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RESEARCH ARTICLE

Severe lung disease characterized by lymphocytic bronchiolitis, alveolar ductitis, and emphysema (BADE) in industrial machine-manufacturing workers

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Abstract

Background: A cluster of severe lung disease occurred at a manufacturing facility making industrial machines. We aimed to describe disease features and workplace exposures.

Methods: Clinical, functional, radiologic, and histopathologic features were characterized. Airborne concentrations of thoracic aerosol, metalworking fluid, endotoxin, metals, and volatile organic compounds were measured. Facility airflow was assessed using tracer gas. Process fluids were examined using culture, polymerase chain reaction, and 16S ribosomal RNA sequencing.

Results: Five previously healthy male never-smokers, ages 27 to 50, developed chest symptoms from 1995 to 2012 while working in the facility's production areas. Patients had an insidious onset of cough, wheeze, and exertional dyspnea; airflow obstruction (mean FEV_1 = 44% predicted) and reduced diffusing capacity (mean = 53% predicted); and radiologic centrilobular emphysema. Lung tissue demonstrated a unique pattern of bronchiolitis and alveolar ductitis with B-cell follicles lacking germinal centers, and significant emphysema for never-smokers. All had chronic dyspnea, three had a progressive functional decline, and one underwent lung transplantation. Patients reported no unusual nonoccupational exposures. No cases were identified among nonproduction workers or in the community. Endotoxin concentrations were elevated in two air samples; otherwise, exposures were below occupational limits. Air flowed from areas where machining occurred to other production areas. Metalworking fluid primarily grew *Pseudomonas pseudoalcaligenes*

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and lacked mycobacterial DNA, but 16S analysis revealed more complex bacterial communities.

Conclusion: This cluster indicates a previously unrecognized occupational lung disease of yet uncertain etiology that should be considered in manufacturing workers (particularly never-smokers) with airflow obstruction and centrilobular emphysema. Investigation of additional cases in other settings could clarify the cause and guide prevention.

KEYWORDS
bronchiolitis, emphysema, occupational lung disease

1 | INTRODUCTION

In 2012, the National Institute for Occupational Safety and Health (NIOSH) received a request from employees at a manufacturing facility to evaluate potential respiratory hazards and lung disease. During the evaluation, we identified five relatively young never-smokers with severe lung disease. Disease onset was insidious and sporadic, occurring without a clear precipitating event and over the course of nearly two decades. Symptoms, though worse at work, did not fully resolve away from the workplace.

Four patients sought care before our evaluation began in 2012 and were given a variety of seemingly unrelated diagnoses: bronchiectasis, lymphocytic bronchiolitis, extranodal marginal zone lymphoma, and nonspecific interstitial pneumonia (NSIP). The fifth patient sought care after undergoing serial spirometry that we offered the current workforce as part of our evaluation.

The facility employed approximately 400 people to make large machines used by industrial customers. In the machine shop, metals (steel, aluminum, and cast iron), and, rarely, plastics were cut using saws, pressurized water, and plasma technology. Cut materials were machined using water-based metalworking fluids, which are sprayed for cooling and lubrication and routinely develop microbial colonization.[1] The resulting pieces were further processed in two welding rooms and two paint booths. In the assembly area, the machines were assembled from component parts and operated to assure quality in handling paper products. The facility also had an administrative area where nonproduction personnel worked. Thus, the potential inhalational exposures in the workplace were varied and included metal and plastic dust, metalworking fluid and associated bioaerosols, welding fumes, solvents, paper dust, and typical office-equipment emissions.

The facility was one of the largest employers in a small rural community. We recognized that in addition to their work, the patients might have had other individual or shared risk factors for lung disease, including familial, avocational, or environmental. In response to the cluster, we conducted a multidisciplinary investigation to determine whether the patients had clinical features consistent with a common disease etiology and whether exposures were present in the workplace with the potential to cause their lung disease as a toxic effect.

2 | METHODS

2.1 | Patient reviews

Clinical data from five patients who developed severe lung disease were reviewed, abstracted, and supplemented by patient interviews. Radiologic reviews were conducted by a chest radiologist (R.J.T.) and reported according to the Fleischner Society.[2] Histopathologic reviews were conducted independently by five chest pathologists (J.L.A., T.V.C., A.D.F., F.H.Y.G., and S.S.), followed by group discussion. In addition, lung tissue from four patients was analyzed by two chest pathologists (J.L.A. and S.S.) for inorganic particles including metals using in situ scanning electron microscopy with energy-dispersive X-ray spectroscopy (SEM/EDS).[3]

2.2 | Workplace environmental evaluation

In 2013, we collected 104 personal air samples and 40 area air samples for thoracic aerosol (particles with median aerodynamic diameter ≤10 μm) and metalworking fluid, analyzed by NIOSH Method 5524,[4] and endotoxin, analyzed by *Limulus* amoebocyte lysate assay.[5] We collected 40 area air samples for elemental analysis by NIOSH Method 7303.[4] We used evacuated canisters to collect 44 area air samples for volatile organic compounds (VOCs), analyzed by gas chromatography-mass spectrometry.[6] In 2016, we collected 90 area air samples for thoracic aerosol, metalworking fluid, and endotoxin, and analyzed as above.

To assess the potential for migration of aerosols generated in the machine shop, we conducted tracer gas testing. We released sulfur hexafluoride in the machine shop and monitored its concentration in other areas of the facility using B&K Model 1302 Photoacoustic Multigas monitors (Brüel & Kjær Sound & Vibration Measurement A/S, Nærum, Denmark) and MIRAN SapphIRe Portable Ambient Analyzers (Thermo Fisher Scientific Inc, Waltham, MA).

Bulk process fluid samples were collected in 2012 (n = 10), 2013 (n = 34), and 2016 (n = 33) for bacterial and fungal culture, endotoxin analysis, and 16S ribosomal RNA (rRNA) gene sequencing. Samples collected in 2012 also underwent polymerase chain reaction (PCR) analysis to detect mycobacterial DNA.[7] DNA extraction was

performed using QIAamp DNA Mini Kit (Qiagen, Dusseldorf, Germany) following manufacturer's instructions. All extracted DNA underwent 16S rRNA gene amplification, purification, and pyrosequencing using the MiSeq platform (Illumina, San Diego, CA). The sequences were analyzed using the Quantitative Insights into Microbial Ecology pipeline for analysis of community sequence data.[8]

2.3 | Human subjects protection

The investigation was conducted according to NIOSH Institutional Review Board requirements for Health Hazard Evaluations. Personal, potentially identifiable details are provided only for those who gave informed consent for publication of this information.

3 | RESULTS

3.1 | Index patient

A 19-year-old man began working at the facility as a machinist in 1979. He was a never-smoker and had no history of respiratory problems. In 1995, he sought care for sinus congestion, cough with sputum production, and wheezing for several months. His oxygen saturation on room air was 95%. He was treated with intranasal steroids for presumed allergic rhinitis. In 2004, he presented with persistent sinus congestion, cough, wheeze, and progressively worsening dyspnea on exertion during the prior 2 years. His oxygen saturation on room air was 91%. Pulmonary function testing documented severe obstruction, air trapping, and reduced diffusing capacity. High-resolution chest computed tomography (HRCT) demonstrated centrilobular emphysema. Transbronchial lung biopsy indicated peribronchial inflammation with predominantly lymphocytes and plasma cells, fibrosis of the bronchial wall and peribronchial tissues, and focal areas of metaplasia. Additional tests, including sweat chloride, total serum immunoglobulin (Ig) G levels, human immunodeficiency virus (HIV)-1 and HIV-2 antibodies, skin prick for *Aspergillus fumigatus*, serum anti-*A. fumigatus* IgE and IgG, serum antinuclear antibody, serum c- and p-antineutrophil cytoplasmic antibodies, α-1 antitrypsin level, and bronchoalveolar lavage fluid culture, did not reveal abnormalities.

The patient was given a diagnosis of bronchiectasis and treated with a rotating schedule of antibiotics, without clinical improvement. In 2006, oxygen saturation on room air was 90%, and he began nocturnal oxygen therapy (2 liters per minute [LPM]). The following year, he transferred to the assembly area as an electrician. In 2011, he retired because of severe dyspnea that worsened at work but also was present with activities of daily living. A year later, his forced expiratory volume in 1 second (FEV_1) had fallen to 30% of predicted, and he required supplemental oxygen at 6 LPM during a 6-minute walk test. In 2014, he underwent bilateral lung transplantation. Histopathologic examination of explanted lung tissue demonstrated bronchiolar lymphocytic infiltrate, lymphoid follicles along alveolar ducts, emphysema, and ectasia of airways.

3.2 | Patient cluster

All five patients were never-smokers who worked in the facility's production areas (including machine shop and/or assembly area) for 1 to 16 years before symptom onset (Table 1). They had similar presentations notable for the insidious onset of post-hire chest symptoms from 1995 to 2012, obstruction or mixed obstruction/restrictive pattern on spirometry, decreased diffusing capacity, and centrilobular emphysema on HRCT (Figure 1).

TABLE 1 Clinical characteristics of five patients with severe lung disease who worked at a manufacturing facility

Characteristic	Range
Year of symptom onset	1995-2012
Age at symptom onset, y	27-50
Employment tenure at symptom onset, y	1-16 N or mean (range)
Department	
Administration	0
Production	5
Smoking status	
Never-smoker	5
Current smoker	0
Former smoker	0
Symptoms during disease course	
Sinus congestion	5
Cough	5
Wheeze	5
Dyspnea on exertion	5
Rash	1
One or more work-related chest symptom	4
Pulmonary function[a]	
Pre-BD FVC, % predicted	85 (63–102)
Pre-BD FEV_1, % predicted	44 (38–56)
Pre-BD FEV_1/FVC, %	43 (29–59)
BD response	2
TLC, % predicted	118 (100–132)
RV, % predicted	207 (144–259)
DLCO, % predicted	53 (32–77)
HRCT features	
Centrilobular emphysema	5
Bronchial wall thickening	2
Centrilobular nodules	0
Air trapping	2/2[b]
Ground glass opacities	0
Bronchiectasis	3
Outcome	
Chronic dyspnea on exertion	4
Lung transplantation	1

Abbreviations: BD, bronchodilator; DLCO, diffusing capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HRCT, high-resolution computed tomography; RV, residual volume; TLC, total lung capacity.

[a]Spirometry shown was conducted by the National Institute for Occupational Safety and Health (NIOSH) in 2013 (n = 4) or 2016 (n = 1). Other tests were conducted by the patients' healthcare providers from 2011 to 2018.

[b]Expiratory scan was available in only two patients.

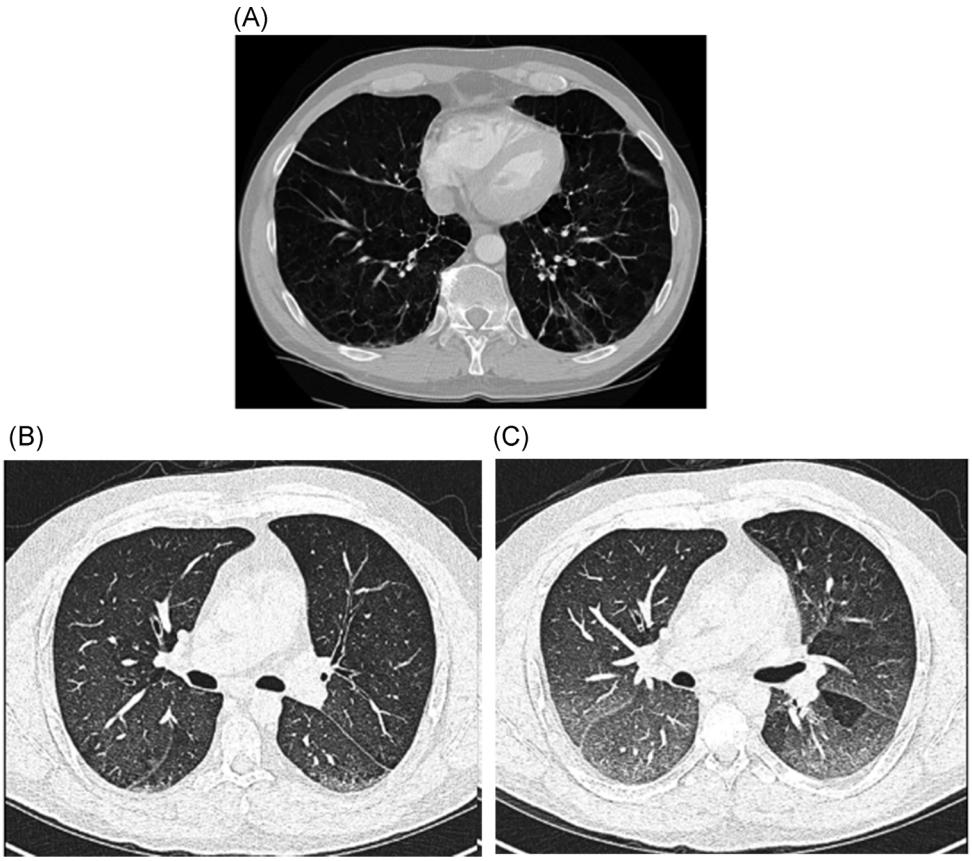

FIGURE 1 Representative high-resolution computed tomography images from five patients with severe lung disease among workers at a manufacturing facility. A, Inspiratory image showing centrilobular emphysema, an unusual finding in relatively young never-smokers. Inspiratory (B) and expiratory (C) images showing patchy preservation of lung attenuation (air trapping) on expiration, indicative of obstructive small airway disease.

Four patients reported a work-related pattern for at least one chest symptom; one reported his chest symptoms were the same at and away from work. One patient experienced an improvement in FEV_1 of 1.7 L over 4 months while he was treated with oral corticosteroids and relocated for 2 months to the administrative area; his FEV_1 subsequently fell 1.5 L over 15 months after he returned to the production area. In the other patients, therapeutic trial of relocation or time away from the facility was not pursued, and corticosteroids or other immunosuppressive therapy did not result in clinical improvement. One patient was initially diagnosed with extranodal marginal zone lymphoma and received three doses of rituximab without symptomatic or functional improvement. Subsequent evaluation for Ig heavy-chain gene rearrangement showed no evidence of a monoclonal population.

One year after lung transplantation, the index patient reported resolution of respiratory symptoms and no longer required supplemental oxygen therapy. The others reported chronic dyspnea that limited their activities, but none had begun oxygen therapy. One patient left employment because of concerns about his respiratory health, with subsequent stabilization of lung function. Of those who continued to work in the facility's production areas, two had further declines in lung function and one experienced stabilization.

Two patients were siblings; no other familial relationships among the patients were known. The five patients shared no prior or concurrent occupational exposures beyond the manufacturing facility. They lived in three different communities. Four reported occasional deer hunting and fishing. Two reported riding all-terrain vehicles, one of whom also engaged in auto racing and repair. One raised six beef cattle and kept a vegetable garden, and another maintained a half-acre plot of clover to attract deer; otherwise, the five did not participate in farming activities. Each denied water damage, mold, or mildew at home. Inquiries to local physicians, regional hospitals, and county and state health departments in the area did not reveal additional cases of lung disease with a similar clinical and pathological presentation.

3.3 | Histopathology

Transbronchial biopsies (n = 5) were abnormal, showing focal lymphoplasmacytic infiltrates and occasional lymphoid follicles lacking germinal centers. The biopsies were of insufficient size to confidently recognize a pattern and were considered nondiagnostic, although in retrospect they reflected the changes seen in subsequent larger specimens.

Review of explanted lung tissue (n = 1) and surgical lung biopsies (n = 4) revealed a similar constellation of changes in all five patients: bronchiolocentric lymphoplasmacytic infiltrates with $CD20^+$ B-cell primary lymphoid follicles without germinal centers involving both respiratory bronchioles and alveolar ducts (Figure 2). There were scattered $CD3^+$ T cells predominantly cuffing the B-cell follicles, with no appreciable interstitial or airway fibrosis, and absence of granulomas (except for a rare granuloma in the explant). Alveolar enlargement with septal wall fragmentation, indicative of mild to moderate histologic emphysema, was also noted for all

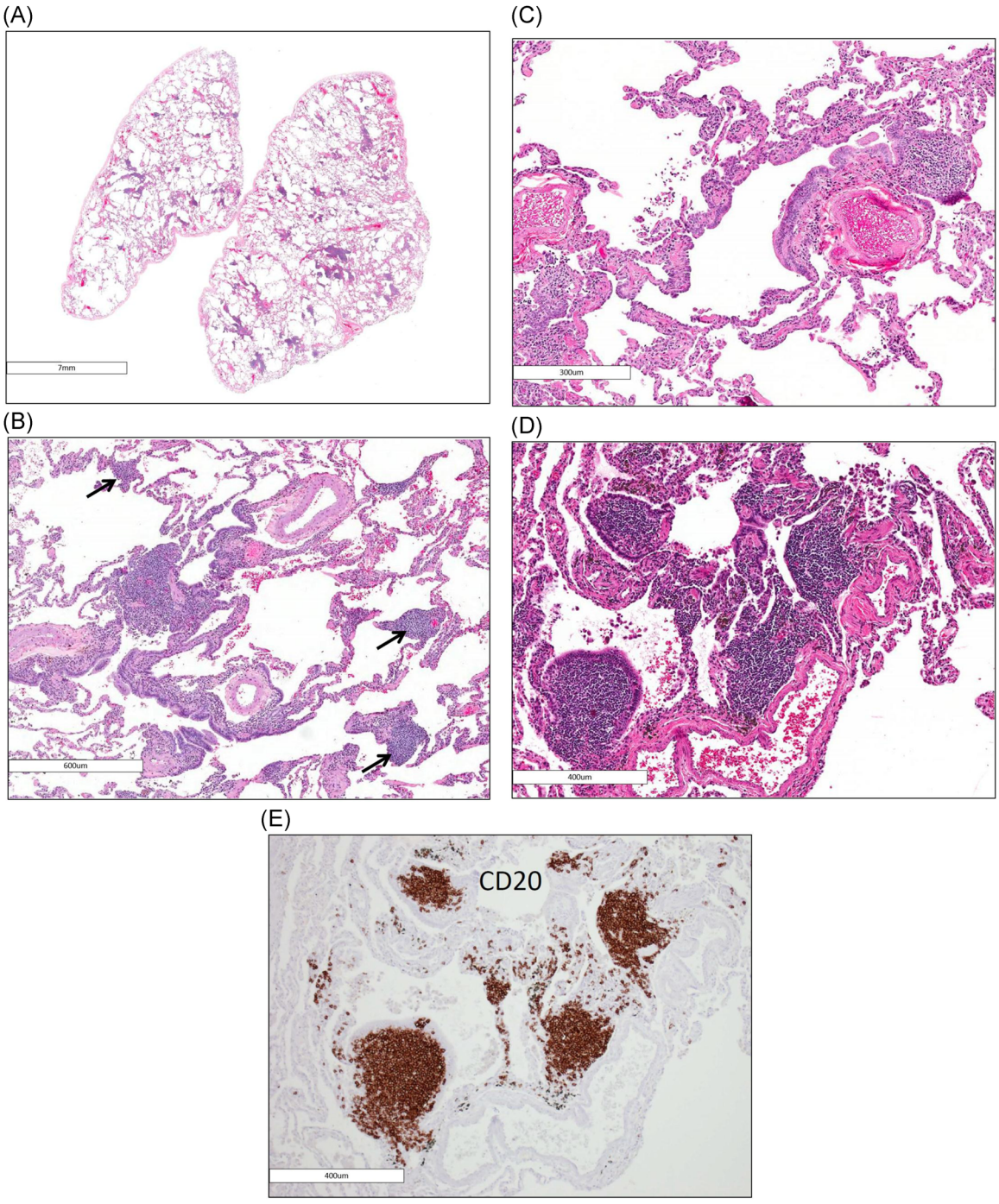

FIGURE 2 Representative hematoxylin and eosin stains of explanted lung tissue and surgical lung biopsies highlight the primary histological features of lymphoplasmacytic infiltrates with primary lymphoid follicles around the distal airways and notable involvement of respiratory bronchioles and alveolar ducts, in addition to diffuse emphysema. A, Low-power view, highlighting peribronchiolar lymphoid aggregates with widespread emphysema. B, Medium-power view, showing nonreactive lymphoid follicles with nodular extensions into the alveolar ducts (arrows); emphysema also appreciated. C, D, High-power views of nodular lymphoid aggregates around a respiratory bronchiole and chronic inflammatory infiltrates expanding the walls of the alveolar ducts. E, Immunohistochemical staining for CD20, a B-cell marker, demonstrating B cells make up the majority of the primary follicles. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Comparison of the histologic features of BADE and entities in the differential diagnosis

Histologic feature[a]	BADE	FB	HP	MZL	DPB	FWL	CB
Respiratory bronchiolar lymphocytic infiltrate	+++	+/−	+/−	++	+	++	−
Lymphoid follicles along alveolar ducts	+++	−	−	+/−	+++	−	−
Emphysema	+++	−	−	−	+/−	+/−	+/−
Primary lymphoid follicles	+++	+	+	+/−	++	+/−	+
Ectasia of airways (bronchiolectasis)	++	+/−	+/−	+	+	+/−	−
Secondary lymphoid follicles (germinal centers)	+	+++	+/−	+/−	+/−	−	+/−
Interstitial fibrosis	+/−	−	+/−	−	−	−	+/−
Nonnecrotizing granulomas	+/−	−	++	+/−	−	−	−
Lymphoplasmacytic inflammation and lymphoid follicles around membranous bronchioles	+/−	+++	+++	+/−	++	++	+/−
Organizing pneumonia	+/−	−	++	−	+/−	−	−
Interstitial foamy macrophages	+/−	−	−	−	+++	−	−
Peribronchiolar metaplasia	−	+	+	−	+/−	−	++
Bronchiolar fibrosis/lumen obliteration	−	+/−	+/−	−	+	−	+++
Luminal mucus stasis	−	+	+/−	−	+/−	−	++
Multinucleated giant cells	−	−	++	−	−	−	−

Abbreviations: BADE, bronchiolitis, alveolar ductitis, and emphysema; CB, constrictive bronchiolitis; DPB, diffuse panbronchiolitis; FB, follicular bronchiolitis; FWL, flock workers' lung; HP, hypersensitivity pneumonitis; MZL, marginal zone lymphoma.
[a]Grading is relative, as follows: − = negative; +/− = minimal; + = mild; ++ = moderate; +++ = severe.

patients. Scattered intraalveolar clusters of foamy macrophages and rare hemosiderin-laden macrophages were considered secondary findings. Focal pleuritis was present in one patient's specimen and, in the explant, there was a focus of organizing pneumonia, a rare granuloma, and mild bronchiolectasis. In three patients, qualitative SEM/EDS revealed only inorganic particles found in the general population (aluminum silicates, silica, titanium, and iron).[9] In one patient, particles of other metals consistent with a history of metalworking (aluminum, copper, molybdenum, and stainless steel) also were detected. Table 2 compares the findings in these patients (which we term Bronchiolitis, Alveolar Ductitis, and Emphysema, or "BADE") with features of lung diseases on the differential diagnosis.

3.4 | Workplace environmental evaluation

On personal air sampling, thoracic aerosol concentrations ranged from less than the limit of detection (<LOD) in nine (9%) samples to a maximum of 1.58 mg/m^3 (Table 3). Thoracic metalworking fluid concentrations ranged from less than LOD in 49 (47%) samples to a maximum of 0.32 mg/m^3, which did not exceed the NIOSH recommended exposure limit (REL) of 0.4 mg/m^3. Endotoxin concentrations ranged from less than LOD in three (3%) samples to a maximum of 116 EU/m^3. There is no NIOSH REL for airborne endotoxin; two samples exceeded the Dutch exposure limit of 90 EU/m^3.[10] All maximum values of thoracic aerosol, metalworking fluid, and endotoxin were measured on production workers.

Concentrations of these analytes on area air sampling were generally lower but highest in production areas. The maximum thoracic aerosol concentrations were 0.36 mg/m^3 in 2013 and 0.28 mg/m^3 in 2016. The maximum thoracic metalworking fluid concentrations were 0.13 mg/m^3 in 2013 and 0.08 mg/m^3 in 2016. The maximum endotoxin concentrations were 83 EU/m^3 in 2013 and 43 EU/m^3 in 2016.

On area air sampling, concentrations of metals (Table 3) and VOCs were low. Specifically, acetone (maximum concentration: 5023 parts per billion [ppb]), ethanol (111 ppb), isopropyl alcohol (68 ppb), toluene (1947 ppb), and m- and p-xylene (1155 ppb) were detected in almost all samples collected in production areas, orders of magnitude below NIOSH RELs (100-1000 ppm). Other VOCs were found in even lower concentrations or not detected.

Tracer gas released in the machine shop was later detected in the assembly area.

Since the early 1990s, the facility mainly used a nonpreserved (without antibacterial biocides) mineral oil-based metalworking fluid reportedly designed, through its constituents, to promote the growth of *Pseudomonas pseudoalcaligenes*.[11] This organism is thought to promote fluid stability by limiting growth of other organisms that digest the fluid.[12] A preserved (with antibacterial biocides) synthetic metalworking fluid was used to a lesser extent. Both metalworking fluids were diluted with municipal water before use. Cultures of municipal water and neat (undiluted) metalworking fluid did not yield bacteria or fungi. In-use nonpreserved metalworking fluid primarily grew *P. pseudoalcaligenes* at 10^3 to 10^9 CFU/mL in 2012 and 2013 and 10^5 to 10^7 CFU/mL in 2016. In-use preserved metalworking fluid grew *Curtobacterium* (10^2 CFU/mL) and *Alcaligenes* (10^6 CFU/mL) species in 2013 and no bacteria in 2016. In-use water (for pressurized cutting) grew several Gram-negative and -positive species (10^6 CFU/mL). For all in-use process fluids, lower concentrations of fungi (maximum 10^3 CFU/mL) were found. PCR for mycobacterial DNA was negative in all samples

TABLE 3 Airborne concentrations of thoracic aerosol, metalworking fluid, and endotoxin from personal samples and metals from area samples at a manufacturing facility with BADE among workers, 2013

Analyte	Number of samples	Number of samples <LOD	Concentration range	Occupational exposure limit[a]
Thoracic aerosol, mg/m^3				
Administration	8	5	<LOD-0.04	…
Production	96	4	<LOD-1.58	
Metalworking fluid, mg/m^3				
Administration	8	8	<LOD	0.4
Production	96	41	<LOD-0.32	
Endotoxin,[b] EU/m^3				
Administration	8	0	0.17-3.58	90 (DECOS)
Production	93	3	<LOD-116	
Metals,[c] µg/m^3				
Aluminum	14	9	<LOD-4.32	10 000
Antimony	5	4	<LOD-0.72	500
Arsenic	20	14	<LOD-1.30	2
Barium	22	12	<LOD-9.65	500
Beryllium	18	8	<LOD-0.01	0.2 (OSHA)
Calcium	36	22	<LOD-1.78	…
Chromium	15	13	<LOD-0.44	500
Cobalt	5	4	<LOD-0.12	50
Copper	34	10	<LOD-1.43	1000
Iron	38	3	<LOD-115	5000
Lanthanum	30	19	<LOD-0.02	…
Lead	11	10	<LOD-0.37	50
Magnesium	19	13	<LOD-0.77	…
Manganese	38	3	<LOD-11.52	1000
Nickel	6	4	<LOD-0.27	15
Phosphorus	17	15	<LOD-0.76	100
Strontium	7	5	<LOD-0.03	…
Thallium	4	3	<LOD-2.39	100
Titanium	32	18	<LOD-0.16	…
Zinc	6	4	<LOD-0.82	…
Zirconium	29	21	<LOD-0.15	5000

Abbreviations: BADE, bronchiolitis, alveolar ductitis, and emphysema; DECOS, Dutch Expert Committee on Occupational Standards; LOD, limit of detection; OSHA, Occupational Safety and Health Administration.

[a]National Institute for Occupational Safety and Health (NIOSH) recommended exposure limit (REL), unless otherwise noted.

[b]Three endotoxin samples were excluded from analyses due to technical issues in the field or laboratory.

[c]Sampling for metals occurred primarily in production areas (specifically, assembly and machine shop). For beryllium, chromium, iron, manganese, and nickel, four of the samples were collected in administration. Concentrations of the following additional metals were below limits of detection in all samples: bismuth, boron, cadmium, gallium, gold, indium, molybdenum, neodymium, palladium, platinum, potassium, selenium, tellurium, tin, vanadium, and yttrium.

tested. The 16S rRNA results demonstrated more diverse bacterial communities than indicated by culture (Figure 3).

4 | DISCUSSION

We report a cluster of cases in which five relatively young men, all never-smokers, had airflow obstruction, impaired gas exchange, and radiologically evident centrilobular emphysema. The histologic features of lymphocytic BADE, although individually nonspecific, formed a unique pattern unlike that of any well-recognized disease entities (Table 2). The findings were not typical of follicular bronchiolitis in connective tissue disease, which has a greater profusion and coalescence of lymphoid follicles with distinct germinal centers (ie, secondary follicles), most prominent along membranous bronchioles. The findings differed from those of hypersensitivity pneumonitis because of general lack of granulomas, presence of B-cell primary follicles, and absence of a more uniform and diffuse alveolar T-cell infiltrate. Features of constrictive bronchiolitis were notably absent in the membranous bronchioles. Furthermore, all of the patients had significant radiologic and histologic evidence of emphysema, which can occur in hypersensitivity pneumonitis,[13] but is not a typical feature of the conditions considered in the differential diagnosis. Additionally, HRCT did not demonstrate radiologic features (such as ground glass or centrilobular nodules) often found in the other conditions.

The identification of a cluster of five patients with a previously unreported and unique disease phenotype in one workplace points to an occupational etiology for BADE. Multiple findings support this assessment. There was a spatial relationship to the site of

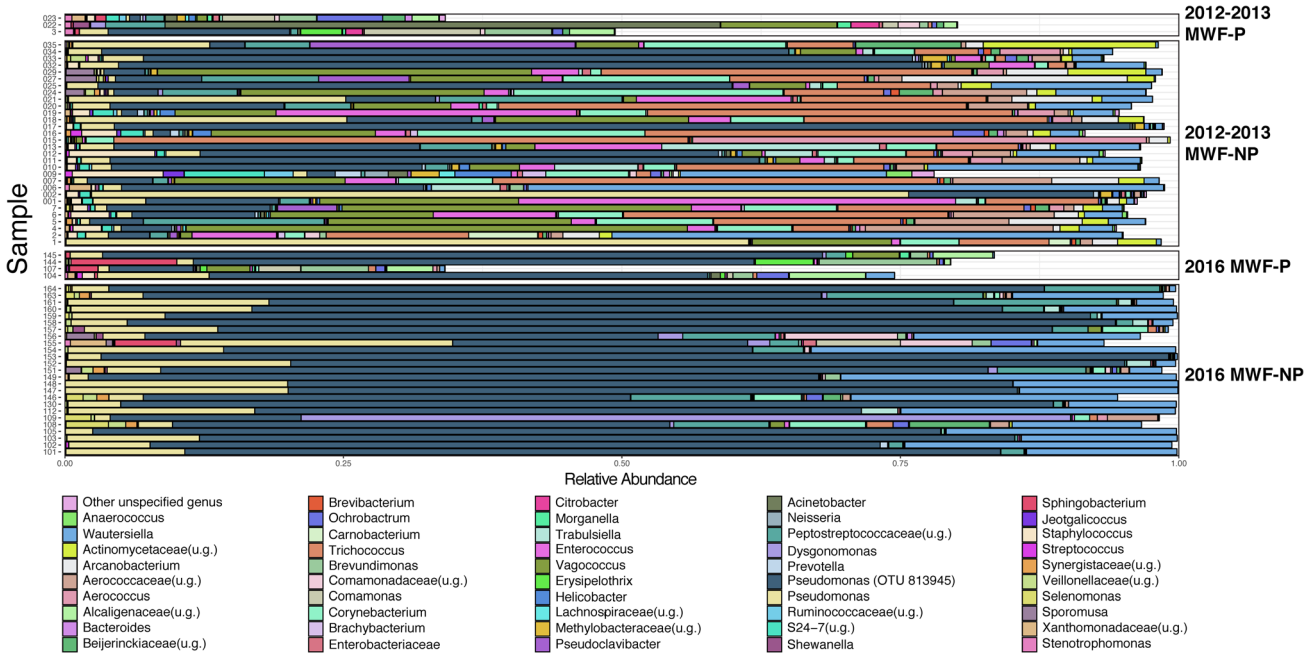

FIGURE 3 Evaluation of the metalworking fluid bacterial microbiome. The histogram represents 16S rRNA taxonomic assignment for each sample. For graphical purposes, data were limited to the 50 most abundant genera, where each color represents relative abundance for each taxon at a genus level. Samples collected in 2013 were more diverse than samples collected in 2016, but each indicated greater diversity than did the corresponding culture. MWF-NP, nonpreserved metalworking fluid; MWF-P, preserved metalworking fluid; rRNA, ribosomal RNA; OTU, operational taxonomic unit; u.g., unspecified genus [Color figure can be viewed at wileyonlinelibrary.com]

employment, as all five patients worked specifically in the facility's production areas. As has been discussed in the literature in relation to cancer, clusters of extremely rare diseases occurring in well-defined occupational settings can be informative about new causes of disease.[14] In addition, there was a temporal relationship to employment, as these men were healthy at hire and experienced insidious onset of respiratory symptoms during employment. Four described a pattern of work-related exacerbation of their symptoms, although they remained symptomatic away from the workplace. One patient had substantial functional improvement during several months away from the production areas, followed by a loss of lung function on return.

We did not find evidence for a nonoccupational etiology. Extensive clinical evaluations of the patients did not identify other explanations for lung disease. Although two were siblings, the other three patients were not related, making a familial disorder less likely. The patients had not worked together elsewhere, nor did they all live in the same community. They had no evident shared inhalational exposures from hobbies or other activities outside of work. Additionally, no other cases outside of the workplace with similar clinical and pathological features were identified by clinicians and public health officials serving the area.

Our evaluation of the workplace environment addressed a variety of potential causative exposures. Given the case clustering in production areas, we focused on exposures related to production processes. We considered exposures to metals, which have been associated with granulomatous, fibrotic, and emphysematous lung diseases in other occupational settings.[15-20] Airborne concentrations of metals were quite low; none approached existing occupational exposure limits. Combined with the limited evidence of metals in lung tissue, these low exposures make metal-related lung disease less likely. Similarly, we examined exposures to VOCs, as some VOCs pose a risk of occupational bronchiolitis,[21-23] and found them to be quite low.

We also evaluated exposures related to the machine shop's use of metalworking fluids, which have been associated with lung diseases including asthma and hypersensitivity pneumonitis in other workplaces.[1,24] While the responsible component remains uncertain, evidence in the literature points to bioaerosols generated when metalworking fluids with microbial colonization are sprayed.[25-30] In our study, air concentrations of metalworking fluid and endotoxin, a cell-wall component of Gram-negative bacteria, were relatively low. However, some metalworking fluid concentrations approached the NIOSH REL, and some endotoxin concentrations exceeded the Dutch exposure limit, indicating the potential for exposures sufficient to impact respiratory health.[10,31] The concentrations were highest in the machine shop, but exposures also occurred in the assembly area, where some of the patients worked. This observation could be explained by the facility's airflow patterns, which provided opportunities for migration of aerosols from the machine shop to other production areas, as demonstrated by the tracer gas test.

A notable aspect of BADE is prominent lymphocytic inflammation of distal bronchioles and alveolar ducts. Bronchus-associated lymphoid tissue (BALT) is not normally present in adult lungs but can be induced by persistent exposure of the lung to antigens and pathogen-associated molecular patterns (PAMPs), as occurs in inflammation or

infection.[32,33] BALT may subsequently have a pathological role, such as contributing to chronic lung inflammation.[33] We found that metalworking fluid and other in-use process fluids were heavily colonized with bacteria. The dominant organism on culture of the primary metalworking fluid was *P. pseudoalcaligenes*, raising the possibility of a pathogenic role in BADE for this organism. However, we found greater bacterial diversity using nonculture methods, suggesting other microbes could play a role. Clearly, additional studies are needed to determine whether there is a role for inhalation of antigenic materials and PAMPs related to metalworking fluid (such as fluid components, colonizing bacteria, bacterial products, or fluid components modified by bacteria) in the pathogenesis of BADE. In addition, it will be important to evaluate the potential pathogenic roles of other aerosols generated in production areas and what role, if any, individual susceptibility plays in BADE's pathogenesis.

Our investigation has several limitations. We characterized exposures in 2012, 2013, and 2016, years after symptom onset in four patients (1995-2007). The company had installed mist collectors on some machines in the intervening years, so exposures likely decreased over time. Nonetheless, during our investigation, two patients who continued working in production areas experienced symptom exacerbation and lung function decline and one incident case occurred, suggesting clinically consequential exposures persisted. Additionally, it is possible we did not identify or measure a contributory occupational exposure, such as one present only intermittently. Finally, we did not evaluate patients' personal environments but relied on self-report, so it is possible we missed a shared domestic or avocational exposure. However, the patients' residence in three different communities, their lack of a common leisure activity that posed a recognized inhalational hazard, and the absence of evidence for additional cases outside of the facility make this possibility remote.

Given the uncertainty about the cause of this novel occupational lung disease, we recommended that the facility take several precautionary measures to protect workers. These included: (a) engineering controls to minimize air movement from the machine shop and reduce inhalational exposures to the lowest levels feasible; (b) administrative controls to limit the number of workers in production areas and in proximity to processes generating inhalational exposures; (c) respirators for production area workers who wished to further reduce their aerosol exposures; and (d) a medical monitoring program to include periodic spirometry and referral of those with concerning respiratory symptoms or new spirometric abnormalities. Serial spirometry with attention to excessive declines could provide early detection of developing functional deficits.[34]

The industrial processes in this facility are not unusual. For instance, the use of metalworking fluids is common, with 1.2 million US workers[35] and many others globally potentially exposed. Therefore, a natural question is why BADE has not been reported earlier. One possibility is that the precise exposure and disease are unique to this facility. Alternatively, it is possible that the disease occurred in other workplaces in the past, but its work-relatedness went unrecognized. The cases we report initially were considered to be idiopathic and given a variety of diagnoses. The size of the cluster, though still modest, ultimately invited scrutiny. A single patient or a smaller cluster in another workplace might escape notice. Another possibility is that past cases of BADE were recognized as occupational but given different diagnoses, such as metalworking fluid-related hypersensitivity pneumonitis, which is often diagnosed without biopsy (76 of 98 cases in one series).[24] In those with biopsy, a spectrum of histopathologic findings has been documented. In one investigation, just one of 11 biopsied workers had granulomas consistent with hypersensitivity pneumonitis; other findings included NSIP, the original diagnosis in one patient with BADE.[25] In another investigation, two of 20 biopsied workers had bronchiolitis, and one also had emphysema,[36] intriguing given our findings. Moving forward, physicians caring for similar manufacturing workers with respiratory symptoms, airflow obstruction, and centrilobular emphysema should include BADE in the differential diagnosis, consider the potential value of serial spirometry for the larger workforce, and alert public health authorities to disease occurrence in other workplaces. Multidisciplinary investigation of additional cases or clusters could help to illuminate the cause and guide preventive strategies.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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John Meyer declares that he has no conflict of interest in the review and publication decision regarding this article.

AUTHOR CONTRIBUTIONS

KJC, MLS, JLA, and LNS contributed to conception and design, data acquisition, data analysis, data interpretation, and drafting the manuscript; RJN, TVC, ADF, FHYG, SS, and RJT contributed to data analysis, data interpretation, and drafting the manuscript; DW, VDB, and RJB contributed to conception and design, and data acquisition; JHP, BJG, and RFL contributed to data acquisition, data analysis, and data interpretation; JMC-G, MAV, and JAC contributed to data interpretation; KK and MJB contributed to conception and design, and data interpretation; and DNW contributed to data interpretation and drafting the manuscript. All authors provided critical reviews of the manuscript and approved the final version to be published. KJC,

RJN, and DNW agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ETHICS APPROVAL AND INFORMED CONSENT

The investigation was conducted according to NIOSH Institutional Review Board requirements for Health Hazard Evaluations. Personal, potentially identifiable details are provided only for those who gave informed consent for publication of this information.

DISCLAIMER

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of NIOSH. Mention of any company or product does not constitute an endorsement by NIOSH.

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