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## **SARCOIDOSIS: EPIDEMIOLOGY, PATHOGENESIS, DIAGNOSIS, AND CAUSAL ASSOCIATIONS WITH OCCUPATIONAL AND ENVIRONMENTAL EXPOSURES**

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## INTRODUCTION

Sarcoidosis has been defined as a “multisystem granulomatous disorder of unknown etiology” and, similarly, as a “relatively uncommon multi-systemic immunological disorder of unknown cause with variable clinical manifestations and outcomes.”<sup>1, 2</sup> Sarcoidosis was first recognized more than 120 years ago.<sup>1-3</sup> During the past 20 years there have been published reports of causal associations between occupational and environmental exposures and development of sarcoidosis, and emergence of a consensus that etiology is multi-factorial.<sup>3,4</sup> Contributing factors include genetic make-up, ethnicity, and exposure to a variety of antigens capable of inducing the inflammatory process that results in granuloma formation. During this period there has been considerable progress in the understanding of pathogenetic mechanisms, and diagnostic methods have been refined.

The purpose of this summary document is to provide basis for assessment of causation in cases of sarcoidosis among workers in the mining sector of Northern Ontario. Clinical, radiologic, and pathologic criteria for diagnosis are presented. Occupational and environmental agents that have been associated with the development of sarcoidosis are described.

## EPIDEMIOLOGY

Sarcoidosis occurs on a global basis. Prevalence is variable and depends on the geographic region. For example, in Argentina and Brazil prevalence is 1 to 5/100,000 persons; and in Denmark and Sweden, 50 to 60/100,000. Worldwide prevalence is 4.7 to 64 per 100,000 persons, while incidence is 1.0-35.5 per 100,000 persons per year.<sup>1,3</sup> The highest rates are in Northern Europe and among African-Americans in the United States; the lowest rates are in Japan.<sup>3</sup> Prevalence among African-Americans is 10 to 17 times that of Caucasians and higher in women compared to men: among African-American females, prevalence is 39.1 per 100,000 persons; among African-American males, 29.8; among Caucasian females 12.1; and among Caucasian males, 9.6.<sup>1</sup> The disease occurs more commonly among those age 30 to 39. In a study by Rybicki et al of incidence of sarcoidosis in members of a Health Maintenance Organization in Detroit, MI, race was the strongest predictor of risk [adjusted relative risk (RR) 3.80, 95% confidence interval (CI) 2.69-5.40]. The predictive value of female gender was of marginal statistical significance (RR 1.29, 95% CI 1.00-1.67).

Incidence is higher in certain exposure groups. For example, a high incidence of sarcoidosis was observed among first responders to the World Trade Center (WTC) attack in New York City on September 11, 2001.<sup>3,6</sup> Generally considered a sporadic disease, sarcoidosis is familial in 3.6 to 9.6% of cases, with higher incidence among siblings.<sup>3</sup>

Interestingly cigarette smoke appears to protect against sarcoidosis, as is the case with other granulomatous lung diseases such as hypersensitivity pneumonitis (HP).<sup>3,7</sup> In a case-control study conducted by Newman et al, the odds ratio (OR) were well below 1.0, indicating a reduced risk or protective effect. For personal use of tobacco at study enrollment, OR was 0.20 (95% CI 0.14-

0.29,  $p < 0.001$ ); and for personal use and passive exposure, OR was 0.70 (95% CI 0.55-0.88,  $p = 0.002$ ).<sup>7</sup>

## **PATHOGENESIS**

Sarcoidosis is an immunologic disorder.<sup>2-4, 8</sup> Pathogenesis is believed to be a three-step process requiring initially 1) exposure to an antigen that is presented to CD4+ T-lymphocytes by antigen-presenting cells (HLA class II molecules), and 2) an inflammatory milieu in which the antigen presentation can take place. There is an up-regulation of the immune response, with activation of alveolar macrophages and dendritic cells and development of memory for the causal antigen (sensitization). HLA polymorphisms are likely genetically determined. Genes may also play a role in T-cell responses, which are likely related to memory from previous antigen exposures.

Chronic beryllium disease (CBD) provides a model for studying the pathogenesis and epidemiology of sarcoidosis.<sup>9, 10</sup> Li et al examined the gene expression profiles in peripheral blood mononuclear cells (PBMNC) of patients with CBD and compared them to a control group and to a group of patients with sarcoidosis.<sup>9</sup> There were 450 genes that were differentially expressed with CBD compared to controls. There was overlap of 287 differentially expressed between CBD and sarcoidosis patients. This finding is reflective of the clinical overlap between these two diseases and predicts epidemiologic similarities.<sup>10</sup> For example, because the pathogenesis of each is immunologic, dose required to produce disease is unpredictable, as is latency. Published epidemiologic studies have shown this to be the case with CBD. Dose-response relationships do not follow patterns established for certain pneumoconiosis such as asbestosis and silicosis. Although there is increased risk with increased levels of exposure, once sensitization has occurred very low dose exposure can trigger granuloma formation – analogous to anaphylaxis following exposure to peanut antigen in a peanut-allergic person.

Granuloma formation is the pathologic hallmark of the disease. The formation of granulomas is dependent on a functioning immune system. Flieder et al describe the histopathology of sarcoid granulomas as follows: “Sarcoid granulomas are well-circumscribed collections of epithelioid macrophages with light eosinophilic cytoplasm and reniform to oval vesicular nuclei, surrounded by a rim of lymphocytes and fibroblasts.”<sup>2</sup> Langhans-type giant cells may be present and may contain inclusion bodies (asteroid, Schaumann). While most sarcoid granulomas are non-necrotizing, in contradistinction to the granulomas typically seen with *Mycobacterium tuberculosis*, up to 40% may contain “small foci of central fibrinoid, granular or eosinophilic necrosis”.<sup>2</sup>

It is thought that within sarcoid granulomas are remnants of causative antigens that form a nidus for granulomatous inflammation.<sup>4</sup> The current consensus is that no single antigen is responsible for the disease; rather, it is likely that a number of different antigens can stimulate granuloma formation.

Sarcoid granulomas may resolve, but with progression of disease, there is development of fibrotic changes that appear to extend from the outer rim inward. End-stage sarcoidosis is characterized

by interstitial pulmonary fibrosis.<sup>9</sup> Factors that pre-dispose to development of fibrosis are not well understood.

Sarcoid granulomas affect multiple organs. The lungs are affected in greater than 90% of patients. Other organs that may be affected include lymph nodes (80-90%); liver and spleen (10-20%); skin (25-35%); eyes (25-80%); heart (5-25%); nervous system (10-25%); and bones (14-38%).<sup>2</sup>

## DIAGNOSIS

The diagnosis of sarcoidosis is based upon three diagnostic criteria:

1. Characteristic clinical and radiological presentation;
2. Evidence of non-caseating granulomas (in two or more organs); and
3. Reasonable exclusion of alternative diagnoses.<sup>3,8,11</sup>

Respiratory symptoms are nonspecific, with the most common being persistent cough. Other symptoms such as fever, fatigue, and weight loss may be seen. Involvement of the skin with erythema nodosum, the eye with uveitis, and the lymph nodes with hilar and/or peripheral lymphadenopathy are clinical indicators of granulomatous inflammation and disease.

Radiographic hallmarks are hilar lymphadenopathy and/or a diffuse micronodular pulmonary infiltrate on chest X-ray. Although chest X-ray is the more important radiographic tool in making the diagnosis of sarcoidosis, chest CT scan is useful in cases in which radiographic findings are atypical, or normal in cases of suspected disease, and in the detection of pulmonary complications such as pulmonary hypertension.<sup>2</sup> On chest CT scan irregular nodules with lymphangitic distribution involving the middle and upper lung zones is characteristic of sarcoidosis. Ground glass opacities may be seen, and often there is air-trapping, a sign of small airway disease.

Pulmonary function tests typically show restriction with reduction in the single breath diffusing capacity for carbon monoxide, a measure of gas exchange in the lungs. Obstruction or a mixed restrictive-obstructive ventilatory deficit may be seen. Obstruction with or without bronchodilator response may be caused by granulomas in the airways of the lungs.

Laboratory abnormalities include abnormal liver function tests indicating granulomatous inflammation of the liver. The angiotensin-converting enzyme (ACE), produced by epithelioid cells in the granuloma, may be elevated in cases of active sarcoidosis and helpful in distinguishing sarcoidosis from other causes of granulomatous disease.<sup>8</sup> Although a specificity of 90% and a positive predictive value of 90% were observed in one large study, the negative predictive value was 60%; so that the sensitivity of the test is inadequate to make it useful as a screening tool.<sup>8</sup> Hypercalcemia is one of the indications for treatment with systemic steroids.

Non-caseating epithelioid cell granulomas are the *sine qua non* of sarcoidosis. Histologic evidence of granulomas in at least one organ is required; and there must be granulomatous inflammation of at least two organs to meet diagnostic criteria.<sup>8</sup> Demonstration of

granulomatous inflammation does not require biopsy of more than one organ. Chest CT scan may demonstrate consistent pulmonary and/or lymph node findings in patients with normal chest X-ray. Liver function tests may provide evidence of granulomas in the liver. PET scan may demonstrate inflammatory changes in the parotid glands or increased uptake in bone or other organs.<sup>3,8,11</sup>

## **PROGNOSIS**

Mortality in individuals with sarcoidosis has been reported at 7.6% in the United States.<sup>3, 12</sup> The most common cause of premature death is the sarcoidosis itself.<sup>3</sup> Pulmonary hypertension related to pulmonary fibrosis may be a significant contributing factor. About 20% of patients have permanent clinical symptoms attributable mostly to pulmonary fibrosis. Approximately 12% require long-term oxygen therapy. An increased incidence of lymphoma has been observed in association with sarcoidosis. Risk for pulmonary embolus is also increased.

## **TREATMENT**

Sarcoidosis may remit spontaneously.<sup>3,8</sup> Consequently, observation of newly-diagnosed cases is advised. Twenty to 70% of patients need systemic treatment, with indications including involvement of the heart, kidneys, and neurologic system; uveitis unresponsive to topical steroids; and hypercalcemia.

The mainstay of systemic treatment of sarcoidosis is corticosteroids. There are no validated guidelines for dose and duration of treatment. Side effects often preclude continued treatment with oral corticosteroids. Other treatment modalities are immunosuppressive, cytotoxic, and anti-malarial drugs.

## **OCCUPATIONAL AND ENVIRONMENTAL CAUSES OF SARCOIDOSIS**

Occupational and environmental exposures have been associated with the development of sarcoidosis. Newman and Newman in their review of occupational causes of sarcoidosis identified as potential work-related causes silicates and other inorganic particles, nanoparticles, metal dusts, WTC dust, metal-working fluids, and microbe-rich environments.<sup>4</sup> As noted above, pathogenesis likely involves exposure to an antigen that can be presented to CD4+ lymphocytes by antigen-presenting molecules and an inflammatory milieu in which the presentation can take place.

In some cases, workplace-related diseases that were once thought to be sarcoidosis have been reclassified or renamed as specific disorders once the causative agent was identified and confirmed. Examples include chronic beryllium disease (CBD) associated with exposure to beryllium; pulmonary granulomatous disease associated with exposure to aluminum; and HP associated with exposure to microbial organisms found in damp work or home environments or as contaminants of metal-working fluids.<sup>13-17</sup>

## Inorganic Particulates and Sarcoidosis

Sarcoidosis has been causally related to occupational exposure to dust created by the collapse of the WTC towers in New York City on September 11, 2001.<sup>6,18-20</sup> Sarcoidosis has also been causally related to occupational and environmental exposure to respirable crystalline silica (RCS).<sup>21-25</sup>

Increased prevalence of sarcoidosis has been observed among first responders to the WTC disaster on September 11. Safirstein et al published a case report of a 37-year-old engineer exposed to WTC dust on and after September 11.<sup>6</sup> The engineer developed biopsy-proven diffuse granulomatous lung disease with onset of symptoms three weeks post-exposure. There was no evidence of extra-pulmonary disease. Tests for CBD were negative.

Among firefighters, incidence of a sarcoid-like granulomatous pulmonary disease increased in the first year following the WTC attack compared with the average for the preceding 15 years: 86/100,000 persons vs 15/100,000.<sup>18</sup> Crowley et al examined incidence of sarcoidosis among 20,000 responders who participated in the WTC Medical Monitoring and Treatment Program over the period July 16, 2002 to September 11, 2007.<sup>19</sup> Sarcoidosis was determined on the basis of self-report of the diagnosis, a biopsy performed post-September 11 and prior to the initial monitoring visit showing non-caseating epithelioid granulomas, and a chest X-ray consistent with the diagnosis. Overall incidence over the more-than five-year period was 229 per 100,000 person-years (95% confidence interval (CI) 136-322 per 100,000 person-years). Age-adjusted annual incidence rate per 100,000 persons for male WTC responders was approximately twice that observed among males in a Detroit Health Maintenance Organization: 23.1 vs. 9.6 for white males and 56.9 vs. 29.8 for black males.<sup>1,19</sup> For females, incidence rates were similar.

Jordan et al observed 43 cases that met diagnostic criteria for sarcoidosis in a group of 45,899 enrollees in the WTC Health Registry.<sup>20</sup> Registry enrollees included first responders, lower Manhattan residents and office workers, and passersby on September 11. Biopsy-proven non-caseating granulomas were necessary to the diagnosis of sarcoidosis. Biopsy sites included mediastinum (25%), transbronchial lung or lymph nodes (20.5%), lung (27.3%), and other (25%). Thus in over 70% of cases, multi-organ involvement was demonstrated by biopsy. Twenty-eight of the 43 cases were matched with 109 controls in a nested case-control analysis. This analysis revealed a significant association between the development of sarcoidosis and the following: work on the debris pile at any time (OR 9.1, 95% CI 1.1-74.0); firefighting on the pile (OR 11.00, 95% CI 1.3-96.1); and hand digging on the pile (OR 8.8, 95% CI 1.1-71.6). Confidence intervals are wide, reflective of small numbers.

WTC dust was created by the burning and collapse of the Twin Towers and their constituent and furnishing materials such as concrete, metal beams, asbestos, manmade vitreous fibers, furniture, carpeting, and computers.<sup>18</sup> The dust was highly alkaline, attributable in part to the concrete dust. In the case reported by Safirstein et al, scanning electron microscopy and energy-dispersive radiographic analysis of lung tissue obtained at biopsy revealed silica, silicates, and calcium oxalate.<sup>18</sup> In none of the other cited studies was the specific dust(s) responsible for triggering granuloma formation identified. Nevertheless, these studies indicate an increased risk

for sarcoidosis among people who are exposed to very high levels of particulate dust similar to that found at the WTC site.

Exposure to RCS has been associated with increased risk for sarcoidosis. Rafnsson et al examined prevalence of sarcoidosis among residents living proximate to a diatomaceous earth processing plant in northern Iceland.<sup>21</sup> Processing of the diatomaceous earth resulted in the transformation of the diatomaceous earth into an amorphous state and then into a form consisting predominantly of respirable crystalline silica: 70% cristobalite and 1-2% quartz. In the population-based case-referent study, eight cases of sarcoidosis were identified from hospital medical records using radiological, histological, and clinical criteria. Six (75%) had a history of occupational exposure to dust from work at the diatomaceous earth plant, either from work in the plant itself or from loading the final product onto shipping vessels. Among 70 referents chosen at random from the population of the district, 15 were ever-exposed and 57 were never exposed. The OR for exposure was 13.2 (95% CI 2.0-140.9). Although the numbers are small and the confidence interval wide, these data indicate a significant association between exposure to crystalline silica and sarcoidosis.

In 2015 Vincent et al published the results of their review of proceedings of a 1930 International Labor Organization (ILO) Conference on silicosis held in Johannesburg, South Africa.<sup>22</sup> The purpose of the review was to examine Conference findings in light of intervening advances in medical knowledge and technology. The authors concluded that the definition of silicosis put forth by Conference participants was restricted in such a way as to obscure possible associations between occupational exposure to silica and the development of inflammatory lung diseases other than chronic silicosis, diseases such as acute silicosis with pulmonary alveolar proteinosis (PAP) and sarcoidosis. The investigators encouraged re-examination of the role of silica in the pathogenesis of “idiopathic” inflammatory lung diseases such as sarcoidosis using detailed occupational histories, advanced methods of mineralogical analysis, and electron microscopy.

RCS exposure has been associated with development of a variety of autoimmune disorders such as rheumatoid arthritis (RA) and Sjogren’s syndrome.<sup>23</sup> Vihlborg et al examined associations between occupational exposure to RCS and sarcoidosis and seropositive RA in a cohort of Swedish iron foundry workers.<sup>24</sup> The cohort consisted of 2,187 silica-exposed males who had worked for one year or more in one of 10 foundries in Sweden and were alive at the time of the initiation of the study. Onset of employment was 1970 or later in close to 80% of participants, with employment duration of two to ten years in 42.8%. Personal air sampling for silica was carried out between 1968 and 2006. Mean silica exposures in mg/m<sup>3</sup> varied by job title, exposure period, and foundry, and were highest for furnace and ladle repairman (0.14 mg/m<sup>3</sup> (range 0.0028-4.9)), the time period 1970-1979 (0.14 mg/m<sup>3</sup> (range 0.003-3.3)), and foundry 4 (0.15 mg/m<sup>3</sup> (range 0.0038-4.9)). Significant increases in incidence of sarcoidosis and RA were observed in association with exposure to silica at concentrations  $\geq 0.048$  mg/m<sup>3</sup> compared with no exposure or exposure at lower levels: standardized incidence ratios (SIR) 3.94 (95% CI 1.07-10.08) and 2.59 (95% CI 1.24-4.76), respectively. These data indicate that silica may trigger granuloma formation at least in part as a result of its immunologic effects.

Silica and other airborne inorganic and organic particulates are found in mines, including gold, nickel, and uranium mines of Northern Ontario. In the case-control study conducted by Newman et al, sarcoidosis cases were more likely than controls to report employment in the general category of dusty trades, industries, or occupations, and in the specific categories of “crustal” dust and silica dust exposure.<sup>7</sup> Sarcoidosis cases were more likely than controls to report as “activities on the job” within these exposure categories “any type of mining.”

Because of the low prevalence of reports of “any type of mining” among controls (proportion of controls < 0.05), there was <90% power to detect a statistically significant association for this variable. Seven hundred six cases of sarcoidosis were recruited from 10 academic centers in the United States and matched to an equal number of controls chosen by random digit dialing to test the hypothesis that occupational and environmental exposures are associated with increased risk for sarcoidosis.

### **Metals and Sarcoidosis**

The inhalation of metal dust can cause a variety of lung diseases. These include granulomatous disorders, interstitial fibrosis, giant cell interstitial pneumonitis (hard-metals disease), chemical pneumonitis, and airways disease.<sup>25</sup> Granulomatous inflammation and HP are associated not only with the inhalation of metal dust and fumes but also with exposure to mycobacteria and fungi.<sup>25</sup> Both occupational and environmental exposures to metals cause granulomatous lung disease; although occupational exposures are more commonly reported.

Metals are capable of causing an antigen-specific granulomatous immune response and “nonspecific ‘innate’ immune system responses characterized by inflammation frequently triggered by oxidant injury.”<sup>25</sup> The beryllium lymphocyte proliferation test (BeLPT) utilizes the immune response of T-lymphocytes to beryllium (Be) salts *in vitro* to distinguish CBD from sarcoidosis.<sup>25,26</sup> Fireman et al used lymphocyte proliferation tests in a pilot study of the responsiveness of sarcoidosis patients to a variety of metals, including aluminum, titanium, nickel, chromium, mercury, and palladium chosen on the basis of occupational history.<sup>27</sup> Of 13 patients with sarcoidosis, nine tested positive to at least one of these metals. Positive BeLPT and other metal-responsive proliferation tests indicate *sensitization* with increased risk for disease, but not the presence of granulomatous disease itself.

Consistent with an immunologic mechanism is the fact that low level exposure to metals has been increasingly recognized as a cause of granulomatous pulmonary disease. An inflammatory response to irritant properties likely plays a role as well. Genetic factors affect risk for exposure-related disease, an association perhaps best shown with CBD and cobalt-related lung disease.<sup>25</sup>

### **Aluminum and Cobalt**

Occupational exposure to aluminum and cobalt has been associated with a variety of pulmonary disorders. Aluminum has been associated with airway disease in the form of “potroom asthma” seen in workers involved in the electrothermal conversion of alumina to aluminum; pulmonary



fibrosis (aluminosis); and granulomatous lung disease.<sup>25</sup> Its mechanism of action is unclear. Smolkova et al reported a case of pulmonary fibrosis in a 39-year-old nonsmoker.<sup>15</sup> Microscopic examination of lung tissue obtained by video-assisted thoracoscopy (VATS) revealed mild interstitial fibrosis without evidence of non-caseating granulomas. After an occupational history of work as an aviation mechanic with exposure to aluminum dust was obtained, a worksite assessment made, and elemental analysis of lung tissue performed, a diagnosis of aluminosis was made.

Tomioka et al reported two cases of granulomatous lung disease, one in a battery manufacturing worker and one in an aluminum processing worker.<sup>14</sup> In case 1, high resolution chest CT scan (HRCT) revealed micronodules with upper and middle lobe predominance and mediastinal lymph node enlargement. Histopathology of lung tissue obtained at VATS revealed non-caseating epithelioid granulomas in the lung interstitium and visceral pleura. ACE was mildly elevated at 24.0 U/L (normal 6-21). In case 2, HRCT revealed diffuse nodular opacities with thickening of the interlobar septae. Histopathology of lung tissue obtained at VATS revealed granulomas composed primarily of multi-nucleated giant cells. Mycobacterial and fungal stains were negative in both cases.

Elemental analysis using electron probe microanalyzer with a wavelength-dispersive spectrometer revealed the presence of the following in the granulomas in both cases: silicon, iron, aluminum, and titanium. In each case, aluminum was widely distributed throughout the granulomas. Noting that silicon, iron, and aluminum may be found in normal human lung, based upon the widespread distribution of aluminum in the granulomas the authors concluded that aluminum could explain the observed granuloma formation in both cases. Despite the mildly elevated ACE level in Case 1, the authors excluded sarcoidosis as the diagnosis on the basis of the absence of other organ involvement and the lack of sensitivity ACE.

Cobalt, like aluminum, has been associated causally with different occupational lung diseases.<sup>25, 28</sup> These include occupational asthma; hard-metals disease with desquamative interstitial pneumonitis (DIP) or giant cell interstitial pneumonitis; and HP. The formation of epithelioid cell granulomas is relatively rare but has been reported.<sup>13,29</sup> Cobalt, like Be, is a sensitizer and positive lymphocyte proliferation tests have been reported in individuals with positive cobalt patch testing.<sup>25</sup> Accordingly an immunologic mechanism is likely. Genetic alterations similar to those seen with Be exposure may contribute to increase in risk for pulmonary disease in cobalt-exposed workers.

### **Other Workplace Exposures**

Other workplace exposures that have been associated with granulomatous lung disease resembling sarcoidosis include fungi and mycobacteria; metal-working fluids contaminated with mycobacteria; and nanoparticles.<sup>4</sup> In the case of occupational or environmental exposure to micro-organisms, the most likely cause of the granulomatous lung disease is HP and that diagnosis should be included in the differential diagnosis.

Chronic granuloma formation has been observed in studies of mice exposed to multiwall carbon nanotubes.<sup>30</sup> Although the appearance and behavior of the granulomas is different from that of sarcoid-like epithelioid granulomas in humans, the presence of macrophage and T-lymphocyte infiltration and production of cell adhesion molecules and certain cytokines indicate a mechanistic response to the trigger similar to that seen in the formation of sarcoid granulomas.

## Conclusions

Published medical and scientific literature provides evidence of an association between occupational and environmental exposures and the development of granulomatous lung disease. Certain of these occupational exposures have been associated with the development of sarcoidosis.

Distinguishing between sarcoidosis and granulomatous lung diseases of more specific causation such as CBD, HP, and aluminum-related granulomatous lung disease can be difficult. Non-caseating granulomas are necessary to the diagnosis in each case. Characteristic features of sarcoidosis that are not typically found in other granulomatous lung diseases, with the exception of CBD, are multi-organ involvement and a typical clinical and radiographic presentation.

The diagnosis of sarcoidosis requires the exclusion of other diseases. The exclusion of other granulomatous lung diseases requires a detailed occupational and environmental history. If this history reveals exposure to an antigen or irritant known to be associated with granuloma formation in the lungs, further testing is needed to confirm causation. Such testing may take the form of immunologic tests such as the BeLPT in the case of CBD or serum-specific IgGs (SSIgG) in the case of HP. Where such testing is not available or has not been standardized, analysis of lung tissue for specific metals to which the individual has been exposed may be helpful in making the diagnosis. In the absence of objective evidence of an alternative diagnosis, sarcoidosis is the likely diagnosis in cases that meet other diagnostic criteria.

The available information indicates that there is more than one cause of sarcoidosis. Work in an occupational setting with exposure to one or more triggers of granulomatous inflammation in the lung is likely to contribute causally to the development of sarcoidosis in at-risk individuals. Such occupational settings include the mines of Northern Ontario.

## REFERENCES

1. Rybicki BA, Major M, Popovich J, Jr., Maliank MJ, Iannuzzi. Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. *Am J Epidemiol* 1997;145:234-241.
2. Flieder DB, Sanders A, Koss MN. Sarcoidosis. In: Hasleton P, Flieder DB, eds. *Spencer's Pathology of the Lung*. Sixth Edition. Vol. 1. Cambridge UK: Cambridge University Press, 2013.
3. Valeyre D, Prasse A, Nunes H, Uzunhan Y, Brillet P-Y, Muller-Quernheim J. Sarcoidosis. Seminar. *The Lancet* 2014;383:1155-1167.

4. Newman KL, Newman LS. Occupational causes of sarcoidosis. *Curr Opin Allergy Immunol* 2012;12:145-150.
5. Deubelbeiss U, Gemperil A, Schindler C, Baty F, Brutsche MH. Prevalence of sarcoidosis in Switzerland is associated with environmental factors. *Eur Respir J* 2010;35:1088-1097.
6. Safirstein BH, Klukowicz A, Miller R, Teirstein A. Granulomatous pneumonitis following exposure to the World Trade Center collapse. *Chest* 2003;123:301-304.
7. Newman LS, Rose CS, Bresnitz EA, Rossman MD, Barnard J, Frederick M, et al. A case control etiologic study of sarcoidosis. Environmental and occupational risk factors. *Am J Respir Crit Care Med* 2004;170:1324-1330.
8. Baughman RP, Culver DA, Judson MA. A concise review of pulmonary sarcoidosis. *Concise Clinical Review. Am J Respir Crit Care Med* 2011;183:573-581.
9. Li L, Silveira LJ, Hamzeh N, Gillespie M, Mroz PM, Mayer AS, et al. Beryllium-induced lung disease exhibits expression profiles similar to sarcoidosis. *Eur Respir J* 2016;47(6):1797-1808.
10. Culver DA. Beryllium disease and sarcoidosis: still besties after all these years? Editorial. *Eur Respir J* 2016;47:1625-1628.
11. American Thoracic Society, European Respiratory Society, and World Association of Sarcoidosis and Other Granulomatous Disorders. Joint Statement. Statement on sarcoidosis. *Am J Respir Crit Care Med* 1999;160:736-755.
12. Swigris JJ, Olson AL, Huie TJ, et al. Sarcoidosis-related mortality in the United States from 1988-2007. *Am J Respir Crit Care Med* 2011;183:1524-1530.
13. Newman LS. Metals that cause sardoisosis. *Semin Respir Infect* 1998;11:212-220.
14. Tomioka H, Kaneda T, Katsuyama E, Kitaichi M, Moriyama H, Suzuki E. Elemental analysis of occupational granulomatous lung disease by electron probe microanalyzer with wavelength dispersive spectrometer: two case reports. *Respiratory Medicine Case Reports*. 2016;18:66-72.
15. Smolkova P, Nakladalova M, Tichy T, Hampalova M, Kolek V. Occupational pulmonary aluminosis: A case report. *Industr Health* 2014;52:147-151.
16. Smolkova P, Nakladalova M. The etiology of occupational pulmonary aluminosis – the past and the present. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2014;158:535-538.
17. Tille-Leblond I, Grenouillet F, Reboux G, Roussei S, Chouraki B, Lorthois C, et al. Hypersensitivity pneumonitis and metalworking fluids contaminated by mycobacteria. *Eur Respir J* 2011;37:640-647.
18. Jordan HT, Stellman SD, Prezant D, Teirstein A, Osahan SS, Cone JE. Sarcoidosis diagnosed after September 11, 2011, among adults exposed to the World Trade Center disaster. *JOEM* 2011;53:966-974.
19. Crowley LE, Herbert R, Moline JM, Wallenstein S, Shukla G, Schechter C, et al. "Sarcoid like" granulomatous pulmonary disease in World Trade Center disaster responders. *Am J Ind Med* 2011;54:175-184.
20. Perlman SE, Friedman S, Galea S, et al. Short-term and medium-term health effects of 9/11. *Lancet* 2011;378:925-934.
21. Rafnsson V, Ingimarsson O, Hjalmarsson I. Association between exposure to crystalline silica and risk of sarcoidosis. *Occup Environ Med* 1998;55:657-660.

22. Vincent M, Chemariin C, Cavalin C, Catinon M, Rosental P-A. From the definition of silicosis at the 1930 Johannesburg Conference to the blurred boundaries between pneumoconiosis, sarcoidosis, and pulmonary alveolar proteinosis (PAP). Historical Perspective. *Am J Ind Med* 2015;58:531-538.
23. Calvert GM, Rice FL, Boiano JM, et al. Occupational silica exposure and risk of various diseases: an analysis using death certificates from 27 states in the United States. *Occup Environ Med* 2003;60:122-129.
24. Vihlborg P, Bryngelsson I-L, Andersson L, Graff P. Risk of sarcoidosis and seropositive rheumatoid arthritis from occupational silica exposure in Swedish iron foundries: a retrospective cohort study. *BMJ Open* 2017;7:e016839. Doi:10.1136/bmjopen-2017-016839.
25. Kellerher P, Pacheco K, Newman LS. Inorganic dust pneumoconias: the metal-related parenchymal disorders. *Environ Health Perspect* 2000;108(Suppl 4):685-696.
26. Fireman E, Haimsky E, Noiderfer M, Priel I, Lerman Y. Misdiagnosis of sarcoidosis in patients with chronic beryllium disease. *Sarcoidosis Vasc Diffuse Lung dis* 2003;20:144-148.
27. Fireman E, Shai AB, Alcalay Y, Ophir N, Kivity S, Stejskal V. Identification of metal sensitization in sarcoid-like metal-exposed patients by the MELISA® lymphocyte proliferation test – a pilot study. *J Occup Med Toxicol* 2016;11:18. <http://doi.org/10.1186/s12995-016-0101-1>.
28. Sprince NL, Oliver LC, Eisen EA, Greene RE, Chamberlin RI. Cobalt exposure and lung disease in tungsten carbide production: a cross-sectional study of current workers. *Am J Respir Med* 1988;138:1220-1226.
29. Satoh-Kamachi A, Munakata M, Kusaka Y, Amishima M, Furuya K, Takahashi T, et al. A case of sarcoidosis that developed three years after the onset of hard metal asthma. *Am J Ind Med* 1998;33:379-383.
30. Huizar I, Malur A, Midgette YA, et al. Novel murine model of chronic granulomatous lung inflammation elicited by carbon nanotubes *Am J Respir Cell Mol Biol* 2011;45:858-866.