Non-tuberculous Mycobacterium Infection Associated with Artificial Stone Silicosis: A Case Series

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ABSTRACT **Background:** The incidence of non-tuberculous mycobacterium (NTM) infections has been rising in patients with chronic lung diseases. These infections cause significant morbidity, mortality, and elevated healthcare costs due to challenges in recognition, delayed diagnosis, and treatment. While NTM infections in natural stone silicosis are documented, the incidence in artificial stone silicosis remains unexplored despite increasing exposure to silica dust.

Objectives: To describe the clinical, radiological, and pathological features of NTM infections in patients with artificial stone silicosis and emphasize the importance of early diagnosis.

Methods: We reviewed the database of a tertiary medical center in Israel from 2010 to 2024 and identified patients with occupational artificial stone silicosis diagnosed with NTM infection.

Results: We found eight patients with occupational artificial stone silicosis, all male, aged 42–74 years. Key symptoms included dyspnea, cough, weight loss, and fever. Computed tomography revealed mediastinal lymphadenopathy, progressive massive fibrosis, calcifications, pulmonary cavitations, pleural thickening, traction bronchiectasis, pulmonary nodules, and honeycombing. Biopsies showed silicotic nodules, birefringent crystals, pulmonary alveolar silico-proteinosis, fibrosis, and honeycombing. Four patients received NTM-targeted antibiotics, and six underwent lung transplantation. Four patients died.

Conclusions: Artificial stone silicosis may be associated with NTM infections. Early diagnosis requires a high degree of clinical suspicion. New or worsening respiratory or systemic symptoms in patients with silicosis should prompt further microbiological evaluation, including sputum culture or bronchoalveolar lavage. Further studies are needed to assess the incidence of NTM infections in this population.

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KEY WORDS: artificial stone silicosis, infection, non-tuberculous mycobacterium (NTM), silicosis

Silicosis is a restrictive lung disease resulting from inhalation of crystalline silica dust. Its incidence has been rising due to occupational exposure to both natural stone dust (metal sandblasters, emerald, coal and gold miners, foundry workers) and artificial stone dust [1]. Recent studies have described artificial stone silicosis as an epidemic in developed countries [2-6]. The most vulnerable population comprises decorative stone workers who cut artificial stone products with high silica content for kitchen and bathroom countertops, particularly those engaged in dry cutting without adequate protective gear.

A few case studies have reported non-tuberculous mycobacterial (NTM) infections in patients with natural-stone-associated silicosis [7-11], and two retrospective observational studies found that silicosis may be a risk factor for NTM infections [12,13]. However, there are no reports on NTM infections specifically in workers with silicosis due to exposure to artificial stone dust. In this study, we reported for the first time, to the best of our knowledge, eight cases of NTM infections in artificial stone workers. The available literature on NTM infections in patients with natural stone silicosis is reported.

PATIENTS AND METHODS

The ethics committee of the Rabin Medical Center approved this study (No. RMC-0344-22), and all procedures were conducted in strict accordance with the Helsinki Declaration. Review of the database of a tertiary medical center in Israel between 2010 and 2024 yielded eight patients with known silicosis who were subsequently diagnosed with an NTM infection. Their demographic and clinical data are summarized in Table 1.

Table 1. Details of eight male patients with artificial-stone silicosis and non-tuberculous mycobacterium infection

Case no.	Age in years	Smoking history	NTM Onset Post-Silica exposure, in years	NTM species detected	Co-morbidities	Presenting complaints	Predominant HRCT findings	Histological findings / biopsy type	Treatment	Outcome
1	55	+	17	*Mycobacterium fortuitum, Mycobacterium avium*	Mononeuropathy, diabetes mellitus	Cough	Mediastinal lymphadenopathy; upper lobe honeycombing; traction bronchiectasis [Figure 1A]	Silicotic nodules; honeycombing; architectural distortion; area with fibrosis; pleural fibrosis with foci of ossification; birefringent crystals on polarized light / lung explant specimens	Anti-fungal therapy, anti NTM therapy, bilateral lung transplantation (October 2018)	Survived
2	42	+	11	*Mycobacterium kansasii*	Glaucoma, Sjögren's disease	Cough, dyspnea for 1 month	Progressive massive fibrosis; mediastinal lymphadenopathy; multiple cavitary lung lesions with thick and irregular wall [Figure 1B]	Silicotic nodules; birefringent crystals on polarized light; positive staining for acid fast bacilli; foci of pulmonary alveolar proteinosis / transbronchial biopsy	Anti-NTM therapy, bilateral lung transplantation (June 2021)	Survived
3	68	–	40	*Mycobacterium kansasii*	Hypertension, diabetes mellitus	Cough, dyspnea for 3 weeks	Progressive massive fibrosis; mediastinal lymphadenopathy with calcifications [Figure 1C]	Lymph nodes showed silicotic nodules; foci of pulmonary alveolar proteinosis; birefringent crystals on polarized light / lung explant specimens	Anti-NTM therapy, Right lung transplantation (October 2016)	Died 21 months after transplantation from CLAD and pneumonia
4	59	–	n/a	*Mycobacterium abscessus* (isolated from autopsy)	Hypertension, depression, chronic renal failure	Cough, dyspnea	Mediastinal lymphadenopathy with eggshell calcifications; traction bronchiectasis; pleural thickening [Figure 1D]	Multiple silicotic nodules with central hyaline collagen; pleural and septal fibrosis / lung explant specimens	Anti-NTM therapy, lung transplantation (2013)	Died 5 years after transplantation from CLAD pneumonia
5	59	+	20	*Mycobacterium genavense*	Osteoporosis, diverticulosis	Abdominal pain (disseminated MAC)	Progressive massive fibrosis	Multiple silicotic nodules with alveolar proteinosis; birefringent crystals on polarized light / lung explant specimens	Anti-NTM therapy, left lung transplantation (March 2016)	Died 4.5 years after bilateral transplantation from PTLD and Aspergillus lung infection
6	58	–	20	*Mycobacterium kansasii*	COPD, obstructive sleep apnea	Dyspnea, cough	Mediastinal lymphadenopathy with eggshell calcifications; bilateral upper lobe fibrosis with cavitary lesions; multiple small pulmonary nodules [Figure 1E]	Scattered silicotic nodules; progressive massive pulmonary fibrosis; birefringent crystals on polarized light/ lung explant specimens	Anti-NTM therapy, right lung transplantation	Survived
7	64	+	36	*Mycobacterium xenopi*	Scleroderma	Purulent cough, dyspnea, low grade fever for 1 week	Mediastinal lymphadenopathy with calcifications; multiple small pulmonary nodules in the left lung and massive fibrosis on the right; pleural thickening [Figure 1G]	Biopsy was not performed	Anti-NTM therapy, lung transplantation candidate	Died of pneumonia prior to undergoing transplantation
8	60	N/A	N/A	*Mycobacterium kansasii*	Heart failure, hyperlipidemia, diabetes mellitus	Cough, weight loss, dyspnea	Mediastinal lymphadenopathy with calcifications; cavitary lesion in right upper lobe; massive fibrosis (Figure 1G)	Biopsy was not performed	Anti-NTM therapy	Survived

CLAD = chronic lung allograft infection, COPD = chronic obstructive pulmonary disease, CXR = chest X-ray, HRCT = high-resolution computed tomography, MAC = *Mycobacterium avium* complex, NTM = non-tuberculous mycobacteria, PTLD = post-transplant lymphoproliferative disorder

All patients were male, aged 42–74 years, with occupational exposure as artificial stone countertop cutters. Five had a history of smoking. Presenting symptoms of NTM infection included cough (n=6), dyspnea (n=6), weight loss (n=1), fever (n=1), and abdominal pain (n=1). The patient with abdominal pain presented with disseminated *Mycobacterium avium* complex infection. The median time from initial silica exposure to the onset of NTM infection symptoms was 20 years (range 11–40 years). Diagnostic evaluation for NTM infection included high-resolution computed tomography (HRCT), bronchoalveolar lavage (BAL)-performed when sputum was negative or unavailable-and lung biopsy in selected cases.

Biopsy was performed on specimens from six patients obtained from lung explants (n=5) or via transbronchial access (n=1) [Figure 1A]. The predominant histological findings were silicotic nodules (n=6), birefringent crystals on polarized light (n=5), pulmonary alveolar silico-proteinosis (n=3), pulmonary and/or pleural fibrosis (n=3), and honeycombing (n=1). Bronchoalveolar lavage culture performed on all samples grew *M. kansasii* (n=4), *M. fortuitum* (n=1), *M. avium* (n=1), *M. genavense* (n=1), *M. xenopi* (n=1), and *M. abscessus* (n=1).

All patients underwent HRCT [Figure 1B-1H]. Predominant findings were mediastinal lymphadenopathy (n=7), progressive massive fibrosis (n=6), calcifications (n=5; including 2 eggshell), pulmonary cavitations (n=3), pleural thickening (n=2), traction bronchiectasis (n=2), pulmonary nodules (n=2), and honeycombing (n=1).

All patients were treated with guideline-based anti-NTM antibiotic regimens. In addition, three patients received antibiotics for bacterial pneumonia, including ceftazidime, levofloxacin, meropenem, and polymyxin E. One patient was also treated for a fungal infection with itraconazole. Six patients underwent lung transplantation, of whom three died during follow-up. Notably, none of the lung transplant recipients experienced recurrence or regrowth of NTM following transplantation. Two patients died from chronic lung rejection and bacterial pneumonia, while one died from post-transplant lymphoproliferative disorder.

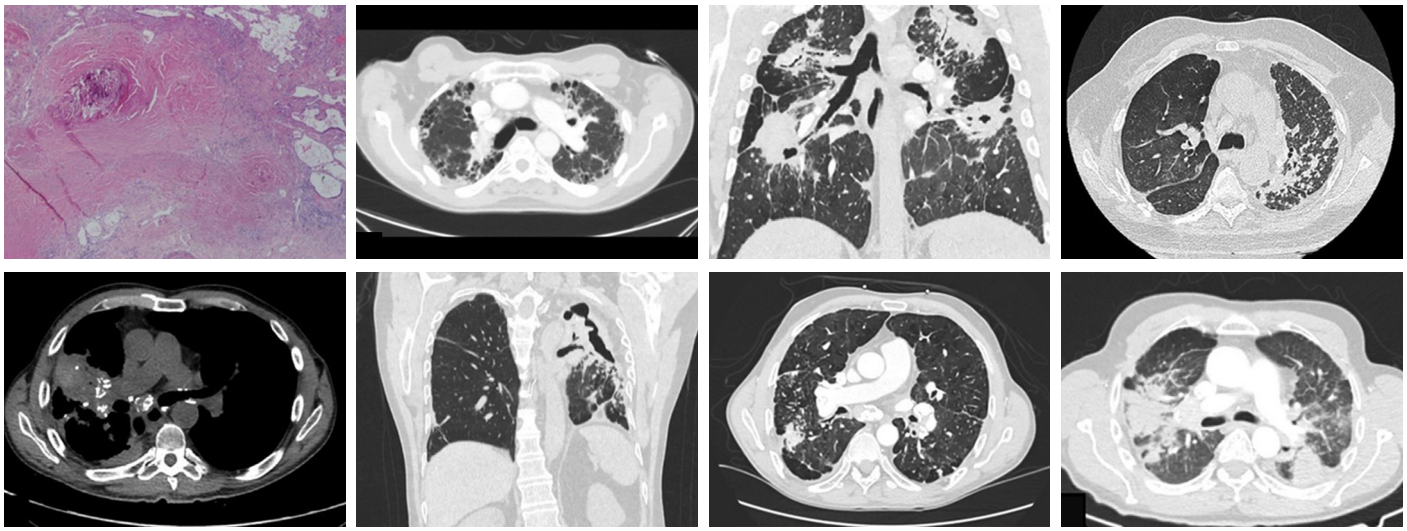
Figure1. Chest CT

[A] Gram-staining of collagenous fibrotic nodule surrounded by histiocytes with pigmented macrophages (hematoxylin and eosin staining 10×)

[B] Axial view: lung window showing paraseptal emphysema, pleural thickening, and reticulation

[C] Coronal view: lung window showing multiple cavitations with consolidation and upper-lobe volume reduction

[D] Axial view: lung window showing transplanted right lung with hyperinflation and shrinking of the left lung with centrilobular nodular ground-glass opacities



[E] Axial view: mediastinal window showing hilar and mediastinal lymphadenopathy with eggshell calcification pattern

[F] Axial view: lung window showing transplanted right lung and volume loss of the left lung with nodular ground glass opacity and pneumothorax

[G] Axial view: lung window showing an irregular mass in the right lower lobe, known as galaxy or cluster signs, with an accumulation of distinct small nodules

[H] Axial view: lung window showing irregular conglomerate masses known as progressive massive fibrosis

DISCUSSION

We present a case series of eight patients with NTM infections associated with artificial stone silicosis. *M. kansasii* was the most frequently isolated species, identified in four of the eight patients. To the best of our knowledge, this study is the largest report to detail NTM infections in patients with silicosis and the first to document NTM infections specifically in patients with artificial stone silicosis. The infection was severe in most cases. In certain cases, lung transplantation was the sole viable option, while other patients were deemed too unwell to meet the eligibility criteria.

A review of the literature revealed five studies describing NTM infections in six male patients aged 45–75 years with silicosis [Table 2]. Four were occupationally exposed to natural stone [7-10]. They worked (one each) as an emerald miner, metal sandblaster, asbestos handler, or silicone carbide smelter. In the other two patients, occupation was not specified [11]. Presenting symptoms included worsening cough (n=1), worsening expectoration pattern or hemoptysis (n=2), low-grade fever (n=1), shortness of breath or dyspnea (n=2), night sweats (n=1), and weight loss (n=1). Five patients were treated with conventional NTM antibiotic regimens including ethambutol, clarithromycin, rifabutin, isoniazid, and rifampin. Improvement and stable chronic condition were reported in two, and three died of the lung disease or a complication associated with it. Treatment and disease outcome were not reported for the sixth patient.

The manufacture and placement of artificial stone countertops are a relatively new source of occupational silica dust exposure worldwide. In 2012, Kramer and colleagues [14]. described a silicosis outbreak in artificial stone countertop workers in Israel. Thereafter, others reported similar outbreaks or a high incidence of silicosis in Spain [2], the United States [3], Iran [4], and China [6], among other countries. Wu et al. [6] found that artificial stone-associated silicosis manifested more severely than natural stone-associated silicosis in terms of shorter duration of exposure before onset, more frequent positive imaging findings, and higher lung transplant eligibility and mortality rates.

Global concerns have been raised by the increase in incidence of NTM infections in patients with chronic lung diseases such as s/p tuberculosis [12,13], pneumoconiosis [12,13], cystic fibrosis [15], and bronchiectasis [16]. An increase has also been seen in lung transplant recipients [17]. The severe structural damage caused to the lung tissue predisposes these patients to aggressive and difficult-to-eradicate infections. In occupationally exposed stone workers, inhaled silica particles activate inflammatory pathways in the distal airways, leading to phagosomal destabilisation with release of toxic contents into the cytosol. This result is followed by pulmonary macrophage destruction, cytokine activation [15], and ultimately, deposition of fibrotic material in the lungs, resulting in irreparable lung damage. Impaired fibrotic lungs are the ideal medium for the aerobic NTM species that is naturally found in the human environment.

NTM infections can have a severe presentation. Outcome in patients with silicosis is poor, thus warranting prompt diagnosis and a high degree of clinical suspicion among treating physicians. We suggest that in patients with silicosis, further evaluation including Mycobacterial sputum culture should be initiated in the presence of new or worsening respiratory complaints namely cough, hemoptysis, dyspnea, and shortness of breath, as well the appearance of systemic signs such as fever, weight loss, and nights sweats. If the results are non-contributory, bronchoalveolar lavage should follow. As cough is the most prevalent presenting complaint, any change in the quality or quantity of expectorated sputum should prompt further evaluation as well. This protocol may pose a challenge to physicians as cough may seem trivial or benign to patients living with a chronic lung disease; therefore, patient education about warning signs should be emphasized.

Our findings highlight the association between NTM infection and artificial stone-associated silicosis. At the same time, they highlight the need for additional epidemiological research to assess the structural and pathological changes induced by exposure to artificial stone dust and their potential impact on prognosis and transplant eligibility. Current guidelines recommend that patients with advanced silicosis undergo yearly tuberculosis screening [18]. Given the rising incidence of NTM infections in patients with silicosis, further studies are needed to explore the incidence of NTM infections in patients with artificial stone silicosis and to evaluate the prognostic benefit of NTM screening using sputum culture.

Two case control studies [12,13] of NTM infections in a total of 257 gold miners in South Africa found that silicosis, smoking, human immunodeficiency virus infection, and past tuberculosis infection were risk factors for the development of NTM infection in this population. Our findings support these studies, suggesting that artificial stone silicosis may be a risk factor as well. However, some questions remain. Is artificial stone silicosis a risk factor for a more severe NTM infection course? Alternatively, is NTM infection a marker of a more severe silicosis disease and thus a potential prognostic factor? Additional studies should continue investigating this association.

Table 2. Details of patients with NTM infection and natural-stone silicosis as reported in the medical literature

Reference	Patient age in years	Country	Relevant exposures (age)	Co-morbidities	Presenting symptoms	Time from silicosis diagnosis to presentation (years)	Isolated species	Treatment	Disease outcome
de Oliveira Abrão, de Araújo Filho [7], 2015	50	Brazil	Emerald mining (20)	TB treated in the past, Smoking (45PY)	Worsening of cough and expectoration pattern	2	*Mycobacterium sherrisii*	Ethambutol, Clarithromycin, Rifabutin	Improvement
Łyżwa et al. [8], 2022	45	Poland	Sandblasting metals (not reported)	None	Persistent low-grade fever, increasing shortness of breath on exertion, night sweats and weight loss	3	*Mycobacterium chimaera*	Rifabutin, Clofazimine	Death
Okuda et al. [9], 2008	75	Japan	Asbestos exposure (not reported)	N/A	Not reported, but the patient was admitted with a diagnosis of pneumonia	N/A	*Mycobacterium avium*	Not reported	Not reported
Kurahara et al. [10], 2013	71	Japan	Silicon carbide smelting (40)	COPD, smoking (>80PY)	Dyspnea, hemoptysis	12	*Mycobacterium kansasii, Mycobacterium avium complex, Mycobacterium abscessus*	Isoniazid, Rifampin, Ethambutol, Clarithromycin, Imipenem / Cilastatin, Amikacin	Death
Barrera et al. [11], 2010	57, 65	Argentina	Not reported	N/A	Not reported	N/A	*Mycobacterium sherrisii; Mycobacterium simiae*	Clarithromycin; Fluoroquinolones and Ethambutol	Death; improvement
Corbett et al. [12], 1999	206 patients with NTM	South Africa	Gold mining (varying)	Silicosis diagnosis in 70 workers; HIV in 27; 97 were treated for TB in the past	N/A	N/A	*Mycobacterium kansasii, Mycobacterium scrofulaceum, Mycobacterium avium complex*	Not reported	Not reported
Sonnenberg et al. [13], 2000	51 male patients with NTM	South Africa	Gold mining (varying)	Silicosis diagnosis in 3 workers; smoking history in 39 workers; 27 were treated for TB in the past; HIV in 18	N/A	N/A	*Mycobacterium kansasii, Mycobacterium scrofulaceum*	Not reported	Not reported

COPD = chronic obstructive pulmonary disease, HIV = human immunodeficiency virus, NTM = non-tuberculous mycobacteria, PY = pack-years, TB = tuberculosis, N/A = not available

CONCLUSIONS

NTM infections can have a severe presentation and carry a high mortality rate in patient with artificial stone silicosis. Prompt diagnosis with a high index of clinical suspicion is required. The possibility of an NTM infection should be considered in a patient with silicosis who presents with new or worsening respiratory complaints or systemic signs. The evaluation should include *Mycobacterial* sputum culture and, if non-revealing, bronchoalveolar lavage. Further studies are needed to clarify the association of NTM infection with artificial stone silicosis and the role of regular NTM screening in occupationally exposed patients.

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Capsule

Target acquired

Patients with estrogen receptor-positive (ER^+) luminal breast cancer benefit from targeted ER therapy, but many patients often have de novo or acquired resistance and require additional treatment. **Singh** et al. explored the use of immunotherapy in mouse models and patients with ER^+ breast cancer to overcome resistance. They identified a population of tumor-associated macrophages recruited by Delta-like ligand 1 on tumor cells that promoted immune suppression. Combined targeting of this ligand and programmed death ligand 1 overcame tamoxifen resistance in preclinical mouse models and patient-derived explants. These results suggest a promising new avenue of treatment that requires further exploration.

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