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Particle exposures and pulmonary sarcoidosis

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Abstract. *Background:* Sarcoidosis is a chronic disease characterized by the formation of non-caseating granulomas with the lung being the most frequently involved organ. The current diagnosis of sarcoidosis requires that the etiology be idiopathic with alternative causes of granulomatous disease excluded. The assessment that sarcoidosis has no known cause has been challenged by numerous case reports, case series, and epidemiologic studies supporting associations of this disease with recognized exposures to particles. *Objective:* The literature is reviewed to test for an association between particle exposures and a diagnosis of pulmonary sarcoidosis. *Methods:* A systematic review of the literature was performed using PubMed/MEDLINE, Web of Science, and TOXNET. *Results:* Particles can impact a development of granulomas comparable or identical to those in sarcoidosis patients. Prominent among these particles which participate in a pathogenesis of sarcoidosis are silicas and silicates, metals and metal oxides, and World Trade Center dust. *Conclusions:* Particle exposure is frequently associated with pulmonary sarcoidosis and should not preclude the diagnosis.

Key words: sarcoidosis, granuloma, foreign body, silica, metals, particulate matter

Introduction

Sarcoidosis is a chronic disease characterized by the formation of non-caseating granulomas in intrathoracic and/or extrathoracic organs (1,2). The prevalence and incidence of sarcoidosis both peak between ages 20 to 39 and are 4.6 to 64 per 100,00 people and 1.0 to 40 per 100,000 people per year, respectively. After idiopathic pulmonary fibrosis, it is the second most common interstitial lung disease (3). In the United States, prevalence is higher among females than males as well as African American relative to Caucasian subjects. Sarcoidosis represents a multifactorial response to an unidentified, inhaled exposure with environmental, host immunologic, and genetic elements interacting to impact disease development (4). It is an immunologically mediated disorder with pathogenesis requiring an exposure to an antigen which, with persistence, is presented to T lymphocytes (CD4+). There is up-regulation of the immune response, activation of alveolar macrophages/dendritic cells, and sensitization culminating in granulomatous inflammation. Subsequently, direct exposure to an environmental agent with systemic distribution leads to multiorgan granuloma formation. Genetic factors participate in susceptibility (5,6). The specific mechanistic pathways that determine the induction, maintenance, and resolution of this systemic granulomatous inflammation remain poorly understood. Individuals experience disease remission within the first few years but over 30–50 % develop some form of a chronic disease requiring treatment to prevent progressive organ dysfunction and fibrosis. The major portal of entry for any etiologic agent of sarcoidosis is assumed to be the respiratory tract. Subsequently, the involvement of the lungs (~90%) and intrathoracic lymph nodes is greatest (7). A significant proportion of individuals

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with sarcoidosis (~40 to 60%) are asymptomatic but the chest radiograph is abnormal in most patients (over 90%). The peripheral lymph nodes and liver are also commonly involved (7). Other tissues which contact the external environment (e.g., eyes and skin) can also demonstrate increased involvement but virtually every organ in the body (e.g. liver, spleen, and heart) can be impacted (4). The diagnosis of sarcoidosis, provided by the American Thoracic Society in 2020, is based on fulfilling several criteria: 1) a compatible clinical presentation, 2) the finding of non-necrotizing granulomatous inflammation in one or more tissue samples, and 3) the exclusion of alternative causes of granulomatous disease (1). The last criterion requires that sarcoidosis be idiopathic (1,4,8). Accordingly, sarcoidosis is not diagnosed if a specific etiology can be identified. After assigning causation to such an exposure, a descriptor ("sarcoidosis-like disease", "sarcoid-like granulomatosis", or "sarcoid-like granulomatous lung disease") is frequently applied (9). This assessment that sarcoidosis has no known cause has been challenged by numerous case reports, case series, and epidemiologic studies supporting associations of this disease with both occupations which include particle exposures and specific particles (10,11). We review the literature supporting particles in the pathogenesis of sarcoidosis.

Methods

A systematic review of the literature was performed using PubMed/MEDLINE, Web of Science, and TOXNET. All available years were included. Case reports, case series, epidemiological studies, editorials, reviews, and letters with a focus on pulmonary sarcoidosis associated with particle exposures were identified examining the databases. The initial search string ("Sarcoidosis"[MeSH] and ("Environmental exposures"[MeSH] or "Silicon dioxide"[MeSH] or "Metals/adverse effects"[MeSH] or "Metals/toxicity"[MeSH] or "Oxides"[MeSH] or "Minerals"[MeSH] or "September 11 terrorist attacks"[MeSH] or "Soil"[MeSH] or Pollen"[MeSH] or "Smoking"[MeSH] or "Particulate matter"[MeSH] or "Air pollutants"[MeSH] or "Air pollution"[MeSH] or "Wood"[MeSH])). There were no filters used for species, sex, age, or language. This search resulted in 236 articles. Those articles not including either cases or epidemiological studies of sarcoidosis were excluded.

Results

Sarcoidosis and occupations

Investigations have associated sarcoidosis and sarcoid-like granulomatous lung diseases with various occupations (12-16) (Table 1).

This pulmonary disease can demonstrate epithelioid granulomas that are pathologically and clinically indistinguishable from sarcoidosis (7,20,30). Granulomatous lung disease was reported in miners (12) and construction workers (27). Significant associations were demonstrated between occupational exposures including those with metal dusts and sarcoidosis mortality (27). However, work with metals was also shown to be protective against sarcoidosis (15,27). In addition, construction and agriculture were suggested to increase the risk for sarcoidosis (14-16). Finally, in a study of 36 pediatric sarcoidosis patients matched with both 36 healthy controls and a group of 21 with sickle-cell disease, pediatric sarcoidosis was associated with indirect exposure to inorganic particles through someone living at home. Co-residents' occupations included construction (31). A metanalysis estimated that 30% of sarcoidosis cases can be attributed to occupational exposures (32). It was not known whether these occupational exposures caused sarcoidosis, impacted the immune system to increase susceptibility, exacerbated subclinical cases, or triggered a granulomatous condition comparable to but distinct from sarcoidosis (7).

Pulmonary sarcoidosis and particles.

Specific particles associated with pulmonary sarcoidosis include silica, silicates, metals and metal oxides, and World Trade Center dust (Table 2).

Silica and silicates.

Prominent among particles which have demonstrated a relationship with sarcoidosis are silica and silicates. There have been several case reports and case series documenting this correlation. An early report recognized pulmonary granulomas in two workers exposed to Portland cement and to mica dusts (33). Using histochemical and X-ray diffraction techniques, abundant inclusions of the inhaled material were identified within the pulmonary lesions. In another case, a 50-year-old woman presented with

Table 1. Occupations associated with sarcoidosis

Miners (12)
Concrete workers, miners, casters, masons, and ceramic and glass manufacturers (13)
Construction workers (14).
Building materials, hardware, garden supplies, mobile homes (13)
Automobile manufacturing (15)
Metal industry (16,17)
Welding (16)
Agricultural workers (15,16)
Work in jobs related to agriculture, water, construction, metal machining, education, and health (18)
Work with insecticides (16)
Jobs with livestock or close human contact (liver or splenic involvement only) (19).
Jobs with exposure to livestock or reactive chemicals (cardiac involvement) (19)
Work in air transport factories (15)
US military workers (20-23)
Firefighters (24,25)
Radiation exposure (15)
Raising birds (15)
Work with musty odors (15)
Work in water supply (16)
Educators/teachers (15,26,27)
Health services (26)
Health care, teaching, sales, banking, and administration (16)
Healthcare providers (28,29)
Sales (26)
Banking (26)
Administration (26)

Table 2. Specific particles associated with sarcoidosis

Silicas and silicates
Metals and metal oxides
Man-made mineral fibers
World Trade Center dust
Soils, agricultural dusts, and pollens
Cigarette smoke particles
Wood stove particles
Other carbonaceous particles
Calcium particles/endogenous particles
Dusts with microbial-derived components

Lofgren syndrome, defined by an acute onset of erythema nodosum, bilateral hilar lymphadenopathy, fever, and migratory polyarthritis, and without granulomatous skin involvement. (34). Computed tomography revealed a foreign body granuloma of the lung containing inhaled particles. Analysis of the particles showed non-crystalline silica, calcite monohydrate, and phenol resin. In a patient treated for hypertension, an association between exposure to anhydrous colloidal silica (used as a vehicle for capsules or tablets in drug formulations) and sarcoidosis was suggested (35). Sarcoidosis was also reported after silica exposure in a tunnel worker, a denim sandblaster, iron-foundry workers, and a plasterer (14,36-38). Two cases of lung and hepatic granulomas in workers exposed to artificial quartz conglomerates were initially diagnosed to be sarcoidosis but later considered consistent with silicosis (39). In another case, pathologic examination of the lung revealed focally infarcted granulomas and chronic inflammation in an industrial worker with exposure to high levels of inorganic dust (most significantly silica, silicon carbide and aluminum compounds) for 28 years (40). The tissue removed from the granulomatous involvement showed significant dust deposition. Despite the inorganic dust deposits, a diagnosis of necrotizing sarcoid granulomatosis was initially made but this was later changed to mixed-dust pneumoconiosis after detailed examination using scanning electron microscopy/energy-dispersive X-ray spectroscopy (SEM/EDS) analysis of individual particles showed predominantly silicon (silica or silicon carbide) and aluminum particles (the latter being consistent with aluminum metal and/or oxide). Two cases of sarcoidosis were observed in a workforce of 30 metal-halide lamp manufacturing workers in Belgium (41). Mediastinal lymph node and open lung biopsy specimens revealed noncaseating epithelioid granulomas. Birefringent particles were

observed in the biopsied tissues and the exposures included amorphous silica and cristobalite. More recently, a patient who worked in cement processing with silica exposure had a lung biopsy which revealed sarcoid-like granulomas with birefringent particles under polarized light; there was no malignancy or infection (42). Based on the pathological findings, he was diagnosed with silicosis-associated sarcoid-like granulomatous lung disease rather than sarcoidosis. Pulmonary manifestations improved after discontinuation of silica exposure and introduction of corticosteroid/azathioprine combination therapy. In another study involving mining, 12 cases of sarcoidosis were observed in a cohort of hard-rock miners in Northern Ontario, Canada: 5 included extrapulmonary sarcoidosis (11). Workers at a plant in Iceland exposed to diatomaceous earth comprised of silica, alumina, and iron oxide) and cristobalite (crystalline silica) were reported to show an increased risk of sarcoidosis with an odds ratio of 13.2 (43). Among samples from 50 patients with sarcoidosis collected by biopsy and/or autopsy sampling, silicon-containing dust particles were present in epithelioid cells and multinucleate giant cells in all (44). In a cohort of exposed workers in Swedish iron foundries, moderate to high levels of silica exposure increased risk for sarcoidosis (45). In an additional epidemiologic study, an elevated risk for sarcoidosis was observed in a group of construction workers specifically exposed to silica and silicates (46). A case-control study of all individuals diagnosed with sarcoidosis in Sweden between 2007 and 2016 revealed that silica dust exposure correlated with an increased risk of developing this disease (with an odds ratio of 1.44 for exposure greater than 10 years among males older than 35 years) (13). Using multivariable logistic regression in 238 patients, sarcoidosis limited to pulmonary involvement was demonstrated to be associated with exposure to inorganic dust (19). Finally, an increased trend in incidence of pulmonary sarcoidosis was observed in epidemiologic investigation of those exposed to silica in the Danish working population followed 1977-2015 (47). Several case reports and case series support an association between talc exposure and sarcoidosis. A chronic, pulmonary granulomatous reaction in two patients exposed to talc was associated with a clinical presentation considered identical to sarcoidosis (48). In both patients (one in the rubber industry and the other exposed to cosmetic talcum powder), lung biopsy showed a deposition of talc particles and a strong granulomatous reaction. There were no extrapulmonary manifestations. A 62-year-old woman was diagnosed with sarcoidosis until a thoracoscopic biopsy revealed the presence of numerous birefringent particles in fibrotic areas of the lung (49). These particles were examined by SEM/EDS and characterized as impure talc. The patient had worked from age 14 to 18 in a factory making rubber hoses where she had an ongoing, intense exposure to talc. The diagnosis was subsequently changed to talc-related lung disease. In another study, two patients who used talc on irritated cutaneous areas developed enlarged lymph nodes and were diagnosed with sarcoidosis (50). A histologic examination with polarized light showed crystalline birefringent particles within vessels in contact with granulomatous areas. *In situ* microanalysis allowed identification of birefringent particles with a size of roughly 0.25 micron as silica or silicate, possibly talc. A 38-year-old woman was initially diagnosed with sarcoidosis but a bronchoscopic biopsy obtained later revealed the presence of numerous foreign body giant cells and birefringent particles forming non-caseating granulomas consistent with talc-related lung disease (51). In a case of bilateral pulmonary nodules and mediastinal and hilar lymphadenopathy, a patient was first diagnosed with sarcoidosis. This was later changed to talcosis based on pathological demonstration of non-necrotizing granulomas, polarizable crystals, and findings on SEM/EDS analysis (52). It was concluded that differentiating between chronic sarcoidosis and talc-related lung disease was difficult even after a complete clinical and histological evaluation. Sarcoidosis has also been associated with exposure to asbestos. In a case of sarcoidosis, Schaumann bodies were observed to be organized around asbestos bodies (53). In a second case report, sarcoidosis was diagnosed in an asbestos worker presenting with bilateral hilar and mediastinal lymphadenopathy (54). In a third case report, lung biopsy confirmed a granulomatous reaction with epithelioid and gigantocellular cells, without caseum, on biopsy in a shipyard worker (i.e., a carpenter) (55). Finally, the incidence and prevalence of sarcoidosis in another epidemiologic study were found to be higher among veterans (serving in the Army, Air Force, and other service branches) than in the general population (56). Gulf War veterans who served in Southwest Asia during the Persian Gulf War, specifically in Iraq, Kuwait, Saudi Arabia,

Bahrain, Qatar, Oman, Afghanistan, or the United Arab Emirates, were found to have a prevalence of lung sarcoidosis (i.e., interstitial lung disease) approximately five times higher than age- and gender-matched peers (22). Silica and silicates associated with dust storms were among the exposures considered possibly responsible for the increased sarcoidosis in military veterans. It was again proposed that sarcoidosis could be associated with exposure to dust storms (57). Supporting this proposal, convoy activities were associated with sarcoidosis in another cohort of military veterans deployed to Afghanistan or Southwest Asia (58). Military veterans with exposures to burn pit smoke, sandstorms, and diesel exhaust demonstrated a higher proportion of silica and silicates in biopsy-confirmed lung disease (59).

Man-made mineral fibers

The records of 50 outpatient sarcoidosis patients revealed that 14 individuals recalled a history of exposure to either glass fibers or rock wool, suggesting that man-made mineral fibers could be related to a chronic granulomatous disease in susceptible individuals (60).

Metals and metal oxides

All metals in the atmosphere are included in particles with the single exception being mercury-based compounds. An association of metallic dust exposure and sarcoidosis has been recognized. Several granulomatosis cases with symptoms similar to or identical to those of sarcoidosis have been attributed to exposure to metals including beryllium, titanium, aluminum, steel, barium, cobalt, copper, gold, rare earths (lanthanides), titanium, and zirconium (61-66). Exposure to beryllium triggers sensitization to the metal and leads to a granulomatous disease identified as chronic beryllium disease (11,67,68). There can be a wide range of work environments that have a potential for beryllium exposure and even relatively low exposures to this metal can be sufficient to generate an immune response. Workers exposed to high levels of beryllium demonstrate a fulminant disease with extrapulmonary manifestations. The clinical and pathological presentation of chronic beryllium disease is similar to and even identical to that of sarcoidosis (30). Histologically, the non-caseating granulomas in the lung of an individual exposed to beryllium can histologically be indistinguishable from those in sarcoidosis (4). With chronic beryllium disease, removal from an exposure is an effective treatment (69). Clinical and histological manifestations of sarcoidosis are observed after exposures to aluminum and its oxide. A case of pulmonary granulomatosis associated with occupational exposure to aluminum dust was described and was deemed to closely resemble sarcoidosis (70). Electron probe microanalysis of the lung biopsy specimen identified aluminum. Another case of sarcoid-like granulomas was reported with exposure to aluminum metal and oxide powders (15). Analytical electron microscopy of lung tissue obtained by transbronchial biopsy revealed aluminum particles within the granuloma. In a third case, a welder in a stainless-steel factory was diagnosed with sarcoid-like granulomatous-induced aluminum disease based on an aluminum-induced blastic proliferation test and immunologic studies (71). SEM/DES studies on induced sputum-retrieved material showed abundant particles of aluminum. An additional case of pulmonary sarcoid-like granulomatosis was diagnosed in a metal reclamation factory worker who had extensive exposure to aluminum dust (72). Yet another case demonstrated bilateral areas of ground-glass attenuation, patchy areas of consolidation, extensive reticular hyperattenuating areas and traction bronchiectasis on chest radiographs and high-resolution CT (65) in a worker with a 15-year aluminum dust exposure. Lung biopsy specimens confirmed the presence of diffuse, noncaseating granulomatous nodules. SEM/EDS revealed large quantities of foreign particles mainly containing aluminum in granulomas. Cases of granulomatous lung disease following occupational exposure to metal dusts other than beryllium were reported in two workers in battery manufacturing and aluminum-processing factories, respectively (73). Analysis by an electron probe microanalyzer with a wavelength-dispersive spectrometer confirmed the presence of aluminum, silicon, iron, and titanium in their granulomas. Aluminum was distributed in a relatively high concentration in the granulomatous lesions. In a patient with a work history of surgical instrument brushing and polishing, electron microscopy analysis of biopsies from pulmonary granulomatous nodules revealed the presence of metal particles (aluminum oxide, iron oxide, titanium oxide, and steel) (74). In a case of a plasterer exposed to construction dust for more than 30 years in the Netherlands, a biopsy of

the lung parenchyma revealed noncaseating granulomas and birefringent particles (37). Mineralogical analysis revealed aluminum and titanium. An additional case presented with rapidly progressive well-defined multiple centrilobular and perilobular nodules on both chest radiography and high-resolution computed tomography (75). SEM/EDS of lung specimens revealed aluminum, iron, titanium, and silica deposition in the lung tissues. A case of desquamative interstitial pneumonia associated with pulmonary granulomatosis was linked to metal (aluminum and zirconium) exposure (76). In another case, a surgical biopsy showed multiple isolated and confluent granulomas in an otherwise normal parenchyma (77). There was a history of exposure to both aluminum dust and silica during a metal polishing processing. Using an X-ray fluorescence spectrometric analyzer, elemental analysis on the grinding wheel powder in the workplace showed a composition of 72.7% of Al_2O_3 and 22.8% of SiO_2. A diagnosis of aluminum-associated sarcoid-like granulomatous lung disease was provided rather than sarcoidosis. Sarcoidosis also presents after exposures to other metal and metal oxide particles. Work in construction with steel and chromium was identified as a risk factor for sarcoidosis in investigation which included epidemiology (37,78-80). Four cases of sarcoidosis were reported in employees with exposure to metal oxides in the iron-steel industry in Turkey (37). In another investigation, the mineralogical content of bronchoalveolar lavage from 20 patients with biopsy-proven sarcoidosis showed dust burdens which were not significantly different between case subjects vs control subjects (81). However, the specific metal particulate load in case subjects was higher in those working with steel and chromium. A relationship between zirconium exposure and granulomatous lung disease was reported and could include multiple organ involvement (82-84). Specific exposures that were associated with sarcoidosis also included titanium (78). As a result of their professional work with amalgam, dental technicians and dentists are exposed to higher metal concentrations than the general population. A dental technician presented with non-caseating foreign body granulomas at histological examination (85). Mineralogic studies showed the presence of aluminum, silica, and silicates. Another case report described occupational exposure to metal-containing agents that resulted in a sarcoidosis-like presentation in a dental surgeon (86). Sarcoidosis-associated pulmonary hypertension was also reported in a dental technician (87). Immunoreactivity to metals, as well as silica, has been described among sarcoidosis patients (80). The proliferation of T-lymphocytes in response to *in vitro* exposure to beryllium (i.e. the beryllium lymphocyte proliferation test) is used in an attempt to distinguish chronic beryllium disease from sarcoidosis (88,89). Other metals can also cause an antigen-specific granulomatous immune response as well as a nonspecific immune response (88). Lymphocytes collected from the blood of 13 patients with sarcoidosis demonstrated a positive reaction to at least one metal in nine patients, of which two tested positive to beryllium and two tested positive to silica (79). In an additional epidemiologic study, a significantly higher percentage of sarcoidosis patients (27.6%) than controls (4.2%) demonstrated an immunological response to metals (or silica) (90). These findings support an etiologic involvement of metals in sarcoidosis, as well as silica, similar to that for chronic beryllium disease.

World trade center dust

Hundreds of compounds were identified in World Trade Center dust generated by and following the aftermath of the September 11 attacks in New York City (91,92). Relatively high concentrations of manganese, aluminum, barium, and titanium reflected building construction materials and paint (91). In addition, chromium, lead, zinc, and a number of organic compounds were present. Another analysis of World Trade Center dust sieved according to particulate matter (PM) size revealed $CaCO_3$ (calcite [limestone]) and $CaSO_4 \cdot 2H_2O$ (gypsum) as major components of PM < 53 µ. $CaSO_4 \cdot 0.5H_2O$ (basanite) and SiO_2 (crystalline silica) were identified as minor components (93). Calcium and sulfate together accounted for 64% of the PM with an aerodynamic diameter < 2.5 µ, suggesting that compounds found in larger PM were present in the more respirable fraction as well. Concrete, gypsum, and synthetic vitreous fibers comprised 80% to 90% of the dust; products of combustion and pyrolysis were included (94,95). Lung disease following exposure to World Trade Center dust included a spectrum of inflammatory injuries and diseases consisting of irritant-induced asthma, non-specific chronic bronchitis, aggravated pre-existing obstructive lung disease (asthma or COPD), and bronchiolitis (94). In

addition, sarcoid-like granulomatous pulmonary disease or interstitial lung disease was noted (92,96,97). Lung tissue from 12 World Trade Center dust-exposed residents and local workers (with abnormal imaging and physiological test results) was reviewed (98). Mineralogical analysis of surgically biopsied lung tissue from five of the 12 patients revealed aluminum silicate, titanium, and talc. Silica was found in four of the five biopsies while steel particles were observed in three. Compared to the years preceding the attack, New York City firefighters had a higher prevalence of sarcoidosis at baseline relative to the general population but diagnoses of biopsy-confirmed sarcoid-like granulomatous pulmonary disease increased significantly during the years following the attack (24,92,96,99). From 1985 to 1998, an average annual incidence rate of 12.9 per 100,000 was observed among New York City firefighters. In the 12-month period following exposure to WTC dust, the incidence rate increased to 86 per 100,000 and by 2015, the average annual incidence rate had decreased to 25 per 100,000. Pathologic evidence consistent with new-onset sarcoidosis was observed in 26 patients; all had intrathoracic adenopathy, and six patients had extrathoracic disease (92). In a group of 45,899 enrollees in the World Trade Center Health Registry, there were 43 cases of biopsy-confirmed sarcoidosis (greater than 70% of these subjects had multiorgan involvement) (100). There were 38 cases of biopsy-confirmed sarcoid-like granulomatous pulmonary disease diagnosed among 19,756 responders (96). This included 37.3% and 24.9% in law enforcement and construction, respectively. The incidence observed in black responders was about double that of white responders. (96). This sarcoid-like granulomatous pulmonary disease was further described/confirmed in firefighters and responders exposed to the World Trade Center dust while working on the debris pile (100). Two additional cases of sarcoidosis after exposure to World Trade Center dust were reported (101). Cases of World Trade Center-related sarcoidosis demonstrated radiographic appearances typical for sarcoidosis with symmetric hilar and mediastinal lymphadenopathy as well as mid to upper lung peri -lymphatic nodules. A dose response relationship between World Trade Center dust and sarcoidosis-like disease was demonstrated (102). Resolution of intrathoracic disease has been observed in subjects with World Trade Center-related sarcoidosis following elimination of exposure (99). Among patients in the World Trade Center Environmental Health Center (WTC EHC) study, 87 were identified with sarcoidosis after 9/11 (103). Sarcoidosis cases were more likely to be African American, local workers, and had more respiratory symptoms compared with non-sarcoidosis WTC EHC patients. Many (46%) had ≥ Scadding stage 3 on chest imaging indicative of possible advanced disease with reduced lung function. Out of seven patients examined, five were diagnosed with sarcoid-like granulomatous disease and two with pulmonary fibrosis following examination of the histologic sections of lung and/or lymph node samples (104). Finally, cases of sarcoid-like granulomatous disease in this group was recently reviewed and called "World Trade Center-related sarcoidosis" (105).

Soils, agricultural dusts, and pollens

Early research, including epidemiologic investigation, supported an association between sarcoidosis and exposure to soil (106,107). Residence in rural areas and employment on a farm increased both exposure to soil and the risk for sarcoidosis (106,108). Agricultural dusts were associated with pulmonary sarcoidosis (109). Pine pollen exposure was also demonstrated to increase the risk for sarcoidosis (110,111).

Cigarette smoking secondhand smoking, and electronic cigarettes

In magnitude, smoking presents the greatest particle challenge in humans. Smoking was reported to reduce the incidence of sarcoidosis (112,113). In the general population, patients with pulmonary sarcoidosis were less likely to be smokers (114). This could be because smoking decreased the likelihood of developing sarcoidosis, or alternatively, smoking reduced the severity of the disease process so that smoking patients were underrepresented among patients with clinically evident disease (114). In another epidemiologic study, smoking was concluded to play a protective role in the occurrence of sarcoidosis (115). In additional investigation, current smokers had a lower risk of developing sarcoidosis with an odds ratio of 0.68 (17,116). Finally, smoking was associated with decreased frequency of bronchovascular bundle thickening among patients with sarcoidosis (117). As a result of this investigation, it was suggested that nicotine might be

protective and was proposed as a potential treatment for sarcoidosis (118). In contrast to this data, there is investigation which suggests either a lack of a relationship or a positive association between smoking/environmental tobacco smoke and sarcoidosis. In 98 newly diagnosed patients with sarcoidosis, the prevalence of smoking was similar in cases and controls (12.2% vs. 15.3%) (119). Logistic regression analyses showed an insignificant association with either active smoking or environmental tobacco smoke exposure. A cohort study of Japanese sarcoidosis patients showed a higher smoking prevalence, suggesting that there could be a different relationship between smoking and the development of sarcoidosis in this population relative to that described in western societies (120). Nodular sarcoidosis is a rare variant of sarcoidosis that presents as multifocal, bilateral, ill-defined nodules in female smokers (121). More recently, an analysis of construction workers based on smoking history showed that ever-smokers had an increased risk of sarcoidosis following exposure to silica (46). Finally, regarding particle exposure with electronic cigarettes, a patient was reported to have developed sarcoidosis following their use (122).

Wood stove particles

Wood stoves and fireplaces for home heating increased the risk for sarcoidosis (108). In another study, woodburning in African American individuals was associated with pulmonary sarcoidosis (109). In addition, use of wood and fossil-based energies was statistically associated with pediatric sarcoidosis in epidemiologic investigation (31).

Air pollution

Air pollution particles have not been associated with causation of sarcoidosis. However, air pollution particles, specifically $PM_{2.5}$, are proposed to worsen sarcoidosis (123). In a small cohort of patients with fibrotic sarcoidosis, $PM_{2.5}$ exposure was associated with increased severity of respiratory symptoms and worsening quality of life (124).

Other carbonaceous particles

Photocopier toner dust functioned as a previously unrecognized antigen involved in the pathophysiology of sarcoidosis in some patients (125).

Calcium particles/endogenous particles

The nature, prevalence, and specificity of birefringent calcific particles in sarcoidosis granulomas were examined using histochemical and microchemical analyses (126,127). Small ovoid particles in macrophages were found in 86% of lymph nodes and in 73% of surgical lung specimens in sarcoidosis patients. These particles were mostly calcium oxalate with some being calcium bicarbonate (127). Larger crystals, those within giant cells, and the birefringent component of a Schaumann complex, were also calcium oxalate. In a smaller number of cases, particles were dolomite and a calcium-sulphur compound. Calcium particles in the biopsies from patients with sarcoidosis were believed to be endogenously derived; their generation was included in the granulomatous response, but their exact significance is unclear (128). In tissue biopsies demonstrating granulomas consistent with sarcoid-like disease, 57% also showed such particulate matter (129).

Dusts with microbial-derived components

While a common cause of pulmonary granulomas, sarcoidosis is not caused by an active infection (7). Antigens related to infectious agents have been demonstrated in sarcoidosis patients. Granulomatous immune responses suggest that these poorly degraded antigens, which are related to the microbial agent, likely contribute to the immune process of sarcoidosis without the presence of viable invasive organisms themselves (7). Numerous components of infectious agents, particularly mycobacteria and *Propionibacterium acnes* have mimicked features of sarcoidosis in animal models (130-133). In addition, mycobacterial and Propionibacterium DNA has been found in lymph nodes from sarcoidosis patients (134,135). Reflecting possible microbial growth, exposures associated with sarcoidosis included indoor exposure to high humidity, water damage, or musty odors (78). Both fungal cell wall agents and bacterial lipopolysaccharide in particles (i.e., organic or biological dusts) have been associated with granulomatous diseases in epidemiologic investigation (15,27,136). In support of such a relationship between sarcoidosis and these substances, there was a high prevalence of new-onset sarcoidosis among workers of a water-damaged building with a history of indoor environmental quality

complaints (137). Compared to controls, subjects undergoing treatment for sarcoidosis (newly diagnosed or recurrent) had higher activities of N-acetyl hexosaminidase (reflecting microbial exposure) in their homes. In an epidemiologic study, exposure to fungi was considered to increase the risk of sarcoidosis (138).

Extrathoracic sarcoidosis and particles

Studies have suggested that sarcoidosis reported in patients after exposure to particles are less likely to have extrapulmonary involvement than unexposed patients (92,139). Patients with chronic beryllium disease, a disorder clinically, radiologically and histopathologically almost indistinguishable from sarcoidosis do have fewer extrapulmonary manifestations. Hepatic, splenic and cardiac involvement are rare, and ocular and neurological impairment have not been reported (140). In the ACCESS (A Case Control Etiologic Study of Sarcoidosis) study, patients with a diagnosis of sarcoidosis who were exposed to agricultural organic dust and wood burning were less likely to have extrapulmonary involvement (109). Sarcoidosis cases who had been exposed to World Trade Center dust could demonstrate extrapulmonary involvement but rarely do (92). One possible explanation for sarcoidosis that is frequently limited to the lungs following dust exposure is that inhaled particles do not readily disseminate systemically. When not removed by the mucociliary escalator, these particles can be transported via the lymphatic system to regional lymph nodes (141). Particles accumulate in lymph nodes and sporadically can be translocated to the systemic circulation where they are filtered from the blood in the liver and spleen. Only small numbers will be taken up by other organs. A major determinant of systemic dissemination of particles is likely to be the magnitude of the exposure (142). In addition, such dissemination may also depend on particle characteristics such as size, surface properties, chemical composition, and solubility (141).

Discussion

Investigation has reported associations of pulmonary sarcoidosis with occupational exposures in miners, construction workers, those working with metal dusts, and agricultural workers. Many of these occupations included exposures which were particle-related but frequently the specific responsible agent, substance, and/or compound could not be delineated. Studies support associations of pulmonary sarcoidosis with silicas and silicates, metals and metal oxides, World Trade Center dust, soils, agricultural dusts, carbonaceous particles, calcium particles/endogenous particles, and biological dusts with microbial-derived components. These include particles with a myriad of structural components presenting at sizes ranging from those with diameters approaching nanometers to microns. These epidemiological and clinical observations find biological plausibility in the current hypothesis on granuloma formation, which can be a pathological response to foreign material with the purpose being to contain and isolate an adverse agent that individual macrophages cannot eliminate (143). While innate granulomas can be formed by macrophages alone, a cell-mediated adaptive immune response often ensues. Macrophages in forming granulomas secrete chemokines that recruit dendritic cells (4). Dendritic cells access antigen in apototic macrophages, and a T cell response is initiated and driven by foreign antigens present in the emerging granuloma (144). Activated lymphocytes secrete cytokines including IL-2, interferon gamma, and TNF alpha, which support development of the maturing granuloma. Both particle-induced granulomas and sarcoid granulomas contain CD4+ T cells, supporting the hypothesis that sarcoid granulomas may be particle-driven (145,146). Granulomas represent a protective response of the host to encapsulate, sequester, and destroy foreign objects, which are frequently particles. The granuloma is the pathological hallmark of sarcoidosis, formed *in vivo* through the recruitment of activated monocytes and tissue macrophages, T and B lymphocytes, fibroblasts, and other matrix-associated cells (4). This focus of chronic inflammation consists of a microscopic aggregation of macrophages immediately surrounded by lymphocytes and plasma cells. It functions as a physical barrier to protect adjacent tissue from damage. The granuloma is not unique to sarcoidosis but is also observed in other diseases and exposures such as infection, malignancy, granuloma annulare, and foreign objects (splinters, bee stings/spider bites, dermal filter/collagen, and surgical stitches) (4). In several studies, monocytes function as precursors to the host cells pivotal in the formation of a granuloma. Both monocytes and monocyte-derived cells were

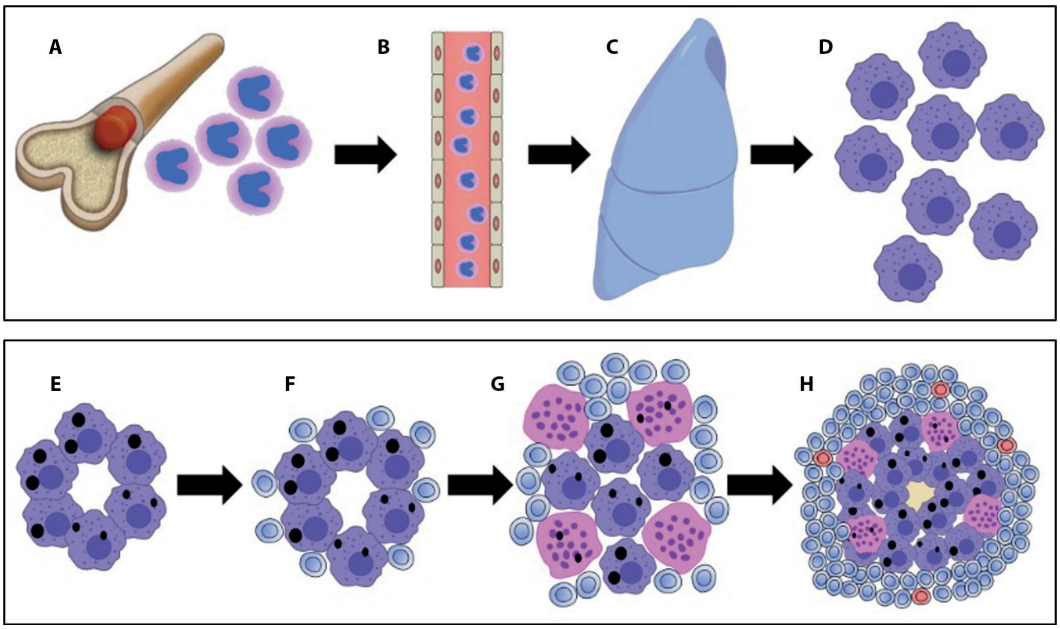

Figure 1. Schematic for particle-associated granuloma formation in sarcoidosis. Particle exposure promotes a release of monocytes from the bone marrow (A) which are observed in increased numbers in the blood (B). Inflammatory mediators' direct movement of the monocytes into the lung (C). Monocytes function as precursors to host cells pivotal to the formation of a granuloma, such as macrophages (D). The macrophages phagocytose the particle (E), aggregate (F), fuse to form multinucleated giant cells (G), and, along with lymphocytes (both T and B cells) and other cell types, form a granuloma (H).

increased in blood and bronchoalveolar lavage of sarcoidosis patients suggesting an inflammatory response (147,148). Monocytes contributed to the macrophage pool during such inflammation/injury (149). Particle exposure stimulates a production of mediators known to accelerate a release of monocytes from the bone marrow (150) (Figure 1).

Accordingly, monocytes increase with particle-associated exposures include smoking (151,152), diesel exhaust particles (153), ambient air pollution (154), and traffic-related pollution (155). This is not unique to exposures in the lung, as an intraperitoneal injection of various particles (i.e., silica, kaolin, and polystyrene latex) in mice caused an inflammatory reaction in the peritoneal cavity with concomitant monocytosis in the peripheral blood (156). Monocytes and their derived cells are pivotal in the response to particles. The major mechanism for clearance of particles deposited in the conducting airways is via the mucociliary escalator while that for particles deposited in the alveolar region is phagocytosis by alveolar macrophages (i.e., a monocyte derived cell) with subsequent transport to the mucociliary escalator (157). Macrophages can also carry the particles across the epithelium into the interstitium and later transport them to the thoracic lymph nodes (158). Ventilation and perfusion are greatest in the dependent part of the lung (159). With a source of lung macrophages being vascular monocytes from the bone marrow, it is expected that their numbers will increase after particle exposure with elevations in the lower lung fields being greater reflecting perfusion. Correlating with augmented populations of macrophages in the lower lung fields after particle exposure, the macrophages can function to increase clearance from these regions of the lung (160). Since injury is contingent on a lack of total clearance, this sequence of events predicts that the biological effects after particle exposure will subsequently be observed in the upper lung fields explaining the predilection of sarcoidosis for these areas. Particle exposure impacts concentrations of serum inflammatory cytokines and promotes a recruitment of monocytes to the lung (161) (Figure 1). Following particle exposure, there are changes in gene expression connected with key pathways (e.g. oxidative stress, protein degradation,

and coagulation) in peripheral monocytes (162). Particle exposure accordingly alters both number and function of macrophages differentiating from locally recruited monocytes in the lungs (163). In addition, monocyte counts and/or percentages can increase with other fibrotic lung diseases (164-171). Monocyte-derived macrophages phagocytose particles to expedite clearance from the lower respiratory tract. With persistence of an exposure such as a particle, these cells have the capacity to fuse, forming multinucleated giant cells (172) (Figure 1). Within a granuloma, these multinucleated giant cells are important mediators of tissue repair/remodeling. They are responsible for removal or sequestration of foreign material, intracellular bacteria, and non-phagocytosable pathogens. In sarcoidosis, multinucleated giant cells in the granuloma are characteristic of a monocyte-macrophage lineage (173). Inhaled particles (colloidal amorphous silica) are phagocytized by alveolar macrophages in the distal respiratory tract (the respiratory bronchiole and alveolar duct region) with only a few free particles observed in type I pneumocytes (174). From the distal airways to the alveolar region, particle-laden alveolar macrophages penetrate into the bronchiolar interstitium. These macrophages then accumulate in bronchus-associated lymphoid tissue (BALT). They are also able to further migrate into the peribronchial and perivascular lymphatics with transport to the regional lymph nodes. Subsequently, the biological response to particle (e.g., granuloma formation) will occur in the distal respiratory tract, interstitium, BALT, peribronchial and perivascular lymphatics, and the regional lymph nodes. The granulomas resulting from particle exposure can be identical in appearance to the epithelioid granulomas observed in sarcoidosis patients. Based on this evidence, the role of particle exposure in initiating pathogenic pathways underlying sarcoidosis is considered more than an incidental statistical association.

Conclusions

Granulomatous inflammation in the lung after particle exposure is included in a wide spectrum of responses to particles. Particles impact the development of epithelioid granulomas that are pathologically and clinically indistinguishable from those observed in sarcoidosis patients (7,20,30). It is proposed that many patients with sarcoidosis have an evident or occult history of particle exposure, and that such an exposure should not preclude the diagnosis (175). Rather than being a mimic, particles may be one of the most common etiological triggers of sarcoidosis (176). These observations are clinically relevant since removal of patients from particle exposure could possibly prevent disease and its progression. An extensive occupational and environmental history in patients with sarcoidosis will frequently uncover particles as a potential driver of disease. Mineralogical analysis using electron microscopy methodology can confirm the diagnosis of sarcoidosis associated with particle exposure.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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