a diagnosis of Sjogren's syndrome was made within a few months after transplantation.

All 40 subjects, with and without autoimmune manifestations, had severe lung disease attributed to silicosis with characteristic findings on radiological studies. Of nine subjects with concomitant autoimmune disease, plain chest radiographs for eight (89%) demonstrated a reticulonodular interstitial pattern consistent with silicosis. Further descriptions of chest radiographic findings are detailed in Table 1. Of the nine subjects included, HRCT studies were available for eight. On HRCT, different subjects displayed various findings, most which included both lung parenchymal and lymph node involvement (Figure 1). In all subjects, excluding Subject 6, pulmonary function testing demonstrated a restrictive pattern and in all subjects but one, where it was measured, a reduced diffusing capacity for carbon monoxide (DLCO) (Table 1). Subject 6 displayed unremarkable pulmonary function test results except for evidence of air trapping.

Pulmonary histological features were available for six subjects and cytology taken from bronchial washing was available for one further subject. In three subjects (2, 5 and 7), the pathological findings were obtained from the lung specimen explanted at the time of lung transplantation. All three underwent lung transplantation in the past 2 years and thus were not included among the 10 cases that underwent lung transplantation included in our previous report [5]. Histology specimens from three subjects (4, 6 and 8) were obtained from lymph node, pleural or transbronchial biopsies.

The predominant feature of all pathological specimens was silicosis. Of note, however, two of these manifested focal or more widespread silicoproteinosis (PAP). For Subject 5, the explanted lung demonstrated multiple fibrotic nodules with areas of confluent fibrosis and extensive features consistent with PAP (Figure 2). For Subject 6, a transbronchial biopsy showed mild interstitial fibrosis with a focal PAP-like pattern and the presence of birefringent particles. In one other (Subject 9), a bronchial washing demonstrated amorphous proteinaceous material consistent with PAP.

Clinical and serological features consistent with a diagnosis of a specific autoimmune disease are summarized in Table 2. Six subjects had clinical input from a rheumatologist subspecialist involved in the diagnosis. Three subjects (1, 3 and 4) had autoimmune manifestations consistent with SSc including: Raynaud's phenomenon (Figure 3), dysphagia and telangiectasia. Subject 5 was diagnosed with Sjogren's syndrome based on a consistent constellation of findings. Subjects 7 and 8 presented with arthritis characteristic of RA, which in context of silica exposure is often referred to as Caplan's syndrome or rheumatoid pneumoconiosis [11]. For Subject 9, clinical manifestations included myositis and arthralgia, with serological markers supporting a diagnosis of polymyositis anti-synthetase syndrome. The remaining subjects (Subjects 2 and 6) presented with a broad spectrum of signs and symptoms leading to a presumptive diagnosis of mixed connective tissue disease (MCD) with lupus-like features. Subject 2 manifested Raynaud's phenomenon, arthritis and pleuritis, while Subject 6 presented with fever, arthritis and erythema multiforme.

Although precise population prevalence data for Israel are not available, based on the upper-end values for international data for this group of autoimmune diseases for all parts of Europe and, to a limited extent, the Middle East, not >3000 per 100 000 adults (3%) would be anticipated [22]. This would equate to 1.2 cases among our cohort of 40, whereas we observed nine patients with

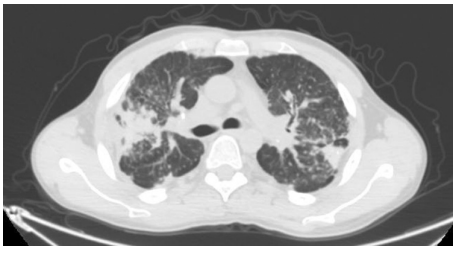

Figure 1. HRCT of Case 5 demonstrates severe fibrotic changes in the upper lobes.

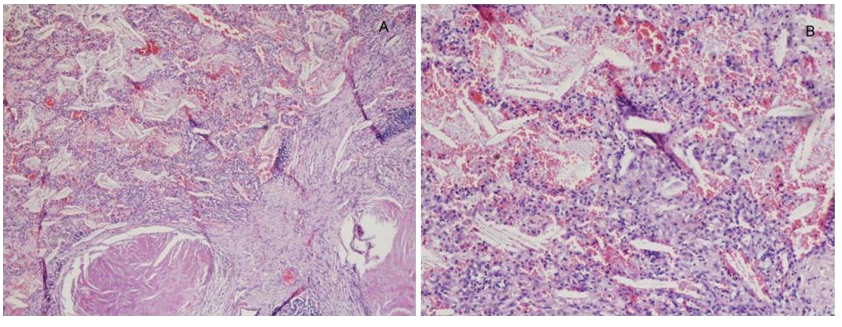

Figure 2. Pathological material from explanted lung at transplantation of Case 5 demonstrating multiple fibrotic nodules, areas of confluent fibrosis and features consistent with PAP. Panel A: At low magnification there are well-circumscribed silicotic nodules surrounded by a rim of histiocytes (haematoxylin and eosin). Panel B: Higher magnification showing a silicotic nodule composed of concentrically hyalinized collagen bundles. The surrounding alveolar space is filled with acellular eosinophilic granular material (haematoxylin and eosin).

Table 2. Symptoms, physical findings, serology and clinical diagnoses among nine cases of silicosis with concomitant autoimmune diseases

Case	Symptoms	Physical findings	Relevant serologies	Clinical diagnosis
1	Raynaud's; Dysphagia	Sclerodactyly; Telangiectasia; Serositis	Anti-Scl-70 (+); SSA (anti-Ro) (+)	SSc
2	Raynaud's; Arthritis	Digital pitting; Arthritis; Serositis; Fever	ANA > 1:160; RNP (+); SSA (anti-Ro) (+)	MCD
3	Raynaud's; Dysphagia	Sclerodactyly; Digital pitting	ANCA (+)	SSc
4	Raynaud's	Digital pitting; Arthritis; Serositis	Anti-Scl-70 (+); RNP (+); SSA (anti-Ro) (+); SSB (anti-La) (+)	SSc
5	Arthritis, Xerostomia	Arthritis	ANA > 1:160; SSA (anti-Ro) (+)	Sjogren's syndrome
6	Arthritis	Arthritis; Fever; Rash	ANA 1:80; RNP (+); SSA (anti-Ro) (+)	MCD
7	Arthritis	Arthritis; Serositis	ANA > 1:160; RF (+)	RA
8	Arthritis	Arthritis	RF (+)	RA
9	Arthritis, Myalgia	Arthritis: Myositis	ANA (+); SSA (anti-Ro) (+); SSB (anti-La) (+); anti-JO-1 (+)	Polymyositis—anti-synthetase syndrome

ANCA, anti-neutrophil cytoplasmic antibody; Anti-Scl-70, anti-topoisomerase; RF, rheumatoid factor; RNP, ribonucleoprotein; SSA, anti-Sjogren's syndrome A; SSB, anti-Sjogren's syndrome B.

Figure 3. Severe digital ulcers due to Raynaud's phenomenon as manifested by Case 4.

concomitant autoimmune disease (23%), yielding an observed to expected prevalence ratio of 7.5 (99% confidence interval 2.6–19.7; $P < 0.01$) [23].

While reviewing the charts of the entire cohort, we found that of the 31 remaining patients in the cohort without clinically manifest autoimmune disease, eight additional persons (26%) manifested elevated titres of anti-nuclear antibodies (ANAs), of which four had ANA titres greater than 1:160 (all prior to transplantation). Of the remaining 23, four patients had a negative ANA titre, while 19 had no ANA titre recorded. Thus, among those actually tested, 8 of 12 (66%) manifested elevated ANA titres. We did not find clinical evidence of autoimmune manifestations in any of the remaining 31 patients.

Discussion

This series of nine clinical cases underscores the importance of silicosis comorbidity due to autoimmune diseases across a range of distinct syndromes. Moreover, despite such comorbidity, lung explant histology was diagnostic solely of silicosis, without concomitant autoimmune-related interstitial pulmonary fibrosis. The magnitude of silica-associated excess risk we observed is consistent with what has been reported by others. For example, SSc has been found to be 3–25 times more prevalent in men exposed to silica than in the male population in general, with even higher rates in frank silicosis [13].

The previous literature on autoimmune disease in silicosis largely has focused on condition-specific associations, in particular for RA and SSc. For example, there has been very little mention either of MCD or autoimmune manifestations across a range of syndromes. This clinical series contributes to our understanding of the association between silicosis and autoimmune disease by intentionally taking a broad approach to this question.

In light of the heterogeneous pattern of the autoimmune disease that we observed, it is noteworthy that three in this series also had pathological features of silicoproteinosis, which is defined as PAP linked to silica exposure [24,25]. Patients with silicoproteinosis clinically present as 'acute silicosis' and can manifest a rapidly progressive downhill course [25]. Autoantibodies against granulocyte-stimulating colony factor linked to the pathogenesis of PAP support the concept that this, too, is an autoimmune disease [26].

Another shared attribute of PAP and rheumatologic diseases associated with silica is that these comorbidities are linked to very high exposure levels of silica dust, a factor characteristic of our artificial stone-associated disease outbreak. A recent study indicated that high levels of silica exposure can result from working in stone countertop fabrication, including work with synthetic stone [27]. This is consistent with our patients' work histories of employment in small workshops cutting synthetic stone often using dry power-saw cutting with inadequate respiratory protection.

Because ours is a clinical case series, it has the limitations inherent to that approach. Nonetheless, we are uniquely positioned to make population inferences from

this series because there is only a single lung transplant centre in Israel and all persons with severe lung disease (independent of causality) are generally referred for evaluation to our institution, which serves as the national tertiary centre for referral. Further, news coverage of the artificial stone silicosis outbreak encouraged primary physicians to refer exposed patients; general public awareness has also led individuals to seek consultation independently as well. Thus, our data reflect national incidence.

Even so, other limitations of this observational study should be acknowledged. Despite the relatively large size of the artificial stone-associated silicosis outbreak in Israel, the absolute number of patients is limited. Therefore, we cannot estimate with precision the frequency of different subtypes of concomitant autoimmune diseases. For the same reason, our failure to observe certain autoimmune entities does not mean that they may not be associated with silicosis. The relatively small number of patients in this series also limits our ability to systematically access the impact of cofactors on autoimmune disease manifestations. For example, cigarette smoking has been reported to be a potentially multiplicative risk factor for seropositive RA in the presence of silica co-exposure [28]. Counterbalancing our small study size, the severity of the silicosis is likely to have enhanced the likelihood that autoimmune disease would be manifested.

We relied on a clinical approach to diagnostic classification of the autoimmune diseases among these patients. Thus, because misclassification is possible, we have provided detailed clinical and serologic data for each subject and have categorized those that were not easily classifiable as having 'overlap' MCD syndromes. Plausibly, other patients with more subtle clinical manifestations of autoimmune disease could have escaped inclusion in this series. Moreover, we did not evaluate a disease-free non-exposed referent group without silicosis for comparison. Nonetheless, even conservatively assuming a prevalence of autoimmune diseases higher than generally reported, the prevalence among our clinical series demonstrated a >7-fold, statistically significant excess.

Another limitation of our case series is that we cannot generalize to persons with silica exposure but without disease that is severe enough to lead to referral for evaluation at a lung transplantation centre. Silica exposure alone, even absent silicosis, may be associated with an increased risk for autoimmune disease [29]. Simple silicosis (as generally defined in the pneumoconiosis literature) certainly can be linked to the development of autoimmunity, as in a recent case report of complicating SLE in that clinical context [30]. Consistent with that observation, we found that, beyond the nine cases of frank disease detailed in this report, more than one in four of the remaining transplant referrals had elevated ANA titres, even presuming that all of those not tested at all were seronegative.

In summary, this clinical series, which reflects the national prevalence of disease, underscores the strong links between silicosis and autoimmune disease. This supports the importance of eliciting relevant symptoms, performing a targeted physical examination and obtaining appropriate serological testing for autoimmune disease among persons with silica-related lung disease. Conversely, it also follows that taking an occupational history for silica exposure is warranted among patients with autoimmune rheumatologic disease. Particularly suspect, in addition to long-established high-risk occupations, is work using synthetic decorative stone such as that manufactured in Israel or related products produced in Spain, the Czech Republic, the USA and potentially other countries as well.

Key points

- Chart review of an advanced silicosis outbreak due to synthetic stone showed a range of autoimmune manifestations, consistent with a variety of diseases.
- Of 40 advanced silicosis patients, 23% had manifestations of autoimmune disease which is more than a 7-fold excess of expected disease in European data.
- These cases underscore the risk of autoimmune complications in silica exposed individuals.

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Conflicts of interest

None declared.

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