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Silicosarcoidosis: Histologic and Clinical Features of an Occupational Granulomatous Disease

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ABSTRACT

Sarcoidosis is a multisystem inflammatory disease of unknown etiology. Growing evidence indicates that occupational exposure to respirable crystalline silica (RCS) is associated with an increased incidence of sarcoidosis. Yet a diagnosis of sarcoidosis rarely prompts investigation to identify preventable exposures. We sought to elucidate features that identify this important clinical syndrome of silicosarcoidosis. We assembled a multinational case series of workers with sarcoidosis who also reported occupational RCS exposure. We characterized clinical and histopathologic findings using a standardized instrument. We also assessed lung specimens using a novel quantitative microscopy technique to measure birefringent dust density in silicosarcoidosis cases and compared them to control groups. We identified 35 silicosarcoidosis cases (97% male, mean age 48 years) from the United States, Israel, and Taiwan who reported 21 ± 9 years of RCS exposure. On histology scoring, 25/29 (86%) had granulomas and 17/18 (94%) with evaluable lung tissue had lymphocytic inflammation and/or lymphoid aggregates. Common lung interstitial findings included silicotic nodules (39%), mixed-dust macules/nodules (44%), and birefringent dust (50%). Quantitative birefringent dust density was significantly greater ($p < 0.001$) in silicosarcoidosis cases compared with healthy controls (147 ± 179 vs. 12 ± 9 particles/mm^2) but lower than in coal miners with silica-related progressive massive fibrosis (623 ± 777). We found significant differences in the frequency of histologic abnormalities in large versus small biopsy specimens, with fewer findings of RCS exposure in smaller tissue samples. The use of the term silicosarcoidosis should enhance recognition of this significant exposure-related granulomatous lung disease and will help guide clinical management that addresses exposure prevention in combination with appropriate pharmacologic treatment.

1 | Introduction

Sarcoidosis is considered a multisystem inflammatory disease of unknown etiology, with an estimated 8 new cases per 100,000 diagnosed annually in the United States [1]. Growing evidence suggests that sarcoidosis is more prevalent in workers exposed to respirable crystalline silica (RCS), World Trade Center dust, metal fumes, military deployment particulates, and other occupational exposures [2–6]. The overlapping clinical features between sarcoidosis and chronic beryllium disease (CBD) have been recognized for decades. Similarly, "hot tub lung" from aerosolized nontuberculous mycobacteria and other forms of antigen-driven granulomatous pneumonitis are often clinically indistinguishable from sarcoidosis except by the exposure history [7, 8].

Once a diagnosis of sarcoidosis is rendered, the search for modifiable exposures often ceases, and the focus shifts to clinical care and follow-up. Yet increasing evidence suggests that this approach may miss critical public health interventions, including exposure control, particularly in workers exposed to RCS dust who present with a mixed clinical picture of silicosis and sarcoidosis [2–4, 9]. We describe the clinical, imaging, and histopathologic findings from a multinational case series of workers exposed to RCS who were initially diagnosed with idiopathic sarcoidosis. We propose that these cases highlight a distinct overlap condition, here termed "silicosarcoidosis," with important implications for disease management, including exposure mitigation and benefits counseling, public health investigations into workplace conditions, treatment considerations, and recognition of the expanding silica-related lung disease spectrum.

2 | Materials and Methods

2.1 | Study Population

We collected cases of workers aged 18 and older with clinical findings of sarcoidosis and occupational histories of workplace RCS exposure. We screened a convenience sample of cases identified by pulmonologists at multiple institutions in three countries, including the Carmel Medical Center (Haifa, Israel), National Taiwan University Hospital (Taipei, Taiwan), Northwestern Medicine—Chicago (Illinois, the United States), National Jewish Health (Colorado, the United States), and University of Colorado School of Medicine (Colorado, the United States). Signed informed consent was obtained from each participant for the collection of de-identified demographic, clinical, imaging, and pathology information in a Research Electronic Data Capture (REDCap) registry [10], and all protocols received Institutional Review Board approval (BRANY #HS-3483).

All cases had clinical or histologic features consistent with a diagnosis of sarcoidosis. Non-necrotizing granulomas visualized on tissue biopsy from any organ were considered consistent with sarcoidosis. Cases lacking evaluable tissue were considered if they had: (A) a historical record of a tissue biopsy consistent with sarcoidosis, or (B) chest imaging features of sarcoidosis as determined by a thoracic radiologist and at least one other clinical manifestation seen in sarcoidosis (e.g., lymphocytic alveolitis on bronchoalveolar lavage, nephrolithiasis, hypercalcemia/hypercalciuria, granulomatous hepatitis, uveitis, or erythema nodosum). These case definitions incorporate recent American Thoracic Society (ATS) guidelines for sarcoidosis diagnosis [11] and represent clinical features that would help differentiate from a diagnosis of silicosis alone. Potential cases were not included if granulomatous inflammation appeared to be caused by other etiologies, such as active mycobacterial or fungal infections.

2.2 | Demographics and Occupational History

We documented date of birth, self-reported gender, smoking status, and smoking pack-years. We also recorded years of work tenure and current or previous work in an industry with a known risk for RCS exposure, including stone fabrication or masonry; cement, concrete, and brick product manufacturing; foundry work; clay product manufacturing; glass/glass product manufacturing; dental technician duties; mining; sandblasting; or other jobs in which a worker reported significant airborne RCS exposure. A worker's primary industry was the industry of the longest duration.

2.3 | Chest Imaging

We collected findings from chest computed tomography (CT) imaging reports. Abnormalities of interest included the presence of calcified or non-calcified mediastinal and hilar lymphadenopathy, ground-glass opacities, small round or linear/reticular opacities, large opacities/nodules/masses exceeding 1 cm in long-axis diameter, emphysema, and honeycombing.

2.4 | Histopathology Scoring

We designed a standardized histopathology scoring form to characterize findings seen in either sarcoidosis or silicosis. All available lymph node and lung tissue samples were de-identified and scored by an experienced occupational pulmonary pathologist (C.D.C.). Lung tissue sections were evaluated under polarized light microscopy (PLM) for the presence and distribution of retained birefringent silica/silicate particulate matter. We also assessed histologic abnormalities based on tissue specimen size. Smaller samples were considered those obtained via transbronchial/endobronchial biopsy or endobronchial ultrasound (EBUS)-guided lymph node aspiration. All other tissue specimens (e.g., wedge resection, cryobiopsy, lobe or lymph node excision, or explant) were categorized as larger samples.

2.5 | Quantitative Birefringent Dust Density

We used a novel quantitative PLM technique [12] to quantify the burden of in situ particulate matter consistent with silica/silicates (QM-PM) in available lung tissue specimens. Briefly, this technique utilizes high-resolution microscopy images

under PLM and an automated algorithm to characterize birefringent particles across an entire specimen. We defined birefringent dust density as the number of particles per area of tissue (particles/mm^2). We compared the birefringent dust density in silicosarcoidosis cases to results previously obtained from 10 healthy controls and from a positive control group of 50 coal miners with progressive massive fibrosis (PMF) lesions containing > 25% silicotic nodules [12, 13].

2.6 | Statistical Analyses

Descriptive statistics are reported on the proportions of workers who had pertinent demographic, clinical, imaging, or histologic features. We used Fisher's Exact Test to compare the frequency of identifying granulomas, mineral dust lesions (silicotic nodules, mixed-dust nodules, or mineral dust alveolar proteinosis [MDAP]), or birefringent dust between the three tissue specimen types (EBUS lymph node aspiration, transbronchial biopsy, or larger lung tissue specimens including explant, wedge resection, and surgical lung biopsy). We used one-way ANOVA following log-transformation and post hoc Tukey's test to compare quantitative birefringent dust density. Significant differences were defined as $p < 0.05$.

3 | Results

3.1 | Case Demographics

We identified 35 cases with sarcoidosis who reported work histories indicating significant RCS exposure, including 25 with confirmed granulomatous inflammation on independent tissue review, 9 with granulomatous inflammation based on previous pathology report, and 1 with clinical and imaging features of sarcoidosis (Case #4). Table 1 shows summary demographics and exposure histories for all cases. Most (97%) were male, with a mean age of 48 years (range 28–69). The mean duration of employment in an industry with RCS exposure was 21 ± 9 years. There were 17 former or current tobacco smokers, who

TABLE 1 | Summary demographics and work history ($n = 35$).

Demographics	*n* missing	Value
Age, mean ± SD [range]	1	48 ± 12 [28–69]
Male, *n* (%)		34 (97%)
Country, *n* (%)		
The United States		16 (46%)
Israel		17 (49%)
Taiwan		2 (6%)
Race/ethnicity, *n* (%)	3	
Non-Hispanic White		10 (31%)
Middle Eastern North Africa		9 (28%)
Ashkenazi Jew		5 (16%)
Hispanic		3 (9%)
Asian		2 (6%)
Sephardic Jew		1 (3%)
American Indian/Alaskan Native		1 (3%)
Black or African American		1 (3%)
Smoking history[a]		
Ever smoked cigarettes, *n* (%)		17 (49%)
Pack-years, mean ± SD	2	22 ± 14
Work history		
Primary industry, *n* (%)		
Stone cutting or masonry		12 (34%)
Mining		7 (20%)
Cement/concrete/brick manufacturing or sandblasting		5 (14%)
Construction		4 (11%)
Other[b]		7 (20%)
Years of exposure, mean ± SD	7	21 ± 9

[a]We defined smokers as those reporting smoking more than 20 packs of cigarettes in a lifetime or more than one cigarette daily for one year. Estimated smoking pack-years were calculated as a product of years of smoking times the average number of packs smoked daily.
[b]Other industries with silica exposure include foundry work, railroad work, fire sprinkler installation, plumbing, and machining.

averaged 22 ± 14 cumulative pack-years. The most common primary employment sectors were stone fabrication or masonry (34%), mining (20%), cement/concrete/brick manufacturing or sandblasting (14%), and construction (11%). Table 2 shows case-specific demographics, occupational and smoking exposures, and clinical features.

3.2 | Case Highlights

We provide detailed summaries for four representative cases of silicosarcoidosis, three of whom were diagnosed initially with only sarcoidosis and one with both sarcoidosis and silicosis, to demonstrate the breadth of exposures and clinical features that characterize this overlap condition. Pulmonary pathology and chest imaging from these cases are highlighted in Figures 1–4.

Case #15: Silicosis and sarcoidosis in a railroad worker. A 53-year-old never-smoker was evaluated by an occupational pulmonologist. The patient reported 20 years of employment as a railroad laborer. His job duties required him to operate heavy equipment to flatten gravel for distribution and to walk through plumes of gravel/rock dust alongside rail cars to regulate the amount that was dumped to maintain the tracks. In high school, he had worked as a brick mason, with exposure to dust from bricks and mortar. Reported symptoms included shortness of breath and fatigue. PFTs showed progressively worsening severe mixed obstructive and restrictive lung disease (FEV1 22% predicted) and diffusion impairment (DLCO 37% predicted). Chest CT showed calcified mediastinal and hilar lymph nodes, conglomerate bilateral upper lobes mass lesions, cicatricial emphysema, and air trapping. Sarcoidosis was diagnosed initially based on a transbronchial biopsy showing non-necrotizing granulomas. The treating physician diagnosed concomitant silicosis based on the exposure history, imaging findings of possible PMF, absence of extra-pulmonary manifestations of sarcoidosis, and worsening lung function despite sustained treatment with prednisone, methotrexate, and azathioprine. He underwent a lung transplant approximately 15 years after diagnosis. Explanted lung tissue showed profuse birefringent material, mature silicotic nodules, and well-formed granulomas (Figure 1).

Case #10: Sarcoidosis in a concrete mixer. A 50-year-old never-smoker reported 2 years of active employment as a concrete mixer driver when he transported wet concrete, dry powder (including granite, quartz, and pea gravel), and sand used for admixture in concrete production. He was promoted to plant operator, where he shoveled and dry-swept rocks/dust that had fallen off conveyor belts in the dusty plant. He had no respiratory symptoms, and PFTs were within normal limits. Chest imaging showed extensive perilymphatic nodularity and areas of confluent nodularity/consolidation. A surgical lung biopsy showed profuse, non-necrotizing granulomas adjacent to mature silicotic nodules, with additional findings of scattered polarizable material and anthracotic pigment (Figure 2).

Case #4: Sarcoidosis in a stone fabricator. A 59-year-old, 32-pack-year former smoker, reported 34 years of cumulative workplace RCS exposure. He spent 32 years in the stone countertop fabrication and installation industry, using both natural and engineered stone products. His job duties included dry sweeping and using an air wand to collect stone dust, as well as cutting, grinding, and polishing countertop surfaces before installation in residential and commercial settings. He worked for many years with poor local exhaust ventilation, rudimentary water suppression methods, and no personal respiratory protection. He also spent 2 years in construction, mixing and laying concrete. He reported respiratory symptoms of shortness of breath and productive cough. Complete resting pulmonary function testing was within normal limits. Chest HRCT imaging showed centrally calcified mediastinal lymphadenopathy, extensive subpleural nodularity with septal thickening, and confluent nodules in the appearance of a pseudoplaque with surrounding small nodules indicating the "galaxy sign," all deemed highly suggestive of sarcoidosis by the thoracic radiologist (Figure 3). Bronchoalveolar lavage showed lymphocytic alveolitis (60% lymphocytes). Diagnosis of silicosarcoidosis was based on clinical findings and work history.

Case #6: Sarcoidosis in a coal miner. A 54-year-old never-smoker reported 24 years of employment as an underground coal miner in dusty, low-seam mines using modern mechanized equipment. His job duties occurred primarily at the mine face and included utility man, roof bolter, jackleg operator, rock duster, continuous miner operator, ram car driver, and safety officer. His medical history was relevant for hypercalciuria and kidney stones. He described progressively worsening shortness of breath and cough. Lung function testing showed a gradual decline from normal to mild fixed airway obstruction, with normal diffusion capacity. Chest imaging showed mediastinal lymphadenopathy with foci of calcification, perilymphatic nodularity, consolidative opacities, and air-trapping (Figure 4a). A surgical lung biopsy showed granulomas, mature silicotic nodules, and anthracotic pigment (Figure 4b).

3.3 | Chest Imaging

All but one worker had available chest CT imaging results. Mediastinal or hilar adenopathy (calcified or non-calcified) was frequent (31/34; 91%). Findings of small, rounded opacities (69%), linear opacities (6%), or both (9%) were also common, including 10 (29%) with large opacities exceeding 1 cm in diameter. Honeycombing (6%), emphysema (12%), and ground-glass opacities (18%) were observed in varying frequencies.

3.4 | Histopathologic Scoring

Granulomatous inflammation was noted in previous pathology reports from all but one case (Case #4). We obtained 32 tissue specimens (from a total of 29 cases, some with more than one tissue sampling modality) for independent scoring (see Table 3 for details of biopsy modality).

Table 4 shows histopathologic features by lung compartment and/or lymph nodes. Overall, 25/29 (86%) cases had non-necrotizing granulomas. Granulomatous inflammation was found most frequently involving the large airways/endobronchium (80%) but was also common in small airways

TABLE 2 | Case-level demographics, employment, and pertinent clinical features ($n = 35$).

ID	Primary sector[a]	Work years[a]	Smoking pack-years	Imaging[b]		Histology		Other features[e]
				LAD	Opacities	Dust[c]	Granuloma[d]	
The United States of America (USA)								
1	Stone cutting or masonry	18	0	N	Y	Unk	(Y)	
2	Stone cutting or masonry	18	22	Y	Y	Unk	(Y)	
3	Stone cutting or masonry	17	13	Y	Y	Y	Y	
4	Stone cutting or masonry	34	32	Y	Y	N	N	BAL lymph 60%, imaging "galaxy sign"
5	Stone cutting or masonry	12.5	6	Y	Y	Y	Y	
6	Mining	24	0	Y	Y	Y	Y	BAL lymph 61%, hypercalciuria, kidney stone
7	Mining	32	0	Unk	Unk	N	Y	BAL lymph 26%, kidney stone
8	Mining	20	Smoked	Y	Y	Y	Y	BAL lymph 26%
9	Mining	27	0	N	Y	Y	Y	
10	Cement/concrete/brick	2	0	Y	Y	Y	Y	
11	Sandblasting	Unk	15	Y	Y	Y	Y	
12	Construction	Unk	0	Y	Y	Y	Y	
13	Construction	28	0	Y	Y	N	Y	BAL lymph 26%
14	Other[f]	17	0	Y	Y	Y	Y	
15	Other[f]	20	0	Y	Y	Y	Y	
16	Other[f]	Unk	30	Y	Y	Y	Y	
Israel								
17	Stone cutting or masonry	25	0	Y	Y	Y	Y	
18	Stone cutting or masonry	10	0	Y	Y	N	Y	
19	Stone cutting or masonry	30	30	Y	Y	N	Y	
20	Stone cutting or masonry	Unk	45	Y	Y	N	Y	
21	Stone cutting or masonry	22	0	Y	Y	Y	Y	
22	Mining	21	0	Y	Y	N	(Y)	
23	Mining	23.5	10	Y	Y	Y	(Y)	
24	Mining	30	22	Y	N	N	Y	
25	Cement/concrete/brick	Unk	22	Y	Y	N	Y	
26	Cement/concrete/brick	Unk	20	Y	Y	N	(Y)	
27	Sandblasting	5	0	Y	Y	Y	Y	

(Continues)

TABLE 2 | (Continued)

ID	Primary sector[a]	Work years[a]	Smoking pack-years	Imaging[b]		Histology		Other features[e]
				LAD	Opacities	Dust[c]	Granuloma[d]	
28	Construction	Unk	0	Y	N	Y	Y	
29	Construction	25	0	Y	Y	Y	Y	
30	Other[f]	25	Smoked	Y	Y	N	Y	
31	Other[f]	16	10	Y	N	Y	Y	
32	Other[f]	30	0	Y	Y	Y	(Y)	
33	Other[f]	35	20	N	N	N	(Y)	
Taiwan								
34	Stone cutting or masonry	8	10	Y	Y	Y	(Y)	
35	Stone cutting or masonry	8	0	Y	Y	Y	(Y)	

Abbreviations: BAL = bronchoalveolar lavage, Unk = unknown.

[a]Work years indicate the cumulative years of employment with occupational dust exposure. The primary sector is the dust-exposed industry in which a worker has been employed for the longest duration.

[b]Imaging findings: LAD = presence of mediastinal or hilar lymphadenopathy (calcified or non-calcified). Opacities = presence of rounded or linear opacities, including large opacities/nodules/masses (> 1 cm).

[c]Histopathology findings reflecting substantial respirable dust exposure, including (1) mineral dust alveolar proteinosis, immature or mature silicotic nodules, mixed-dust nodules, or (2) birefringent material on polarized light microscopy (Y = yes; N = not reported by a local pathologist or observed on independent review; Unk = not reported by local pathologist and tissue was not available for independent review).

[d]Granulomas: Y = non-necrotizing granulomatous inflammation seen on formal pathology scoring for workers where tissue samples were retrieved for independent review; (Y) = granulomatous inflammation based on a previous pathology report; N = no granulomas observed on tissue histopathology.

[e]Denotes other findings compatible with sarcoidosis, for example, hypercalciuria, kidney stones, lymphocytic alveolitis on bronchoalveolar lavage, and cardiac or ocular sarcoidosis.

[f]Other industries with silica exposure include foundry work, railroad work, fire sprinkler installation, plumbing, and machining.

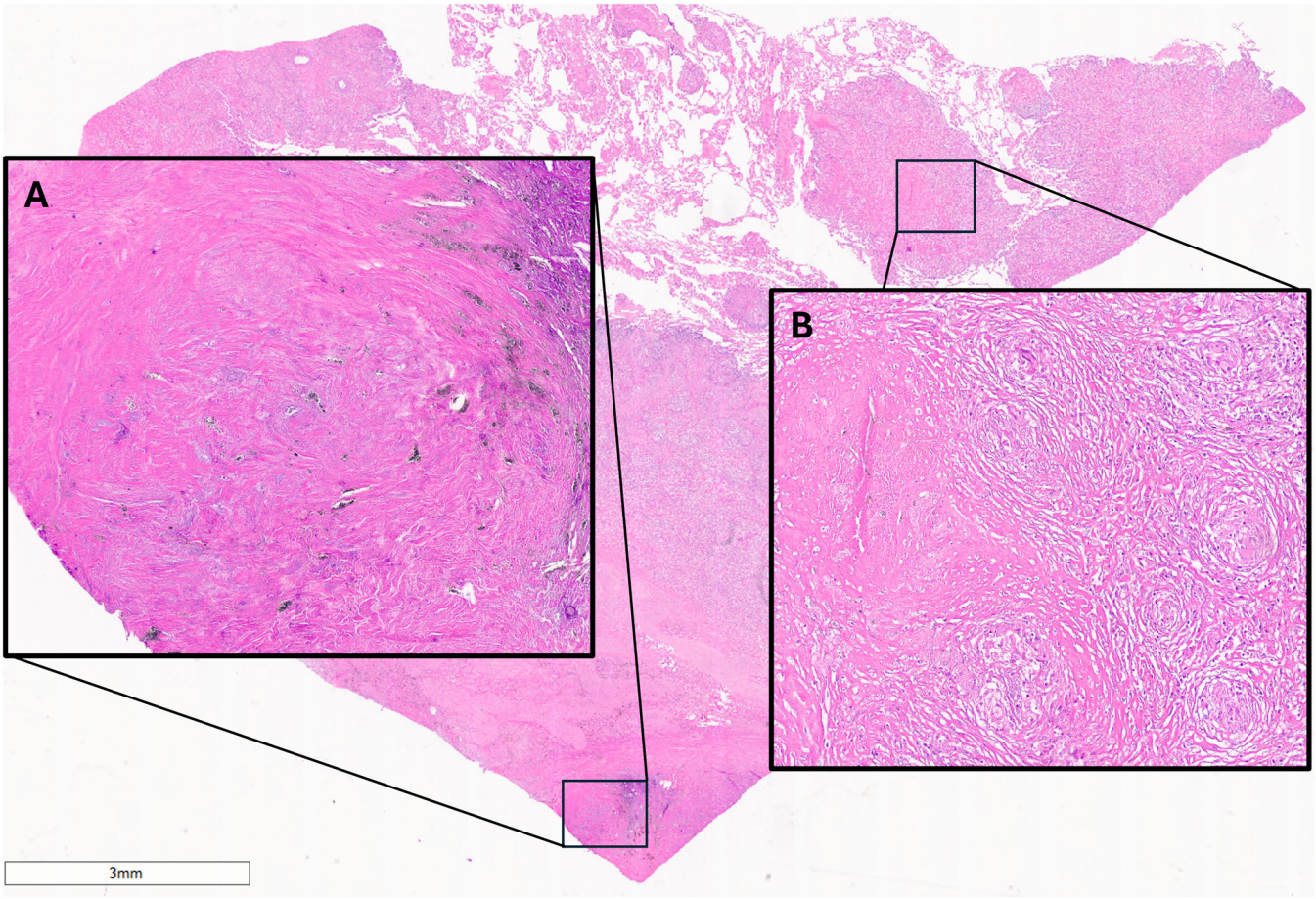

FIGURE 1 | Hematoxylin and eosin (H&E)-stained lung tissue from a never-smoker railroad laborer with 20 years of employment (Case #15), showing mature silicotic nodules in proximity to non-necrotizing granulomas. (A) High-power view of the silicotic nodule demonstrating a rounded fibrotic lesion composed of concentric collagen fibers, and anthracotic pigment deposition admixed with the collagen. (B) The clustered granulomas highlighted by coalescing tight clusters of epithelioid histiocytes and multinucleated giant cells surrounded by collagen.

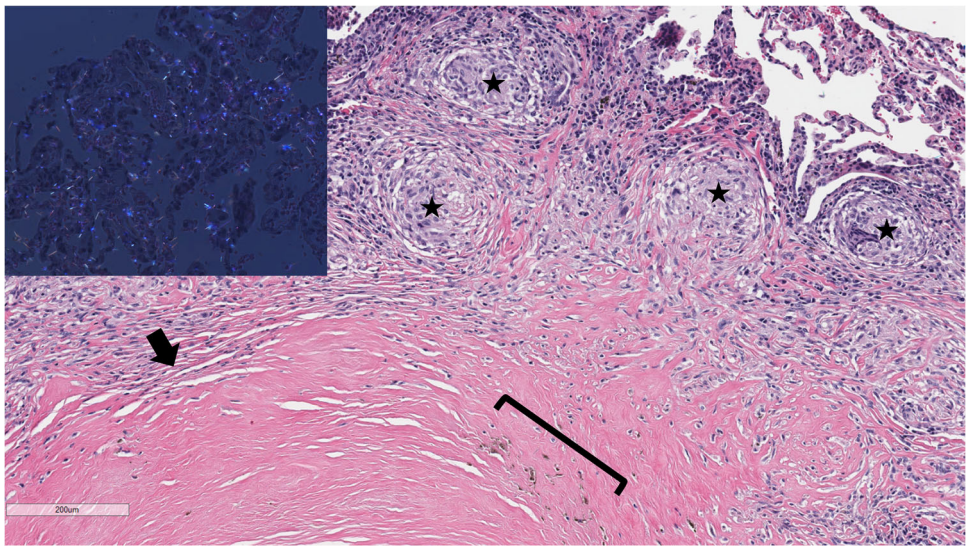

FIGURE 2 | H&E-stained lung tissue from a never-smoker concrete mixer driver with 2 years of employment (Case #10), showing mature silicotic nodules (arrow) containing areas of anthracotic pigment (bracket), adjacent to numerous non-necrotizing granulomas (stars). The Inset image shows lung tissue elsewhere from this same case under polarized light microscopy, highlighting profuse birefringent material consistent with retained silica and silicate particles within a dust nodule.

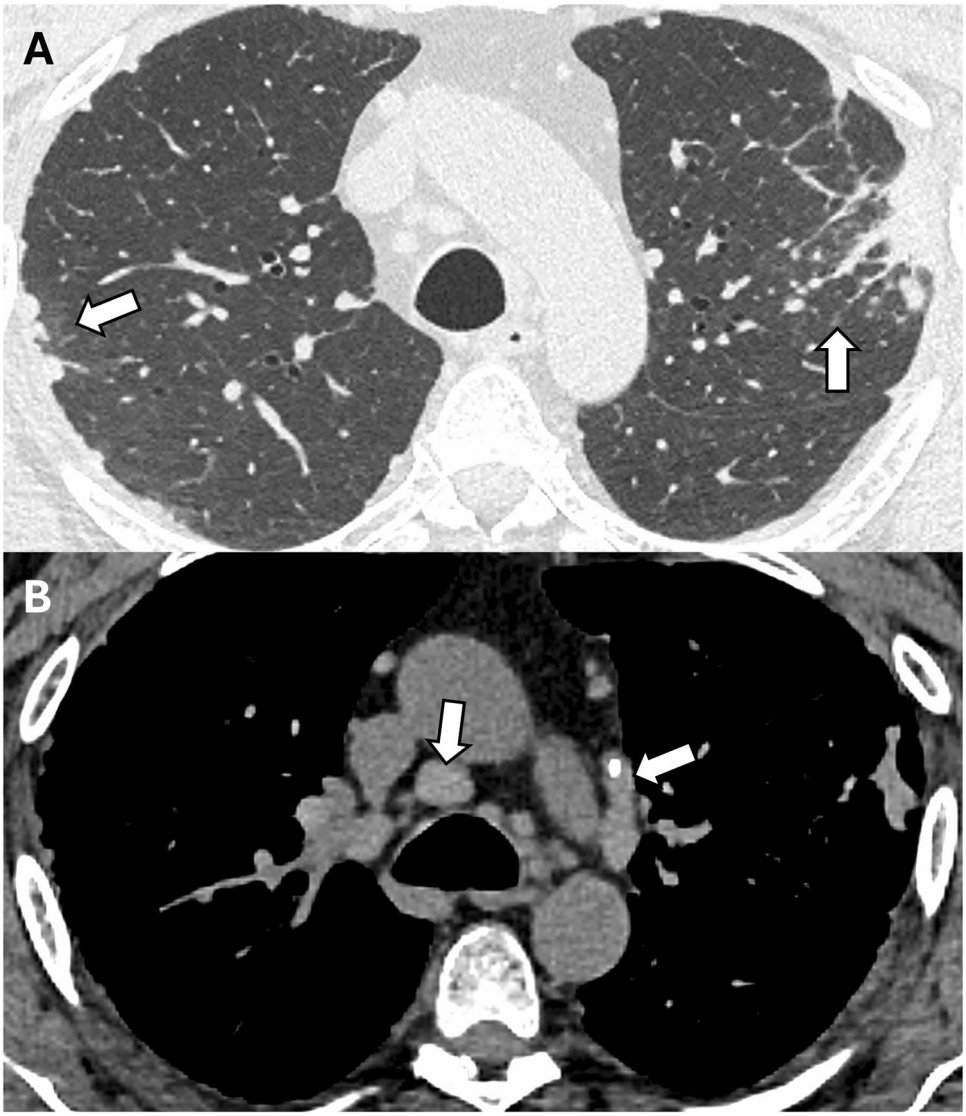

FIGURE 3 | Chest CT images from a 32-pack-year former smoker with 34 years of employment, including 32 years as a stone fabricator/installer and 2 years as a concrete worker (Case #4). (A) Lung windows show extensive subpleural nodularity in the right lung and confluent nodules in the appearance of a pseudoplaque with surrounding small nodules indicating the "galaxy sign" in the left upper lung. (B) Mediastinal windows highlight mediastinal and hilar lymphadenopathy, including some with central calcification. This constellation of imaging abnormalities was deemed highly suggestive of sarcoidosis by the thoracic radiologist, and the worker had 60% lymphocytes on bronchoalveolar lavage.

(73%) and the interstitium (56%). In addition to granulomas, lymphocytic inflammation and/or lymphoid aggregates were nearly ubiquitous and noted in 17/18 (94%) with any evaluable lung tissue.

Within the lung interstitium, 7/18 (39%) cases had silicotic nodules (including 3 with immature and 6 with mature nodules), 44% had mixed dust macules/nodules, and 50% had birefringent particles under PLM. MDAP, a marker of high-intensity dust exposure, was observed in only one case. In 10 samples with evaluable pleural tissue, 40% had pleural-based silicotic nodules, 30% had birefringent particulates, and 50% had granulomas.

Among 17 lymph node samples, 12 (71%) showed substantial RCS exposure based on the presence of silicotic nodules and/or birefringent material and 13 (76%) had granulomas. For the six cases with both lung and lymph node tissue available, all had either silicotic nodules or birefringent particles in lymph nodes, and 5/6 (87%) also had these abnormalities noted in lung tissue. Three of five (60%) cases with granulomas in lymph node samples also had granulomas present in lung tissue.

3.5 | Histology Findings by Biopsy Modality

We found statistically significant differences in histopathologic abnormalities based on large versus small tissue biopsies (Table 5). Examining 12 larger tissue specimens, 83% had non-necrotizing granulomas, 92% had mineral dust lesions, and 10/11 (91%) had birefringent dust. Granulomas were found in similar proportions of smaller samples. In contrast, none of the transbronchial biopsies and only 13% of EBUS aspiration samples had mineral dust lesions, and only 13% of transbronchial biopsies showed birefringent dust.

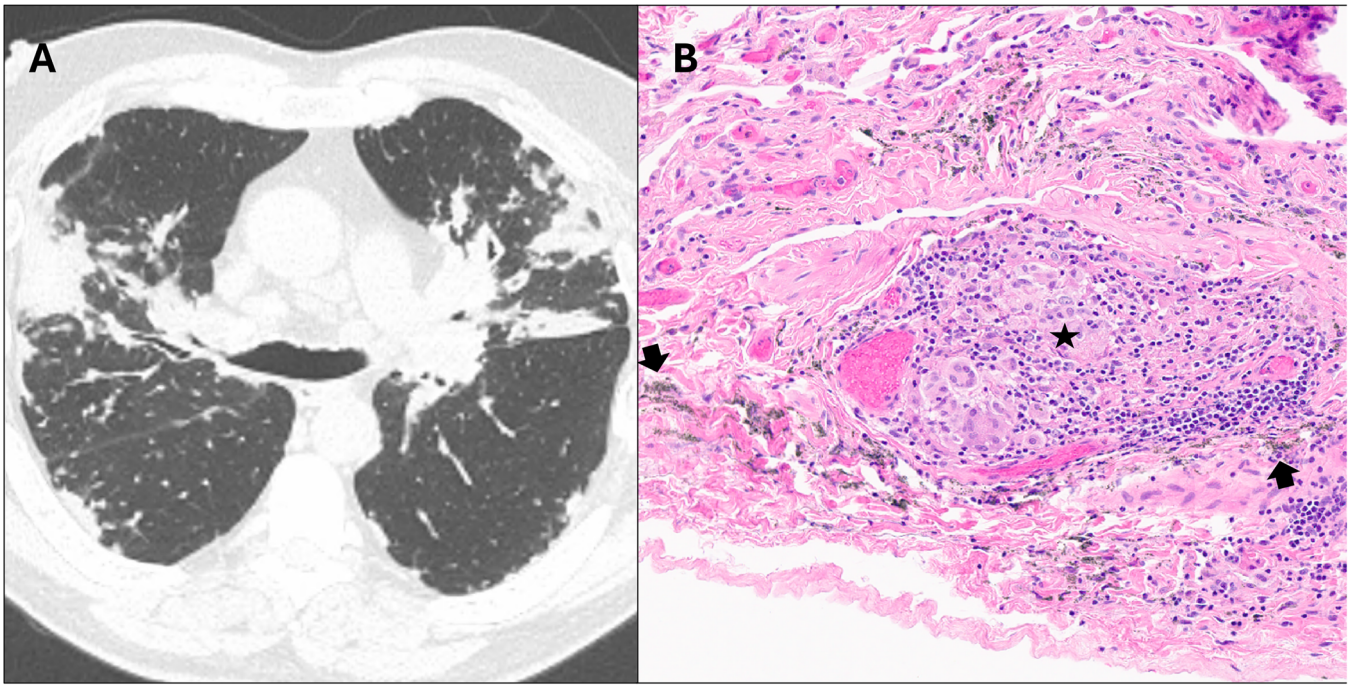

FIGURE 4 | Imaging and H&E-stained lung tissue in a never-smoker coal miner with 24 years of mining tenure (Case #6). (A) Chest CT shows extensive perilymphatic and pleural-based nodularity with large consolidative opacities, and (B) lung tissue shows a pleural-based granuloma (star) adjacent to retained anthracotic pigment (arrows). Silicotic nodules were also present (not shown).

TABLE 3 | Tissue samples available for histology scoring ($n = 32$)[a].

Type of biopsy, *n*	
Endobronchial ultrasound (EBUS)-guided lymph node	12
Transbronchial biopsy	7
Wedge or other sublobar resection	6
Cryobiopsy	2
Lobectomy	2
Explanted lung from transplantation	1
Endobronchial biopsy	1
Mediastinoscopy (excisional lymph node)	1
Number of lobes/samples scored, median (range)	1 (1–4)

Note: One participant had both a transbronchial biopsy and mediastinoscopy (lymph node excision) samples available; both samples were scored. Two participants had both a transbronchial biopsy and EBUS-guided lymph node biopsy scored.

[a]Cases not available for scoring: two cases from the United States, three cases from Israel, and one case from Taiwan.

3.6 | Birefringent Dust Distribution

All 10 of the large-sample cases found to have birefringent particulate matter had dust within nodules and macules, with only one showing birefringence within granulomas. All seven EBUS samples with birefringent dust had particulates in lymphoid tissue, and one also had scattered birefringent dust within granulomas. The one transbronchial biopsy case with birefringent dust had particulates observed in the mixed-dust nodules. Overall, 17 (100%) specimens had birefringent particulate matter distributed within silicotic/mixed-dust lesions or lymphoid tissue, while only 2/17 (12%) had birefringent dust noted within granulomas. A representative example from Case #3 is shown (Figure 5).

3.7 | Birefringent Dust Density

QM-PM confirmed significantly greater birefringent dust density in 18 silicosarcoidosis cases with evaluable lung tissue compared to 10 healthy controls (147 ± 179 vs. 12 ± 9 particles/mm^2), but less particulate density compared to lung tissue from 50 coal miners with silica-related PMF (623 ± 777) ($p < 0.0001$; $p < 0.001$ for all pairs; Figure 6).

4 | Discussion

We describe a multinational case series of 35 workers from a range of industries with occupational RCS exposure who presented with clinical features of silicosis and sarcoidosis. We utilized a standardized histologic scoring instrument to assess lung and lymph node findings from the majority of cases and found pathologic features of granulomatous inflammation, dust nodules, birefringent particulate matter, and increased birefringent dust density compared to healthy lung tissue. Most of these cases had been diagnosed on initial clinical evaluation with sarcoidosis, and opportunities to address both the medical and public health management of silicosis were missed until the role of silica exposure was recognized. As workplace exposures are estimated to contribute substantially to 30% of all

TABLE 4 | Pertinent histology scoring findings by lung zone, summarized per person ($n = 29$).

Large airways present, *n* (%)	10 (34%)
Granulomas	8 (80%)
Lymphocytic inflammation or lymphoid aggregates	9 (90%)
Birefringent material	0 (0%)
Small airways present, *n* (%)	11 (38%)
Granulomas	8 (73%)
Lymphocytic inflammation or lymphoid aggregates	8 (73%)
Smooth muscle hypertrophy	1 (9%)
Peribronchiolar metaplasia	5 (45%)
Interstitium present, *n* (%)	18 (62%)
Granulomas	10 (56%)
Lymphocytic inflammation or lymphoid aggregates (interstitial)	8 (44%)
Asteroid bodies, Schaumann bodies, or multinucleated giant cells	12 (67%)
Histiocytes	3 (17%)
Silicotic nodules (immature)	3 (17%)
Silicotic nodules (mature)	6 (33%)
Mixed dust macules/nodules	8 (44%)
Progressive massive fibrosis	2 (11%)
Birefringent material (interstitial)	9 (50%)
Interstitial fibrosis	7 (39%)
Emphysema	8 (44%)
Airspaces present, *n* (%)	17 (59%)
Mineral dust-associated alveolar proteinosis (MDAP)	1 (6%)
Vessels present, *n* (%)	18 (62%)
Granulomas in vessel walls	2 (11%)
Pleura present, *n* (%)	10 (34%)
Granulomas	5 (50%)
Lymphocytic inflammation or lymphoid aggregates	5 (50%)
Silicotic nodules (immature)	1 (10%)
Silicotic nodules (mature)	4 (40%)
Birefringent material	3 (30%)
Acute or chronic pleuritis	3 (30%)
Lymph node scored, *n* (%)	17 (59%)
Granulomas	13 (76%)
Silicotic nodules (mature)	5 (29%)
Birefringent material	10 (59%)

sarcoidosis cases [3], we propose that the term "silicosarcoidosis" be used to describe granulomatous lung disease in the presence of a significant occupational history of exposure to RCS.

4.1 | Histopathology of Silicosarcoidosis

Histopathologic findings in silicosarcoidosis are heterogeneous. Besides the common findings of granulomas and dust nodules with birefringent particles on larger sample sizes, other findings of silicosis and sarcoidosis may aid in diagnosis. Dust lesions may have qualities of mature and immature silicotic nodules [14, 15], though MDAP was uncommon in this case series. Notably, granulomatous and particulate involvement of the pleura was common and should be assessed routinely in lung tissue samples with available pleura. Interstitial fibrosis and hyperinflation with emphysematous changes are features of both diseases and are therefore less useful in distinguishing this overlap condition, as are the classic features of sarcoidosis, including asteroid bodies, Schaumann bodies, multinucleated giant cells, and lymphocytic inflammation or lymphoid aggregates.

Several histologic findings emerged that may be useful in making the diagnosis of silicosarcoidosis. In 17 specimens with birefringent material, all had dust-laden silicotic nodules, mixed-dust nodules/macules, or lymphoid tissue, but only two had birefringent particulates found within granulomas. These findings suggest that silicosarcoidosis may not be a localized foreign-body reaction to silica, as can occur with food or particles accidentally aspirated into the lung or following intravenous illicit drug use [16–18]. Instead, the absence of detectable retained birefringent dust within granulomas suggests that silica-related granulomatous inflammation may be a systemic inflammatory reaction.

Additionally, we found that the volume of the tissue specimen is important for diagnostic clarity. Fiberoptic bronchoscopy and EBUS-guided lymph node aspiration were insensitive in detecting the histologic abnormalities of silicosis, although they are commonly used to diagnose sarcoidosis [11]. There are several reasons for this observation. First, silicotic and mixed-dust nodules are often larger than granulomas (see Figure 2), as histopathologic granulomas are typically 0.3-0.4 mm in diameter, while silicotic or mixed-dust nodules are typically 1–3 mm and can coalesce to form conglomerate PMF lesions larger than 10 mm [15, 19, 20]. The American College of Chest Physicians recommends using a 21- or 22-gauge needle (inner bore diameter 0.4–0.5 mm) for EBUS lymph node aspirations, which can lead to truncation or architectural distortion of dust nodules during tissue acquisition [21, 22]. Second, smaller tissue samples and those that reflect airway-centered inflammation may be less reliable for identifying markers of fibrogenic dust than for verifying the presence of granulomas. Granulomas were found in 75%–92% of bronchoscopic and EBUS samples, while only one case with dust nodules and eight cases with birefringent dust (mainly in lymph nodes) were identified using these diagnostic techniques. Notably, larger tissue samples obtained via surgical biopsy, lobectomy, cryobiopsy, or explant had greater yield for the findings of silicosarcoidosis. In the absence of larger samples, the diagnosis of silicosarcoidosis relies on a detailed occupational history of exposure to RCS, in combination with histologic granulomatous inflammation.

4.2 | Scientific Foundation for Silicosarcoidosis

Recognition that silica exposure causes granulomatous inflammation dates back at least to the 1929 and 1930 International

TABLE 5 | Summary of pertinent silicosarcoidosis findings from independent histology scoring, stratified by tissue specimen type ($N = 32$).

		Histology findings		
Biopsy specimen type	***N***	**Granulomas**	**Mineral dust lesions[a]**	**Birefringent dust**
EBUS-guided lymph node	12	11 (92%)	0 (0%)	7 (58%)
TBB	8	6 (75%)	1 (13%)	1 (13%)
Larger sample[b]	12	10 (83%)	11 (92%)	10 (91%)*
p[c]		0.65	< 0.0001	0.002

Abbreviations: EBUS = Endobronchial ultrasound, TBB = Transbronchial or endobronchial biopsies.
*One of the 12 larger samples was only available as high-resolution digital images and thus not available for viewing under polarized light microscopy (PLM). The percentage here reflects 10/11 (91%) cases where PLM could be independently performed; though notably, this particular case was noted to have positive birefringent dust on the original pathology report.
[a]Includes abnormal histology findings of silicotic nodules (mature or immature), mixed-dust macule/nodules, and/or mineral dust alveolar proteinosis.
[b]Includes larger tissue samples from a wedge or other sublobar resection, cryobiopsy, lobectomy, or explanted lung, which may have included both evaluable lung and lymph node tissue. One sample also had a mediastinoscopy (excision lymph node), which was included in this modality group.
[c]Calculated using Fisher's Exact Test. Significant pairwise differences were observed for pathology findings of mineral dust lesions (EBUS vs. Large, $p < 0.0001$; TBB vs. Large, $p < 0.0001$) and for birefringent dust (TBB vs. Large, $p = 0.001$).

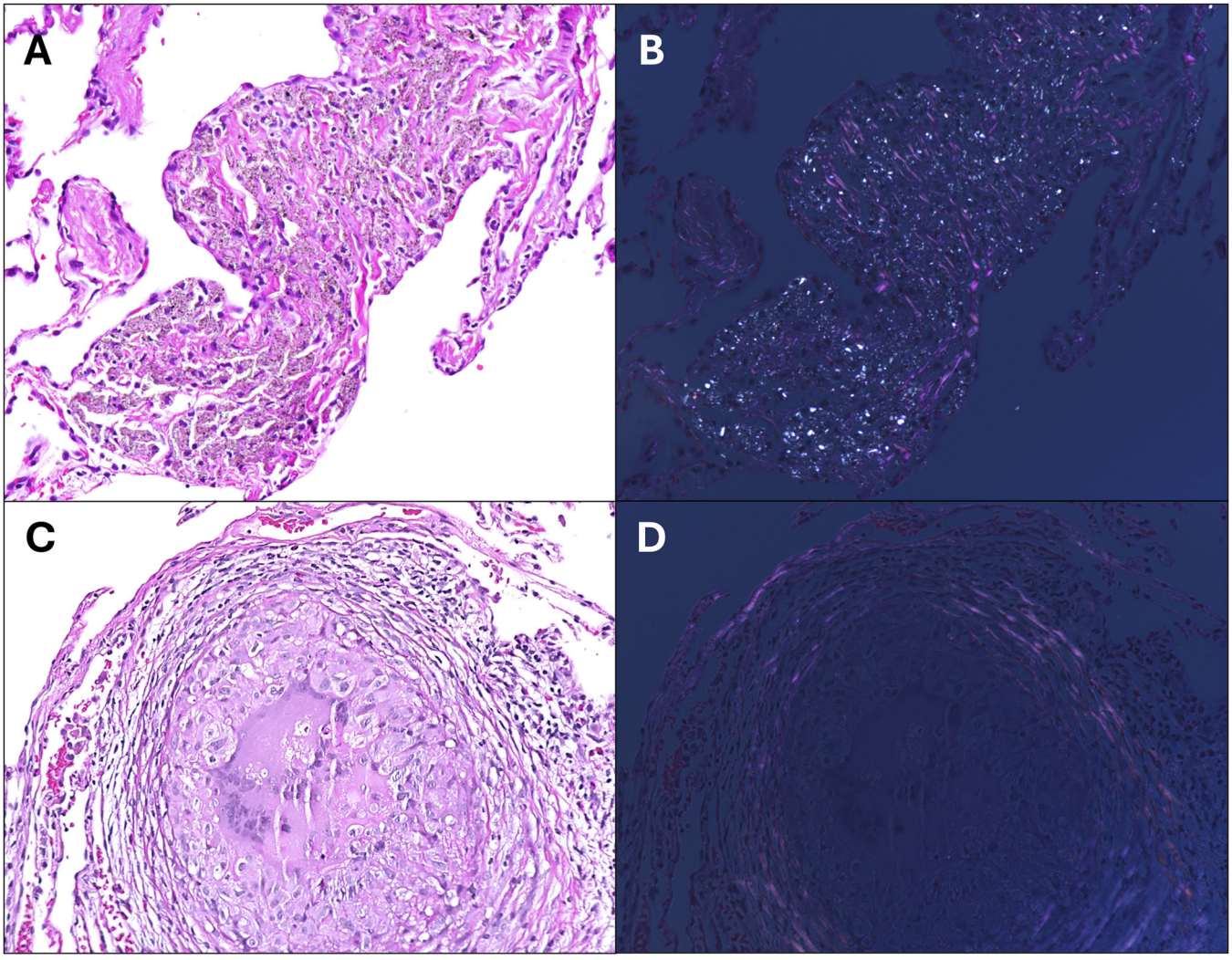

FIGURE 5 | Hematoxylin and eosin (H&E)-stained lobectomy tissue from a stone fabricator with 17 years of employment and 13 pack-years of smoking (Case #3), showing extensive non-necrotizing granulomas and silica nodules/macules. Representative high-power H&E images show (A) a silica dust macule with anthracotic pigment and a few strands of collagen and (C) a non-necrotizing granuloma with a multinucleated giant cell in the center, surrounded by epithelioid histiocytes, concentric collagen, and minimal chronic inflammation. The same features are shown under polarized light microscopy and highlight (B) the heavy burden of weakly (dull-white) and strongly (bright-white) birefringent dust, indicating retained silica/silicate particles within the nodule along with collagen fibers (linear violet bands), and (D) absence of birefringent dust within the granuloma.

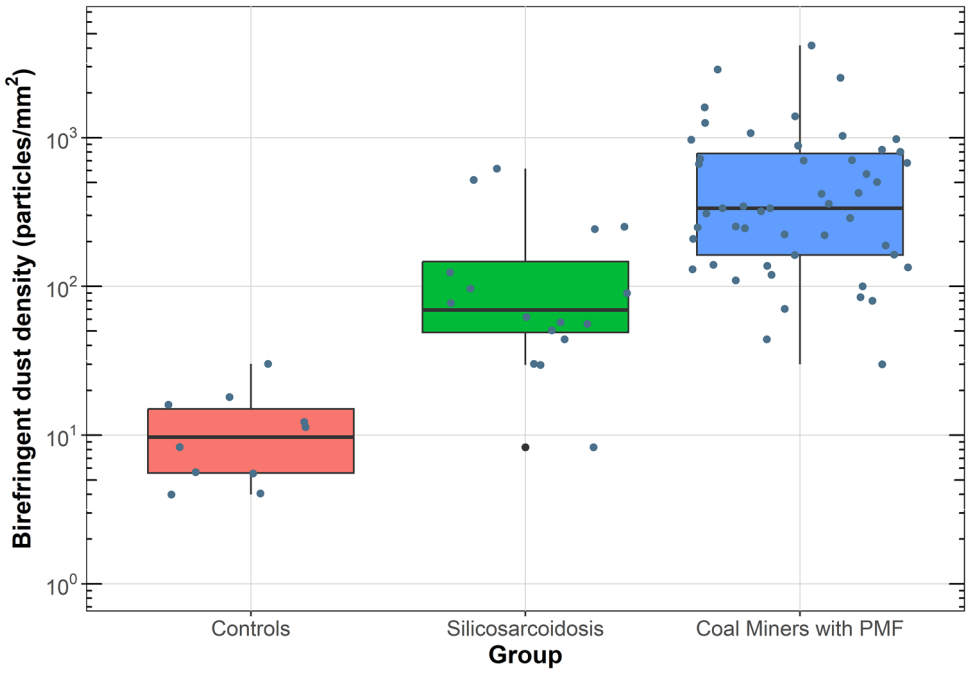

FIGURE 6 | In situ birefringent dust density (particles/mm^2) measured using quantitative polarized light microscopy (QM-PM), comparing lung tissue samples from healthy controls ($n = 10$), workers with silicosarcoidosis ($n = 18$), and coal miners with silica-related progressive massive fibrosis (PMF) ($n = 50$). There was a significant difference among means for all three groups following log transformation ($p < 0.0001$; $p < 0.001$ for all pairs).

Labour Office Conferences on Silicosis, during which a consensus definition of silicosis was crafted. The historical background of these conferences is detailed in a 2015 article in the *American Journal of Industrial Medicine* by Vincent et al. [23, 24]. At the 1929 Conference in Lyon, France, attendees discussed the possibility that two early stages of silicosis included bronchiolitis and dust-laden phagocytes in lymphoid tissue, likened to "a pseudo-tuberculosis granuloma (i.e., to say a granulomatosis reaction with epithelioid and giganto-cellular reaction)." At the follow-up 1930 conference in Johannesburg, South Africa, the final definition of silicosis was limited to requiring silicotic nodules and excluded pulmonary alveolar proteinosis and sarcoidosis, which "did not constitute the disease silicosis." Vincent and co-authors hypothesize that, perhaps for economic reasons, delay in the identification of and search for links with exposure to silica provided grounds for labeling sarcoidosis as idiopathic.

A number of epidemiologic and clinical studies over the past century have since bolstered the causal link between exposure to RCS and the development of granulomatous inflammation. A large retrospective cohort analysis in Sweden found that workers with medium-to-high RCS exposure had greater sarcoidosis incidence (RR 1.83, 95% CI [1.14, 2.95]) [25]. A later Swedish case–control analysis further underscored these findings [26]. An Icelandic study found increased odds of sarcoidosis among diatomaceous earth workers exposed to crystalline and amorphous silica and silicates [27]. A case–control study of 237 sarcoidosis patients from three countries compared to 474 age- and sex-matched controls found increased odds of sarcoidosis (OR 1.07, 95% CI [1.01, 1.14]) with stone dust exposure [28]. Using a quantitative job exposure matrix, a recent Danish study found significant dose-dependent increases in incidence rate (1.06, 95% CI [1.04-1.07]) for sarcoidosis per 50 μg/m^3-years of occupational RCS exposure [29]. Oliver et al. described 12 cases of sarcoidosis in Ontario hard-rock miners [30]. A recent California-based case series of engineered stone workers with silicosis described granulomas in 14/34 (41%) of those who underwent tissue biopsy [31].

Approximately 2 million U.S. workers are exposed annually to RCS [32]. In recent decades, an epidemic of short latency, severe, progressive silicosis has been described in multiple countries related to the fabrication of engineered stone [31, 33–41]. Similarly, recent studies of contemporary U.S. coal miners implicate silica exposure in the unexpected surge of severe PMF [12, 13, 42]. Our large silicosarcoidosis case series includes workers in stone fabrication, masonry, mining, construction, cement work, and sandblasting. This suggests that the large population of workers in these industries is at risk for granulomatous inflammation as a complication of increasing RCS exposure. However, the specific host susceptibility and exposure-related risk factors leading to silicosarcoidosis remain to be elucidated.

In addition to shared histologic features and epidemiologic associations, the pathogenic mechanisms of silicosis and sarcoidosis overlap. RCS exposure increases expression of TNF-α, IL-1β, and TGF-β, known mediators of granuloma formation in sarcoidosis [43–45]. Rats consistently developed granulomatous lung inflammation 27 weeks after RCS inhalation [46]. Both diseases typically have lymphocyte-mediated lung inflammation [7, 47] and often have clinical features of autoimmunity. For example, over 20% of engineered stone workers in recent studies had RCS-associated autoimmunity [31, 38, 40, 48]. Further research on mechanisms of silicosarcoidosis may

provide insight into the complex interplay between occupational/environmental exposures and risks for autoimmune diseases, but previous work has established biological plausibility [47].

4.3 | Implications of a Silicosarcoidosis Diagnosis

A nonsystematic search of the literature reveals many case reports of silicosarcoidosis using a range of terminology. These include descriptive but lengthy indicators such as "silica-induced sarcoidosis," "silica-associated sarcoidosis," "silica-induced granulomatous inflammation," "sarcoid-like granulomatosis induced by silica," "sarcoid-like granulomatous lung disease," and "sarcoid-like reaction due to exposure to dust other than beryllium," while others remain agnostic to a causal link by simply reporting the "coincidence" or "coexistence" of silicosis and sarcoidosis [25, 49–72]. Though these reflect the same or similar overlap conditions as cases in our study, confusion in terminology for the last century underscores the urgent need for clear nosology. Our study adds to the growing evidence for a causal link between silicosis and sarcoidosis and provides a comprehensive histopathologic description of silicosarcoidosis.

For these reasons, we propose using the term silicosarcoidosis to unify future efforts to further characterize this distinct entity, explore gene–environment interactions, develop clear research agendas and clinical guidelines, and motivate management considerations that include both pharmacological and exposure reduction efforts. Compared to other previously published terms, silicosarcoidosis benefits from brevity, clarity, and searchability. Agreement on terminology provides a critical starting point to facilitate future scientific investigation of this unique and understudied population.

This approach draws from parallel discussions in Asthma-COPD Overlap (ACO). The literature on ACO reflects that a distinct asthma and COPD overlap condition had existed since the 1960s and for decades was referred to as the "Dutch Hypothesis." [73] The Dutch Hypothesis was a singular term used to describe this condition before ACO gained traction in the 2010s, but the Dutch Hypothesis term had no specific link to disease descriptors. When the more descriptive term ACO entered the lexicon, the field took a major step forward. Previously, individuals with ACO often were excluded from clinical trials/studies of asthma or COPD alone. Creating a diagnostically accurate term that was simple to articulate and remember provided the foundation for studying this unique population and subsequently enabled a multinational group to develop consensus definitions using major and minor diagnostic criteria [74, 75]. Nearly a decade of scientific investigation utilizing the ACO terminology and definitions has since revealed that "the balance of evidence now favors the view that asthma and COPD are distinct diseases that have differing genetic predispositions but may coexist in an individual" [76]. As the ACO example illustrates, the term silicosarcoidosis, even if loosely or imperfectly defined at this time, creates the long overdue foundation needed to develop more detailed consensus case definitions, improve patient care, and expand research into pathogenic mechanisms and treatment. As further evidence grows for other exposures linked to sarcoidosis, a similar approach may be beneficial for characterizing their associations.

Silicosarcoidosis cases are likely underdiagnosed. Most dust-exposed patients with a compatible work history and typical chest imaging findings do not require tissue biopsy for diagnosis of pneumoconiosis. In our cases of silicosarcoidosis, chest CT imaging showed lymphadenopathy and small or large opacities in over 90%. Since the chest imaging findings in sarcoidosis and silicosis are nearly indistinguishable, the proportion of patients diagnosed with silicosis who have concomitant granulomatous inflammation is unknown. Our study raises but cannot answer the question of when to obtain biopsy confirmation in patients in whom silicosis and sarcoidosis may both be present.

Other manifestations can occur as a consequence of RCS exposure, including chronic obstructive pulmonary disease, lung cancer, inflammatory kidney disease, and mycobacterial lung infection [32]. Sarcoidosis most commonly involves the lungs, but most other organ systems can be affected as well, including cardiac, ocular, kidney, and neurologic involvement. While we did not have complete clinical information on all our silicosarcoidosis cases, several had kidney and other organ system involvement. Evaluation for extra-pulmonary disease manifestations of silicosarcoidosis that may require treatment should be part of standard clinical care [11, 77].

Several exposure-related granulomatous diseases share features of silicosarcoidosis, including hypersensitivity pneumonitis (HP), hot tub lung due to nontuberculous mycobacterial aerosols, and CBD [25, 78]. CBD is clinically indistinguishable from sarcoidosis, but a compatible occupational history coupled with positive beryllium lymphocyte proliferation testing confirms CBD [79]. Workers with a genetic marker of susceptibility (HLA-DPB1Glu69 positive) are at greatest risk for CBD, and a similar gene–environment interaction might also inform risk for the silicosarcoidosis variant. In all cases of granulomatous lung disease, a detailed exposure history is essential, particularly where exposure mitigation and benefits counseling are needed.

Little is known about how a diagnosis of silicosarcoidosis informs pharmacologic treatment, but unlike asthma and COPD occurring in the same individual, the typical management approaches for silicosis and sarcoidosis are quite different. The use of the term silicosarcoidosis will help assure that clinicians carefully consider appropriate pharmacotherapy for granulomatous inflammation as well as efforts to minimize ongoing silica exposure, regardless of whether silicosarcoidosis represents coexistent silicosis and sarcoidosis versus sarcoidosis triggered by silica exposure. In the few published case reports, response to immunosuppression has been variable [34, 52, 53, 58, 62]. International collaborations to enable well-designed clinical trials in workers with silicosarcoidosis will be important in establishing evidence-based treatment. Future studies may reveal distinct clusters of clinical and longitudinal silicosarcoidosis phenotypes that might benefit most from targeted treatment regimens, akin to other conditions with multiple endotypes. In the meantime, we follow recommended pharmacologic guidelines for treating sarcoidosis [80], with careful clinical follow-up to assess response to treatment.

4.4 | Strengths and Limitations of the Study

Our study has several strengths. First, the study cohort includes workers from multiple countries representing many different racial and ethnic groups, with employment in a broad range of RCS-exposed industries. Second, we had comprehensive exposure histories and relevant tissue samples for most workers. For those without available tissue, other clinical features were consistent with silicosarcoidosis. Third, we implemented a detailed and standardized pathology scoring form that, for the first time, describes the spectrum of histologic features that characterize silicosarcoidosis. Finally, we utilized a novel microscopy technique to quantify the density of in situ silica/silicates in available lung tissue specimens and compared the burden to other control groups.

This study also has a number of limitations. First, cases of silicosarcoidosis occurred mostly in men. This likely reflects the predominance of males in high-risk industries such as coal mining, stone cutting/masonry, and construction [81]. Second, we obtained convenience samples from several institutions and were unable to assess disease prevalence. Third, we did not compare histologic findings in cases of silicosarcoidosis with cases of silicosis or sarcoidosis alone, instead relying on conventional histologic definitions of each entity. Given these limitations, future research is needed to further characterize the clinical features of silicosarcoidosis that will lay the groundwork for a consensus case definition, including frequency of extra-pulmonary involvement and rates of disease progression [82, 83], response to pharmacologic treatment combined with removal from silica exposure, lung tissue mineralogy, and potential gene–environment interactions.

5 | Conclusion

We found a range of histologic abnormalities in a multinational case series of workers with silicosarcoidosis that overlap with features of both silicosis and sarcoidosis. Small tissue biopsy modalities may be insensitive for diagnosing silicosarcoidosis and highlight the importance of taking a detailed occupational history with a diagnosis of sarcoidosis. The use of the term silicosarcoidosis should enhance recognition of this important form of sarcoidosis and, crucially, will guide clinical management that addresses workplace exposure prevention in combination with appropriate pharmacologic treatment.

Author Contributions

Jeremy T. Hua, Carlyne D. Cool, Lauren M. Zell-Baran, and Cecile S. Rose conceptualized the study. Jeremy T. Hua, Carlyne D. Cool, Einat Fireman Klein, Yochai Adir, Lukas J. Lee, Robert A. Cohen, Richard C. Kraus, E. Brigitte Gottschall, Silpa D. Krefft, Charles Van Hook, and Cecile S. Rose performed data acquisition or interpretation. Carlyne D. Cool independently reviewed and scored histopathology. Lauren M. Zell-Baran and Jeremy T. Hua performed data analyses. Jeremy T. Hua drafted the initial manuscript with critical input from Cecile S. Rose. All authors critically reviewed and approved the final manuscript.

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Disclosure

Parts of this manuscript were presented at the 66th Annual Thomas L. Petty Aspen Lung Conference, June 4–7, 2024, Aspen, CO.

Ethics Statement

The collection of de-identified data into a Research Electronic Data Capture (REDCap) database was approved by the IRB (BRANY #HS-3483).

Conflicts of Interest

J.T.H. and S.D.K. report medicolegal consulting in occupational lung diseases. All other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. John Meyer declares that he has no conflicts of interest in the review and publication decision regarding this article.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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