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Occupational Causes of Sarcoidosis

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Abstract

Purpose of review—Sarcoidosis, the multiorgan, granulomatous disease of unknown etiology, remains mysterious. Several important investigations in the past two years add to accumulating evidence for both occupational and environmental causes of granulomatous inflammation.

Recent findings—This review considers the most recent studies that contribute to the hypothesis that sarcoidosis occurs when individuals are exposed to foreign antigens and to inorganic particulates that promote inflammation. Major recent findings, such as those emerging from the study of World Trade Center responders, the study of nanoparticles, and cases of work-associated sarcoidosis support the probability that occupational, as well as environmental, exposures to inflammatory stimuli trigger sarcoidosis-like illness. Major recent studies of microbially-rich indoor environments, including moldy indoor workplaces and mycobacterially-contaminated settings, contribute to the evidence that a variety of microbial antigens serve as targets for the hypersensitivity immune response in an inflammatory milieu.

Summary—There is increasing evidence that sarcoidosis can occur in workplace settings in which there is exposure to both foreign antigens and inorganic triggers of inflammation that promote an exuberant granulomatous immune response. It is likely that sarcoidosis has more than one cause.

Keywords

Sarcoidosis; Occupation; Granuloma; Nanoparticle; World Trade Center

Introduction

Sarcoidosis, the multiorgan, granulomatous disease of unknown etiology, remains a challenge. For nearly 100 years, researchers have used a variety of approaches to identifying the cause of this disorder. Over the past decade, the emerging consensus is that there is no

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single cause for this disorder. More likely, any number of antigens may be able to serve as the nidus for the granulomatous inflammation that results when a proinflammatory microenvironment has been created. Genetic susceptibility probably contributes to sarcoidosis risk, as well, although this paper will focus more specifically on recent developments related to exposures in the workplace.

Several important investigations published in the past two years have added to accumulating evidence for both occupational and environmental causes of granulomatous inflammation. This paper considers the most recent studies that contribute to the hypothesis that sarcoidosis occurs when individuals are exposed to foreign antigens *and* to inorganic particulates that promote inflammation. Major recent findings, such as those emerging from the study of World Trade Center responders, the study of nanoparticles, and cases of work-associated sarcoidosis support the probability that occupational, as well as environmental, exposures to inflammatory stimuli trigger sarcoidosis-like illness. Major recent studies of microbially-rich indoor environments, including moldy indoor workplaces and mycobacteria-contaminated settings, contribute to the evidence that microbial antigens serve as popular targets for the hypersensitivity immune response in this disease.

Workplaces that May Cause Sarcoidosis

Long lines of evidence have suggested that certain workplace settings are associated with sarcoidosis risk. To place the most recent literature in proper context, Table 1 summarizes some of the historically important associations between work and sarcoidosis and sarcoidosis-like illness. The strength of association varies across studies, however a number of important themes have emerged from this body of research. First, as illustrated by the National Institutes of Health multicenter study, A Case Control Etiologic Study of Sarcoidosis (ACCESS), microbially-rich workplace environments are associated with this disorder. These include water sources that serve as reservoirs for microbial contaminants that can then be aerosolized, agricultural settings rich in mold and protein antigens, and water-damaged work environments reported as having mold/mildew exposures. Secondly, a number of studies have implicated employment in metal industries. This is not a surprise, given that it has been well-established that a number of metals can cause granulomatous inflammation and disease that mimics sarcoidosis, including beryllium, zirconium, titanium, rare earth elements, and aluminum. Additionally, many metal workers may have exposure to mycobacteria-contaminated metalworking fluids that are known to trigger a form of hypersensitivity pneumonitis often mistaken for sarcoidosis. Third, work environments that produce high levels of inorganic particulate matter emerge as places of higher risk for development of sarcoidosis. Examples include exposures to wood stoves, fireplaces, talc, man-made mineral fiber, hard rock dust (silica), intense agricultural activities, and others described below.

Because the workplace can be a source of antigens and of inflammatory stimuli, it is not surprising that over time researchers have been able to identify work settings in which sarcoidosis risks are elevated based on epidemiologic findings and, in some cases, immunologic confirmation. Further research is required to better pinpoint specific agents in these environments that confer the risks. Almost certainly, this will require a multifaceted

approach that capitalizes on exposure science, immunology, microbiology, epidemiology, and experimental pathology and toxicology. As reflected in some of the citations below, the goal will be to establish causation, akin to the discovery of beryllium as a cause of sarcoidosis in the 1940s (now chronic beryllium disease) and of mycobacteria species as causes of what is now called metalworking fluid hypersensitivity pneumonitis. As is generally the case, workplace-related illnesses that were once thought to be sarcoidosis become reclassified and renamed as specific disorders, once the causative agent has been confirmed. It is important to emphasize that although most of us are trained to consider granulomatous conditions like hypersensitivity pneumonitis to be different from sarcoidosis, in clinical practice and in many outbreak investigations, these conditions are clinically and pathologically inseparable, until a point source or etiologic agent has been discovered. Frequently the first clinical diagnosis is “sarcoidosis.” It is only later, when a cluster of cases or a point source of exposure has been discovered, that clinicians and pathologists revise their diagnosis from idiopathic (i.e. sarcoidosis) to specific (e.g. hypersensitivity pneumonitis). While a case can be made that these clinical entities are immunologically and pathogenically distinct, the extensive overlap of clinical signs, symptoms, imaging, and pathology make it important for us to continue to consider hypersensitivity pneumonitis as part of the family of sarcoidosis-like illnesses. The onus is on researchers and clinicians to seek occupational and environmental causes for every case of idiopathic granulomatous disease, regardless of which diagnostic label we apply. When cases of granulomatous disease are confined to the lungs with little or no evidence of adenopathy, we can clinically diagnosis hypersensitivity pneumonitis, even while we pursue further investigation to identify the causative agent. We can even make a final diagnosis of hypersensitivity pneumonitis when the antigen eludes us. But most cases of granulomatous pneumonitis are less clear-cut. Those cases are often called sarcoidosis. Unfortunately, because clinicians are taught that sarcoidosis has no known cause, we often fail to make the same efforts to pursue the etiology of sarcoidosis and sarcoidosis-like illness in the workplace as we do when we suspect hypersensitivity pneumonitis..

Occupational and Environmental Sources of Antigen

As discussed above, at our current state of knowledge, we can think of sarcoidosis as having multiple causes and as requiring both an antigen and a trigger of inflammation. In some instances, the antigen may possess properties that make it both the antigenic target for an adaptive immune response as well as the adjuvant trigger of innate immunity. Several recent studies have significantly advanced our understanding of the role of molds and mycobacteria as two likely occupational causes of sarcoidosis.

Indoor air and mold

Much of the literature on the subject of mold exposure in damp indoor environments has been recently reviewed [1]. An important series of studies by some of these authors has focused on sarcoidosis, as well as other respiratory disorders, occurring in occupants of a historically water-damaged office building. The building, which had a history of indoor environmental quality complaints, was found to have a high prevalence of new-onset sarcoidosis among occupants [2]. This group had previously investigated a 20-story office

building with a similar increase in the incidence of respiratory conditions, including three cases of physician-diagnosed post-occupancy sarcoidosis. Sixty employees filed workers' compensation claims for building-related health conditions. That investigation identified water incursion and an exposure-response relationship between fungal concentrations and several of the respiratory complaints. Unfortunately, despite building-wide remediation of the water damage and fungal problem, a follow-up study published in 2011 demonstrated persistent health problems in employees who continued to work in the building, as well as many new cases of respiratory illness, including four people with hypersensitivity pneumonitis, akin to sarcoidosis [3]. These exposure and epidemiologically based studies do not provide insight into possible mechanisms. Two recent papers performed in homes of patients with sarcoidosis suggest that when household air sampling is conducted, fungal cell biomass can be detected, as marked by the presence of N-acetylhexosaminidase (NAHA), and that if these levels remain high, sarcoidosis recurrence is more likely to occur [4]. These same authors recently extended this observation by demonstrating that there is both in vitro and in vivo reactivity to fungal cell wall agents in blood monocytes obtained from sarcoidosis patients. Beta-glucan, chitin, and endotoxin induced pro-inflammatory cytokine production in vitro. In addition, there was a statistically significant correlation between high fungal cell wall agents in home air samples and spontaneous secretion of IL-12 in sarcoidosis patient cell cultures [5]. These lines of research are beginning to converge, providing epidemiologic and increasingly plausible experimental evidence for this hypothesis.

Mycobacteria and Workplace Sarcoidosis

Almost since the first discovery of sarcoidosis, clinicians and researchers have speculated about the role of mycobacteria. Much of this has stemmed from the strong histologic similarities between tuberculosis, non-tuberculous mycobacterial infection, and sarcoidosis. Three new papers lend further credence to the hypothesis that mycobacterial antigens cause at least some cases of sarcoidosis, and that many of these may be work-related. Extending an earlier line of investigation, Oswald-Richter and colleagues demonstrated the ability of CD4+ and CD8+ blood and bronchoalveolar lavage T cells from sarcoidosis patients to recognize mycobacterial antigens, as compared to controls [6]. Approximately half of the sarcoidosis patients demonstrated an in vitro blood cell response to one or more of the antigens. Sarcoidosis patients' bronchoalveolar lavage cells recognized multiple mycobacterial antigens, proliferating in four of five patients tested. Although the subject numbers are small, there was a suggestion that T cell responses to these mycobacterial antigens abated when patients' clinical sarcoidosis resolved. This study becomes particularly interesting in the occupational setting when it is taken in context with two recent studies [7, 8] that remind us that metalworking fluids continue to be contaminated by mycobacteria and can cause a sarcoidosis-like occupational form of hypersensitivity pneumonitis. Figure 1 illustrates the aerosol that is generated when these semi-synthetic oils are sprayed onto metal parts while they are being machined. Of note, Tillie-Leblond and colleagues analyzed metalworking fluids from a car engine manufacturing plant where there were 13 cases of suspected hypersensitivity pneumonitis [7]. Sera from these patients were compared to serum from exposed coworkers and healthy unexposed controls. The results reaffirmed the finding that *M. immunogenum*—a new species of mycobacteria that was originally

discovered by studying metalworking fluids, was present in the workplace fluids and that patients' serum contained *M. immunogenum* antibodies. A likely conclusion from this body of work is that if we were to systematically test the blood of patients with sarcoidosis who report having worked in metal machining industries, we would likely discover them to have an occupational, mycobacteria-targeted form of granulomatous inflammation.

Contribution of Inorganic Particulates to Sarcoidosis Risk

For more than 20 years, some of us have speculated that in order to develop sarcoidosis, an individual must be exposed to not only an antigen that can be presented to CD4+ T lymphocytes by antigen presenting cells, but that this event must occur in an inflammatory milieu. Be it in the lung, skin, or other organ, T cells will proliferate, differentiate, secrete inflammatory cytokines, attract other cells, and thus promote granuloma formation in the presence of two things: persistent antigen and an adjuvant signal that triggers an innate immune response. It is likely that a number of different exposures that promote innate immunity trigger an adaptive immune response to even some seemingly innocuous, nonpathogenic agents. Case reports and small case series over the years have suggested that a variety of inorganic dusts can play this "second hit" role, including a variety of silicates, man-made mineral fibers, and more recently, the complex, alkaline dust generated by the collapse of the World Trade Center in 2001. Several studies have recently increased the likelihood that inorganic particulate exposures contribute to sarcoidosis pathogenesis.

Occupational Particulate Exposure and Sarcoidosis Risk

Three recent papers regarding the World Trade Center disaster have extended our appreciation of the role of airborne inorganic particulate exposure in sarcoidosis. These papers build on earlier case reports and published longitudinal data that showed an increase in sarcoidosis among firefighters and emergency first responders. A recent review nicely summarizes most of the evidence [9]. Jordan and colleagues followed World Trade Center health registry participants, including 43 with biopsy- and clinically-confirmed patients with sarcoidosis. They stratified individuals in their cohort based on self-reported dust cloud exposures and observed that more intensive rescue and recovery activities were associated with increased disease risk [10]. Some such cases of World Trade Center sarcoidosis-like illness demonstrate extensive, multiorgan involvement [11]. Additionally, Crowley and coworkers calculated an extraordinarily high annual incidence rate of 229 sarcoidosis cases per 100,000 person years, based on record review of nearly 20,000 individuals in their World Trade Center medical surveillance program [12], providing independent confirmation of what had previously been published in a cohort of New York City firefighters and emergency response personnel. The implication of these studies is that sarcoidosis risk is increased among people who are exposed to very high levels of irritant, inorganic dust. World Trade Center dust is a highly alkaline, mixture that the U.S. Geological Survey has characterized as containing mostly the components of concrete, including gypsum, anhydrite, and manmade vitreous fibers. These epidemiologic studies do not go so far as to demonstrate the components or the mechanism by which this dust triggers granuloma formation. However, taken as a whole, this body of literature on World Trade Center sarcoidosis helps validate the many case series and case reports of the past few decades

reporting sarcoidosis occurring after exposure to silica, talc and other inorganic triggers. Along these same lines, a recent case report used x-ray microanalysis to demonstrate that the granulomas in the lungs of a dental surgeon with sarcoidosis contained the same inorganic dust as is used in dental cleaning procedures [13]. In another case report, a young male developed sarcoidosis after exposure to concrete slurry that is used in tunnel excavation [14].

Nanoparticles and Sarcoidosis

Based on their size and composition, nanoparticles have long been on our list of materials that we would predict to be potential triggers for sarcoidosis. Several recent toxicology studies have made it even more important that nanoparticles be considered a class of particles that may be implicated in granuloma formation. Huizar and colleagues have reported a murine model of chronic granulomatous lung inflammation induced by multiwall carbon nanotubes [15]. As in other mouse models, the granulomas in these animals are more loosely formed and transient compared to humans with sarcoidosis. However, the authors' ability to demonstrate macrophage and T cell infiltration and elaboration of cell adhesion molecules and cytokines suggest that the nanotubes are inducing a response that may be mechanistically related to what has been described in humans. Additionally, *in vitro* studies show cellular uptake and cytotoxicity, with increased reactive oxygen species formation and pro-inflammatory protein production [16]. Although more 'environmental' than occupational, one more piece of the nanoparticle hypothesis is provided by a nanotoxicology study of metal wear particles produced by metal-on-metal arthroplasty. *In vitro* and *in vivo* studies have shown macrophage/monocyte response, pro-inflammatory cytokine production, and inflammasome formation [17]. In the face of these toxicological hints, it would seem to be only a matter of time before human case reports would appear. In 2011, Song and Tang reported follow up exposure, pathology, and clinical data on seven female workers who had been exposed to polyacrylate nanoparticles for 5 to 13 months and were hospitalized with shortness of breath and pleural effusions. Two of these women subsequently died with progressive respiratory failure. Pathology findings included culture-negative foreign-body granulomas along the pleura, as well as progressive pulmonary fibrosis, inflammation, and foreign-body granulomas in the pleura. Nanoparticles found in the patients' tissue and effusions were the same raw materials that they were exposed to in the plant, particularly silica nanoparticles and nano- and microscale silicates [18]. Notably, the clinical features and pathology associated with these nanosilicates did not match the clinical features and non-caseating granulomas of sarcoidosis, but rather suggest a more fibrotic response akin to accelerated pneumoconiosis. Nonetheless, these studies from China require us to remain alert to pulmonary and pleural diseases in the future, especially as nanoparticles become even more ubiquitous in industrial production. In keeping with the precautionary principle, efforts need to be made to protect workers and provide medical surveillance for pulmonary and other nanoparticle-associated health consequences.

Conclusions

There is mounting evidence that sarcoidosis can occur in workplace settings in which there is exposure to inorganic triggers of inflammation that promote an exuberant granulomatous

immune response to a number of different antigens. It is likely that sarcoidosis has more than one cause. Occupational and environmental exposure histories should be carefully collected to identify potential workplace triggers for sarcoidosis.

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Abbreviations

ACCESS	A case control etiologic study of sarcoidosis
NAHA	N-acetylhexosaminidase

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individuals exposed to dust from the World Trade Center disaster, the researchers reported an increased rate of sarcoid-like disease in firefighters, in the first year after 9/11.

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Key Points

- Workplace exposures are associated with the development of sarcoidosis
- Mycobacterial, fungal, and other microbial antigens are targets for the granulomatous immune response
- Exposures to inorganic particulate matter can promote an inflammatory response leading to granuloma formation
- Occupational and environmental exposure histories should be carefully considered in patients with sarcoidosis



Figure 1. METALWORKING FLUID EXPOSURES CAN CAUSE SARCOIDOSIS-LIKE ILLNESS IN METAL MACHINING INDUSTRIES. Metal parts are commonly flooded with synthetic and semi-synthetic oils that serve as coolants during machining. Such fluids are commonly recycled and can become contaminated with mycobacteria, endotoxin, and microbial antigens. Workers often develop hypersensitivity pneumonitis that is initially mistaken for sarcoidosis.

Table 1

Examples of known occupational causes of sarcoidosis and sarcoidosis-like illness

Disease	Examples or industry or occupation	Known or suspected agent	Evidence
Hypersensitivity pneumonitis	Agriculture, metalworking, lifeguards, bird handlers, others	Fungal antigens, bacterial antigens, including mycobacterial antigens	Epidemiologic, clinical, immunologic, microbiologic, animal models
Chronic beryllium disease	Defense industries, electronics, alloy manufacture	Beryllium	Epidemiologic, clinical, immunologic
Granulomatous lung disease	Mining, manufacturing, agriculture, transportation	Aluminum, barium, cobalt, copper, gold, rare earth metals, titanium, zirconium	Epidemiologic, clinical, immunologic
Nanoparticle-related granulomas, pleural and pulmonary fibrosis	Manufacturing	silica nanoparticles, carbon nanoparticles	Clinical, immunologic, animal models
Silicosis	Mining, construction	Silicates, talc	Epidemiologic, clinical, immunologic
Psittacosis	Bird handling	Bird protein antigens, bacterial antigens	Epidemiologic, clinical, microbiologic
Sarcoidosis-like illness	World Trade Center emergency response and clean up	World Trade Center dust (inorganic dust)	Epidemiologic Clinical
Sarcoidosis	Agriculture	Mold, bacteria, silicates	Epidemiologic
	Wood burning	Silicates	Epidemiologic
	Mining	Silicates	Epidemiologic
	Transportation	Metal dust, inorganic particulate	Epidemiologic
	Metal industries	Metal dust, metalworking fluid aerosols	Epidemiologic
	Firefighting, emergency response	Inorganic dust, fumes	Epidemiologic
	Construction	Inorganic dust	Epidemiologic
	Office work (indoor air)	Mold, bacteria, other microbial contaminants	Epidemiologic Immunologic